Cardiac sympathetic imaging in the diagnosis of cardiac autonomic neuropathy in pre-diabetes

Fahad Waqar, MD,[a] and Myron C. Gerson, MD[b]

[a] Division of General Internal Medicine, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH
[b] Division of Cardiovascular Health and Disease, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH

Received Jan 23, 2015; accepted Jan 23, 2015
doi:10.1007/s12350-015-0082-y

See related article, pp. 1262–1268

Cardiac autonomic neuropathy is a common and frequently underdiagnosed complication of diabetes with significant associated cardiovascular morbidity[1] and mortality.[2] The reported prevalence of cardiac autonomic neuropathy, although extensively studied and reported in both type 1 and 2 diabetes, has been variable due to a variety of available testing methods as well as different diagnostic criteria used.[3] The Toronto Consensus Panel recently published guidelines for diagnosing and classifying cardiac autonomic neuropathy using previously known non-invasive tools for cardiovascular reflex testing.[4] The American Diabetes Association also considers these cardiovascular reflex tests to be sensitive and specific for diagnosing cardiac autonomic neuropathy, and therefore, the current standard for evaluating both sympathetic and parasympathetic function.[5]

Cardiac autonomic neuropathy is not as well studied in pre-diabetic states of impaired glucose tolerance (IGT) and impaired fasting glucose, as it is in types 1 and 2 diabetes. There is, however, a growing body of evidence suggesting that a significant number of patients may have developed cardiac autonomic neuropathy during their pre-diabetes stage even before development of diabetes. A study by Vinek et al[6] concluded that as many as 7% of patients have cardiac autonomic neuropathy at the time of initial diagnosis of type 1 or 2 diabetes. This finding suggests that a significant proportion of patients may have developed cardiac autonomic neuropathy during their pre-diabetes stage. This is also supported by the likely chronicity of the most widely accepted mechanisms of pathogenesis of cardiac autonomic neuropathy resulting from neuronal cellular injury, inflammation, microvascular ischemia, autoimmunity, and oxidative stress induced neuron death directly or indirectly triggered by a hyperglycemic state.[7]

The role of I-123 metaiodobenzylