Multimodality imaging approach to Fabry cardiomyopathy: Any role for nuclear cardiology?

Wanda Acampa, MD, PhD,[a] Adriana D'Antonio, MD,[a] Massimo Imbriaco, MD,[a] Antonio Pisani, MD,[b] and Alberto Cuocolo, MD[a]

[a] Department of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy
[b] Department of Public Health, University of Naples Federico II, Naples, Italy

Received Mar 26, 2020
doi:10.1007/s12350-020-02124-1

Anderson–Fabry disease (AFD) is a multisystem X-linked disorder of lipid metabolism frequently associated with progressive glycosphingolipid accumulation in cardiac, renal, and nervous cells. The diagnosis of AFD is usually assessed by enzyme assay and genetic tests, but advanced cardiac imaging can be useful in detecting early signs of the disease. Echocardiography and cardiac magnetic resonance are the first-line imaging modalities to investigate cardiac involvement in AFD, but the recent introduction of new molecular and hybrid imaging techniques opens to a wider range of diagnostic applications. This article aims to provide an overview of nuclear cardiology techniques in diagnosis and clinical management of AFD.

Key Words: Cardiomyopathy • MRI • PET • hybrid imaging • multimodality

Abbreviations

AFD	Anderson–Fabry disease
Gb3	Globotriaosylceramide
LV	Left ventricular
LVH	Left ventricular hypertrophy
CMR	Cardiac magnetic resonance
LGE	Late-gadolinium enhancement
ERT	Enzyme replacement therapy
FDG	Fluorodeoxyglucose
PET	Positron emission tomography
STIR	Short time inversion recovery
COV	Coefficient of variation
SUV	Standardized uptake value
MIBG	Metaiodobenzylguanidine
CMD	Coronary microvascular dysfunction

CARDIAC INVOLVEMENT IN ANDERSON–FABRY DISEASE

Anderson–Fabry disease (AFD) is an X-linked recessive lysosomal storage disorder, caused by the deficiency of a-galactosydase A, resulting in progressive accumulation of glycosphingolipids, in particular globotriaosylceramide (Gb3), in a variety of cells and tissues, in particular vascular endothelial cells, cardiomyocytes, smooth muscle cells, renal cells, and neuronal cells.[1] Male individuals are primarily affected, but female heterozygotes may also display symptoms ranging in severity, possibly due to skewed X-chromosome inactivation.[2] Glycosphingolipid deposition in the endothelium has been considered the cause of the

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12350-020-02124-1) contains supplementary material, which is available to authorized users.

The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarizes the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

Reprint requests: Alberto Cuocolo, MD, Department of Advanced Biomedical Sciences, University of Naples ''Federico II'', Via Pansini 5, 80131 Naples, Italy; *cuocolo@unina.it*

J Nucl Cardiol 2022;29:1439–45.
1071-3581/$34.00

vascular abnormalities in AFD; however, there is no directly proportional relationship between vascular damage and the amount of Gb3 deposition. Hence, it has been proposed that other mechanisms could be involved. It is believed that the primary enzymatic defect produces a cascade of events that causes endothelial dysfunction and impaired arterial remodeling, causing occlusive phenomena and thrombosis of small and medium arteries with the corresponding infarction in the medium and long term. In AFD, there are not only changes in arteries due to endothelial damage but there is also accelerated hypertrophy in the medium-caliber arteries, with increased intima-media thickness, affecting the distensibility of the arteries, due to hypertrophy of the smooth muscle cells. Gb3 deposition, microcirculation ischemia, and impaired expression of adhesion molecules in myocardial cells promote inflammation, increased extracellular matrix deposition, and fibrosis. On the light of these evidences, it has been proposed a 3-phase cardiac phenotype of AFD: accumulation, myocyte hypertrophy with inflammation, and fibrosis with left ventricular (LV) impairment.[3]

Classic AFD may present itself with specific signs and symptoms, although some patients with genetically proven disease could not show these signs and symptoms, being considered to have non-classic or atypical AFD. Often the first presentation of non-classic AFD patients is unexplained LV hypertrophy (LVH), but these patients may also present with renal dysfunction or stroke.[4,5] Cardiac involvement is the leading cause of death and premature mortality is also predicted by evidence of myocardial fibrosis, which has been demonstrated to be not necessarily associated with LVH.[6] AFD multi-organ manifestations usually occur during the third and fourth decade of life (and this is also what happens in the cardiac involvement with the onset of LVH), but many symptoms of the disease can occur before 10 years of age, frequently resulting in a mean time between the onset of symptoms and correct diagnosis in these patients of over 15 years, emphasizing the importance of an increased disease awareness.[7]

The diagnosis of AFD is usually assessed by enzyme assay and genetic tests but it has been demonstrated that 3-phase-specific phenotypic pattern of disease shows typical abnormal findings at advanced cardiac imaging, which can be useful in detecting early signs of AFD in patients with or without LVH.[8] The multi-pathway diagnosis of AFD is linked to the natural history of the disease. Echocardiography is usually the first-line imaging modality to look for cardiac involvement in suspected or established AFD.[5] Cardiac magnetic resonance (CMR) imaging is an established diagnostic tool to assess myocardial storage and other disease processes such as inflammation in patients with AFD. In particular, it has been largely demonstrated on the usefulness of late-gadolinium enhancement (LGE)-CMR technique for assessment of myocardial fibrosis in the setting of cardiac involvement of patients with AFD.[9–11] Yet, low native T1 has been shown to represent sphingolipid accumulation in these patients.[12,13] Hanneman et al.[14] recently reported the results of the largest study on the association between CMR findings and outcomes in AFD. The results demonstrated the strong relationship between the presence and severity of LGE and an increased cardiac arrhythmia risk in AFD. Finally, myocardial strain measured by global longitudinal strain using feature-tracking CMR has been recently shown to be impaired with hypertrophy, storage (measured by low native T1), and LGE.[15] Although CMR plays an increasingly relevant role in the management and stratification of patients with AFD, the clinical course of the disease is very heterogeneous and diagnosis is still challenging. Novel concepts that consider alternative molecular pathways linking Gb3 storage and fibrosis have recently been proposed, as well as alternative imaging modalities.[8,16]

ADVANCED MOLECULAR CARDIAC IMAGING

The possible use of specific probes (biomarkers) to image the different pathways opens new opportunities not only for early detection of tissue damage (such as inflammation and fibrosis) but also for disease characterization. Biomarkers interact directly and chemically with surroundings and alter the image according to molecular changes differently from traditional imaging methods which primarily image differences in qualities such as density or water content. Moreover, it allows for quantitative tests, imparting a greater degree of objectivity to the study and a greater reproducibility for the follow-up of patients after specific enzyme replacement therapy (ERT). As it has been demonstrated, the role of acute and chronic inflammation triggered by glycosphingolipid storage in cardiomyocytes in early phases of disease, thus ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), has gained an increasingly relevant role in early diagnosis and therapy monitoring.[16] Cells involved in infection and inflammation are activated lymphocytes, neutrophils, and macrophages that express high levels of surface glucose transporter proteins with high affinity to ^{18}F-FDG (mainly GLUT1 and GLUT3) and exhibit high intracellular levels of hexokinase and phosphatase activity promoting accumulation of ^{18}F-FDG. ^{18}F-FDG PET imaging has been widely used in inflammation and infection status in

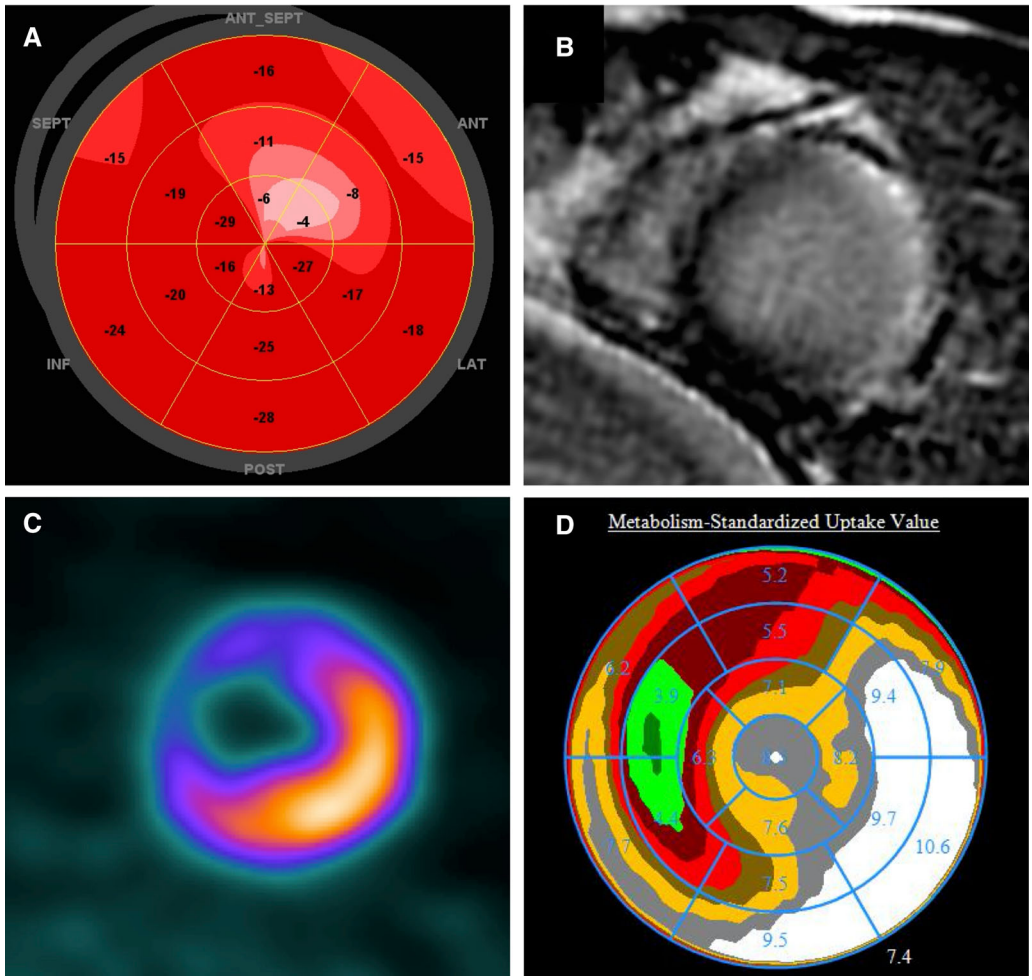

Figure 1. Speckle-tracking echocardiography, cardiac magnetic resonance, and ^{18}F-FDG PET in a patient with AFD. (**A**) Bull's-eye rendering of left ventricular global longitudinal strain (− 23%). (**B**) Late-gadolinium enhancement (LGE) in the lateral left ventricular wall. (**C**) Corresponding PET showing focal tracer uptake matching the area of LGE. (**D**) Polar map of ^{18}F-FDG standardized uptake value (coefficient of variation 0.38).

different diseases showing a high diagnostic accuracy.[17] The chance to use ^{18}F-FDG in advanced molecular imaging combining PET and MR in hybrid imaging opened a significant window for the early detection of cardiac involvement in patients with AFD.[16] CMR allows the direct assessment of cardiac fibrosis by LGE,[11,18] meanwhile T2-weighted short time inversion recovery (STIR) black-blood imaging enables detection of myocardial edema with high diagnostic accuracy and may allow differentiation of acute from chronic myocardial lesions,[19] on the other hand ^{18}F-FDG PET is highly sensitive to metabolically active processes.

Nappi et al.[20] investigated the potential role of hybrid PET/MR imaging in the assessment of cardiac involvement in a group of fourteen patients with AFD and without cardiac symptoms. They found in six patients focal LGE, indicating intra-myocardial fibrosis, and in four of them positive T2-STIR sequences. All patients with LGE and positive T2-STIR MR images had focal ^{18}F-FDG uptake in the corresponding myocardial segments indicating myocardial inflammation, also confirmed by elevated cardiac troponin I values. Imbriaco et al.[21] suggested a potential relationship between progressive myocyte sphingolipid accumulation and inflammation, evaluating by ^{18}F-FDG PET/MR imaging a group of twenty female AFD patients without cardiac symptoms. They calculated the coefficient of variation (COV) of the standardized uptake value (SUV) in each patient as the SUV standard deviations divided by the average SUV as an index of heterogeneity of ^{18}F-FDG uptake, finding out that normal and abnormal COV values are correlated with T1 mapping parameters

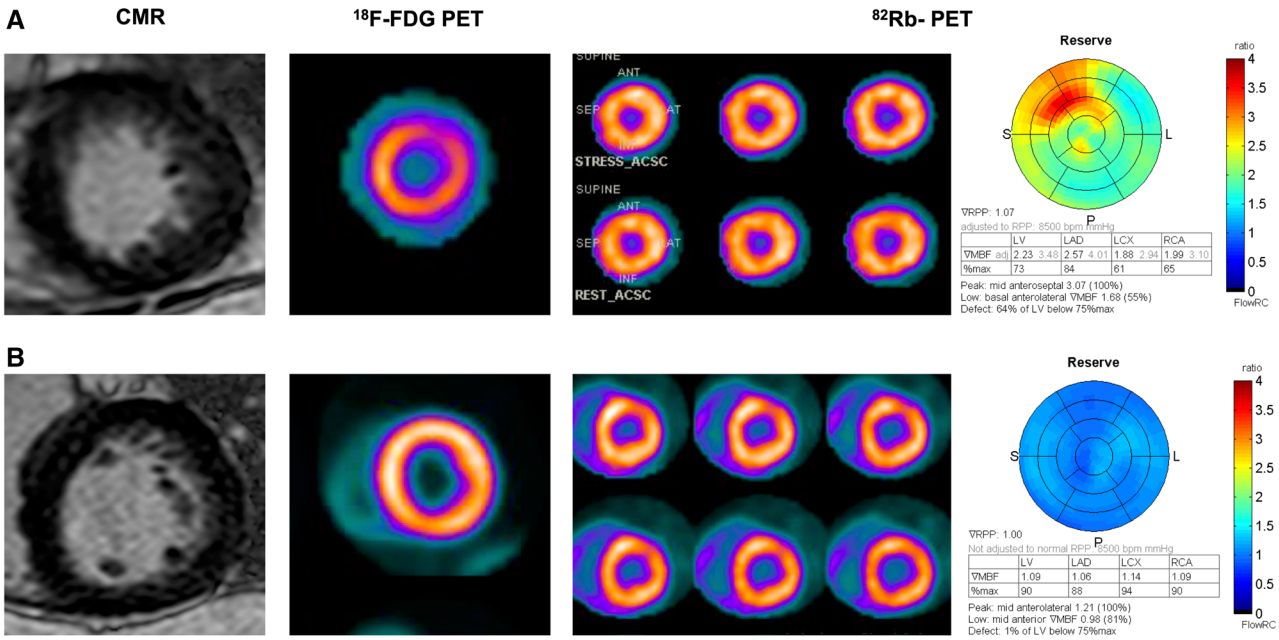

Figure 2. Cardiac magnetic resonance (CMR), ^{18}F-FDG PET, and stress-rest ^{82}Rb PET in two patients with AFD. (**A**) 48-year-old woman and (**B**) 53-year-old man. Both patients had normal LV mass, thickening, and size on cine images without evidence of late-gadolinium enhancement at CMR. Both patients also had homogeneous ^{18}F-FDG myocardial uptake and normal perfusion by stress-rest ^{82}Rb imaging. On the contrary, myocardial perfusion reserve was normal in the first patient and severely reduced in the second.

assessed by CMR. They also showed a significant signal alteration on T1 sequences in the inferolateral LV wall, corresponding to focal ^{18}F-FDG uptake at PET imaging. These results suggest the feasibility of ^{18}F-FDG PET/MR imaging for the early detection of cardiac involvement and in particular of focal inflammation, even in non-hypertrophic stage. This approach may allow definition of the pathophysiological pattern in every single patient, which would help in customization of the therapeutic strategy. Although the small number of patients recruited does not allow generalization of the results, they may provide guidance and input for further investigations. Spinelli et al.[16] investigated the relationship between metabolic abnormalities assessed by ^{18}F-FDG PET/MR imaging and impaired longitudinal function assessed by echocardiography in AFD. The results of PET/MR cardiac imaging compared to those of speckle-tracking echocardiography in 24 heterozygous females carrying α-galactosidase A mutation and without LVH showed worse global longitudinal systolic strain, in patients with normal compared with those with abnormal COV. The authors conclude that in females carrying α-galactosidase A mutation, focal ^{18}F-FDG uptake represents an early sign of disease-related myocardial damage and is associated with impaired LV longitudinal function, further supporting the hypothesis that inflammation plays an important role in glycosphingolipids storage disorders.[16] Typical findings of speckle-tracking echocardiography, CMR, and ^{18}F-FDG PET in a AFD patient are illustrated in Figure 1.

SYMPATHETIC CARDIAC INNERVATION IMAGING

SPECT using ^{123}I-metaiodobenzylguanidine (MIBG) is a non-invasive imaging method that allows to measure post-ganglionic pre-synaptic noradrenergic uptake in vivo, providing a useful evaluation of sympathetic neuronal damage after myocardial infarction, in hypertrophic and dilated cardiomyopathy, and after cardiac transplantation.[22,23]

^{123}I-MIBG is thought to share similar uptake and storage mechanisms as norepinephrine but is not metabolized by monoamine oxidase, thus remaining into myocardial sympathetic nerve endings. ^{123}I-MIBG imaging can be considered a challenging technique for early detection of cardiac involvement in AFD. In AFD patients, several studies have shown Gb3 storage in neural cells particularly affecting small, unmyelinated nerve fibers and symptoms reflecting progressive loss of function in both peripheral somatic and autonomic nerve

cells.[24,25] These findings may reflect not only the direct infiltration of Gb3 into the cardiac conduction system, but also a possible cardiac autonomic denervation as another contributory factor accounting for the variety of conduction disturbances seen in AFD patients. From Imbriaco et al.[26] it emerged that 20% of patients with AFD showed a regional reduction of ^{123}I-MIBG uptake in the inferolateral LV wall, without evidence of myocardial fibrosis on CMR. Of these patients, 40% was in New York Heart Association class I and not under ERT, suggesting that degenerative changes in cardiac sympathetic nerves may precede clinical symptoms as well the onset of myocardial fibrosis. Moreover, in AFD patients, reduced ^{123}I-MIBG cardiac uptake and impairment in systolic function are related, as indicated by the worsening of segmental longitudinal strain as MIBG uptake score increased.[27] These findings confirm that sympathetic denervation can be found at a very early stage of disease-related cardiomyopathy.

GLYCOSPHINGOLIPID AND ENDOTHELIAL DYSFUNCTION IN AFD

The pathophysiology of AFD includes different molecular abnormalities that involve damage to the endothelial and muscle cells of the vessels, cardiomyocytes, and cardiac conduction system. Glycosphingolipids, particularly Gb3, induce lysosomal degradation resulting in endothelial dysfunction in AFD. Dysfunction of endothelial cells stimulates the increased expression of adhesion molecules for inflammatory cells.[28] Inflammatory cell migration and vascular inflammation generate an oxidizing environment. The accumulating inflammatory cells produce abundant reactive oxygen species and secrete inflammatory cytokines/chemokines and growth factors that contribute to endothelial dysfunction and vascular smooth muscle cell proliferation. Microvascular angina can be the first manifestation of AFD cardiomyopathy preceding the development of LVH. Microvascular involvement may be a useful parameter to distinguish the relative contribution of storage in vascular cells, particularly, endothelium vs myocytes. Frustaci et al.[29] presented a significant experience of microvascular angina as pre-hypertrophic presentation of AFD comparing mother (60-year-old) and her daughter (36-year-old) with a divergent AFD structural phenotype. Endomyocardial biopsy of mother showed severe glycolipid accumulation of myocardiocytes, while a small arteriole is nearly unaffected. CMR from the mother showed the presence of a moderate LVH with combined diffused edematous imbibitions. Endomyocardial biopsy in the daughter showed mosaic of normal and minimally affected cardiomyocytes attributable to LVH (also confirmed by CMR) and hyperplasia of muscle with severe Gb3 accumulation in cardiomyocytes and small arteriole with smooth muscle cells infiltrated by glycolipid bodies. There are several potential pathophysiological mechanisms underlying coronary blood flow impairment in AFD, and these include those mediated by LVH (reduced capillary density, extravascular compression forces) as well as those directly affecting the microvasculature (endothelial dysfunction due to Gb3 storage, nitric oxide pathway dysregulation, or microvascular remodeling). According to these evidences, it is clear on the potential role of myocardial perfusion imaging in an early phase aiming to provide a non-invasive evaluation coronary circulation in patients with microvascular angina and/or suspected or known AFD.[30]

Quantitative PET measurement of absolute myocardial blood flow and myocardial perfusion reserve improves the accuracy of perfusion imaging in detecting multi-vessel coronary artery disease and in defining the extent and functional importance of stenosis.[31–33] PET has also the advantage to use different tracers and isotopes, such as ^{13}N-labeled ammonia, ^{15}O-water, and ^{82}Rb, without substantially affecting the accuracy of the results.[34–37]

As regard AFD, Tomberli et al.[38] demonstrated, using ^{13}N-PET, that hyperemic blood flow values are blunted both in patients with and without LVH, reflecting a mild-to-severe coronary microvascular dysfunction (CMD). Moreover, a milder coronary microvascular impairment was found in patient without LVH as compared with those with LVH. These findings show that microvascular function is impaired in AFD patients irrespective of any other evidence of cardiac involvement, suggesting that LVH per se is indeed a likely contributor to CMD, rather than a cause and proposing that early detection of subclinical cardiac involvement, as allowed by PET studies of microvascular function, may become a critical element in clinical decision-making and targeted therapy in AFD patients.[38] Figure 2 reports CMR, ^{18}F-FDG PET, and stress-rest ^{82}Rb PET in two AFD patients. Although both patients had normal CMR findings and myocardial perfusion imaging, coronary perfusion reserve was normal in the first patient and severely reduced in the second. Further studies aimed at elucidating the mechanism of Gb3-mediated vascular dysfunction might provide an important clue to the understanding of the sequential phase of AFD in the early stage (pre-hypertrophy) and of the possible new frontiers of AFD treatment. It should be considered that ERT with recombinant human α-galactosidase was approved for clinical use in 2001. Prior studies showed that this therapy is able to reduce microvascular deposits of Gb3 from the kidneys, the skin, and the heart.[39,40] However, there is still limited evidence showing that

ERT can be effective in preventing progression of LVH and, in parallel, improving myocardial function,[10] and no studies investigating the long-term effects on cardiac performance have yet been published. More recent studies demonstrated that ERT cannot significantly influence disease progression and clinical outcome, in patients with an advanced stage of the disease.[41] Early diagnosis and management of AFD represent a promising strategy to reduce organ damage, morbidity, and premature mortality in adulthood, supporting the need to integrate the diagnostic pathway with early multimodality imaging to assess organ involvement as the global cardiac functional status.[42]

CONCLUSION AND FUTURE DIRECTIONS

Considering such evidences, it is clear that nuclear medicine techniques may allow a comprehensive evaluation of coronary, myocardial, and sympathetic function. PET imaging enables the quantification of coronary blood flow and perfusion reserve in AFD patients in a way that can be readily integrated within the clinical workflow and may be useful as an early marker of CMD in clinical studies.[38] Early detection of subclinical cardiac involvement, as allowed by PET assessment of microvascular function, may become a critical element in clinical decision-making especially in young AFD patients. Particularly, CMD may represent a viable treatment target, potentially relevant to the prevention of disease progression and outcome.[38] Furthermore, is it possible to hypothesize that the severity of CMD may be an important predictor of adverse outcome, as for other genetically determined cardiomyopathies. Integrated multimodality imaging using PET/MR acquisition has been shown to provide at the same time information on intra-myocardial fibrosis and areas of active myocardial inflammation in patients with AFD, even at early stage.[20] This approach may allow definition of the pathophysiological pattern in every single patient which would help in customization of the therapeutic strategy. It is unknown whether, at this early stage of AFD, ERT may improve or revert vascular obstruction.[21] Moreover, ^{123}I-MIBG myocardial scintigraphy showed good accuracy in detecting cardiac adrenergic denervation due to autonomic nervous degeneration and impaired sympathetic function observed in patients with AFD.[24–27] To summarize multimodality imaging might play a crucial role in management of AFD patient, from early diagnosis to therapeutic targets, however, there is still need of new and wider evaluations.

Disclosure

W. Acampa, A. D'Antonio, M. Imbriaco, A. Pisani, and A. Cuocolo declare that they have no financial conflict of interest.

References

1. Desnick R, Ioannou Y, Eng C. Alpha-galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, et al., editors. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill; 2001. p. 3733-74.
2. Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, et al. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry. Mol Genet Metab. 2008;93:112-28.
3. Nordin S, Kozor R, Medina-Menacho K, Abdel-Gadir A, Baig S, Sado DM, et al. Proposed stages of myocardial phenotype development in Fabry disease. JACC Cardiovasc Imaging. 2019;12:1673-83.
4. Pisani A, Visciano B, Imbriaco M, Di Nuzzi A, Mancini A, Marchetiello C, et al. The kidney in Fabry's disease. Clin Genet. 2014;86:301-9.
5. Perry R, Shah R, Saiedi M, Patil S, Ganesan A, Linhart A, et al. The role of cardiac imaging in the diagnosis and management of Anderson–Fabry disease. JACC Cardiovasc Imaging. 2019;12:1230-42.
6. Weidemann F, Sanchez-Nino MD, Politei J, Oliveira JP, Wanner C, Warnock DG, et al. Fibrosis: A key feature of Fabry disease with potential therapeutic implications. Orphanet J Rare Dis. 2013;8:116.
7. Linhart A, Kampmann C, Zamorano JL, Sunder-Passmann G, Beck M, Mehta A, et al. Cardiac manifestations of Anderson–Fabry disease: Results from the international Fabry outcome survey. Eur Heart J. 2007;28:1228-35.
8. Cuocolo A, Nappi C, Gaudieri V, Pisani A, Imbriaco M. New insights for early assessment of cardiac involvement in Anderson–Fabry disease. J Nucl Cardiol. 2019. https://doi.org/10.1007/s12350-019-01635-w.
9. Imbriaco M, Spinelli L, Cuocolo A, Maurea S, Sica G, Quarantelli M, et al. MRI characterization of myocardial tissue in patients with Fabry's disease. Am J Roentgenol. 2007;188:850-3.
10. Imbriaco M, Pisani A, Spinelli L, Cuocolo A, Messalli G, Capuano E, et al. Effects of enzyme replacement therapy in patients with Anderson–Fabry disease: A prospective long-term cardiac magnetic resonance imaging study. Heart. 2009;95:1103-7.
11. Imbriaco M, Messalli G, Avitabile G, Cuocolo A, Maurea S, Soscia E, et al. Cardiac magnetic resonance imaging illustrating Anderson–Fabry disease progression. Br J Radiol. 2010;83:e249-51.
12. Sado DM, White SK, Piechnik SK, Banypersad SM, Treibel T, Captur G, et al. Identification and assessment of Anderson–Fabry disease by cardiovascular magnetic resonance non contrast myocardial T1 mapping. Circ Cardiovasc Imaging. 2013;6:392-8.
13. Thompson RB, Chow K, Khan A, Chan A, Shanks M, Paterson I, et al. T_1 mapping with cardiovascular MRI is highly sensitive for Fabry disease independent of hypertrophy and sex. Circ Cardiovasc Imaging. 2013;6:637-45.
14. Hanneman K, Karur GR, Wasim S, Wald RM, Iwanochko RM, Morel CF. Left ventricular hypertrophy and late gadolinium enhancement at cardiac MRI are associated with adverse cardiac events in Fabry disease. Radiology. 2020;294:42-9.

15. Vijapurapu R, Nordin S, Baig S, Liu B, Rosmini S, Augusto J, et al. Global longitudinal strain, myocardial storage and hypertrophy in Fabry disease. Heart. 2019;105:470-6.
16. Spinelli L, Imbriaco M, Nappi C, Nicolai E, Giugliano G, Ponsiglione A, et al. Early cardiac involvement affects left ventricular longitudinal function in females carrying a-galactosidase A mutation: Role of hybrid positron emission tomography and magnetic resonance imaging and speckle-tracking echocardiography. Circ Cardiovasc Imaging. 2018;11:e007019.
17. Jamar F, Buscombe J, Chiti A, Christian PE, Donohoe KJ, Israel O, et al. EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. J Nucl Med. 2013;54:647-58.
18. Nordin S, Kozor R, Bulluck H, Castelletti S, Rosmini S, Abdel-Gadir A, et al. Cardiac Fabry disease with late gadolinium enhancement is a chronic inflammatory cardiomyopathy. J Am Coll Cardiol. 2016;68:1707-8.
19. O h-Ici D, Ridgway JP, Kuehne T, Berger F, Plein S, Sivananthan M, et al. Cardiovascular magnetic resonance of myocardial edema using a short inversion time inversion recovery (STIR) black-blood technique: diagnostic accuracy of visual and semi-quantitative assessment. J Cardiovasc Magn Reson. 2012;28:14-22.
20. Nappi C, Altiero M, Imbriaco M, Nicolai E, Giudice CA, Aiello M, et al. First experience of simultaneous PET/MRI for the early detection of cardiac involvement in patients with Anderson–Fabry disease. Eur J Nucl Med Mol Imaging. 2015;42:1025-31.
21. Imbriaco M, Nappi C, Ponsiglione A, Pisani A, Dell'Aversana S, Nicolai E, et al. Hybrid positron emission tomography magnetic resonance imaging for assessing different stages of cardiac impairment in patients with Anderson–Fabry disease: AFFINITY study group. Eur Heart J Cardiovasc Imaging. 2019;20:1004-11.
22. Toba M, Ishida Y, Fukuchi K, Shimotsu Y, Takamiya M, Komamura K, et al. Sympathetic reinnervation demonstrated on serial iodine-123-metaiodobenzylguanidine SPECT images after cardiac transplantation. J Nucl Med. 1998;39:1862-4.
23. Verschure DO, Lutter R, van Eck-Smit BL, Somsen GA, Verberne HJ. Myocardial 123I-MIBG scintigraphy in relation to markers of inflammation and long-term clinical outcome in patients with stable chronic heart failure. J Nucl Cardiol. 2018;25:845-53.
24. Bertelsen AK, Tøndel C, Krohn J, Bull N, Aarseth J, Houge G, et al. Small fibre neuropathy in Fabry disease. J Neurol. 2013;260:917-9.
25. Alamartine E, Sury A, Roche F, Pichot V, Barthelemy JC. Autonomic nervous system activity in patients with Fabry disease. Open J Intern Med. 2012;2:116-22.
26. Imbriaco M, Pellegrino T, Piscopo V, Petretta M, Pellegrino T, Piscopo V, et al. Cuocolo, Cardiac sympathetic neuronal damage precedes myocardial fibrosis in patients with Anderson–Fabry disease. Eur J Nucl Med Mol Imaging. 2017;44:2266-73.
27. Spinelli L, Imbriaco M, Giugliano G, Nappi C, Gaudieri V, Riccio E, et al. Focal reduction in left ventricular 123I-metaiodobenzylguanidine uptake and impairment in systolic function in patients with Anderson–Fabry disease. J Nucl Cardiol. 2019. https://doi.org/10.1007/s12350-019-01734-8.
28. Satoh K. Globotriaosylceramide induces endothelial dysfunction in Fabry disease. Arterioscler Thromb Vasc Biol. 2014;34:2-4.
29. Frustaci A, Russo MA, Francone M, Chimenti C. Microvascular angina as prehypertrophic presentation of Fabry disease cardiomiopathy. Circulation. 2014;130:1530-1.
30. Camici PG, Rimoldi OE. The clinical value of myocardial blood flow measurement. J Nucl Med. 2009;50:1076-87.
31. Assante R, Acampa W, Zampella E, Arumugam P, Nappi C, Gaudieri V, et al. Coronary atherosclerotic burden vs. coronary vascular function in diabetic and nondiabetic patients with normal myocardial perfusion: A propensity score analysis. Eur J Nucl Med Mol Imaging. 2017;44:1129-35.
32. Assante R, Acampa W, Zampella E, Arumugam P, Nappi C, Gaudieri V, et al. Prognostic value of atherosclerotic burden and coronary vascular function in patients with suspected coronary artery disease. Eur J Nucl Med Mol Imaging. 2017;44:2290-8.
33. Zampella E, Acampa W, Assante R, Nappi C, Gaudieri V, Mainolfi CG, et al. Combined evaluation of regional coronary artery calcium and myocardial perfusion by (82)Rb PET/CT in the identification of obstructive coronary artery disease. Eur J Nucl Med Mol Imaging. 2018;45:521-9.
34. Fiechter M, Ghadri JR, Gebhard C, Fuchs TA, Pazhenkottil AP, Nkoulou RN, et al. Diagnostic value of 13N-Ammonia myocardial perfusion PET: Added value of myocardial flow reserve. J Nucl Med. 2012;53:1230-4.
35. Slomka PJ, Alexanderson E, Jacome R, Jimenez M, Romero E, Meave A, et al. Comparison of clinical tools for measurements of regional stress and rest myocardial blood flow assessed with 13N-Ammonia PET/CT. J Nucl Med. 2012;53:171-81.
36. Murthy VL, Lee BC, Sitek A, Naya M, Moody J, Polavarapu V, et al. Comparison and prognostic validation of multiple methods of quantification of myocardial blood flow with 82Rb PET. J Nucl Med. 2014;55:1952-8.
37. Gaudieri V, Acampa W, Rozza F, Nappi C, Zampella E, Assante R, et al. Coronary vascular function in patients with resistant hypertension and normal myocardial perfusion: A propensity score analysis. Eur Heart J Cardiovasc Imaging. 2019;20:949-58.
38. Tomberli B, Cecchi F, Sciagrà R, Berti V, Lisi F, Torricelli F, et al. Coronary microvascular dysfunction is a nearly feature of cardiac involvement in patients with Anderson–Fabry disease. Eur J Heart Fail. 2013;15:1363-73.
39. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, et al. Safety and efficacy of recombinant human alpha-galactosidase: A replacement therapy in Fabry's disease. New Engl J Med. 2001;345:9-16.
40. Schiffmann R, Kopp JB, Austin HA III, Sabnis S, Moore DF, Weibel T, et al. Enzyme replacement therapy in Fabry disease: A randomized controlled trial. JAMA. 2001;285:2743-9.
41. Vedder AC, Breunig F, Donker-Koopman WE, Mills K, Young E, Winchester B, et al. Treatment of Fabry disease with different dosing regimens of agalsidase: Effects on antibody formation and GL-3. Mol Genet Metab. 2008;94:319-25.
42. Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P, Fila M, et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clin Genet. 2019;96:107-17.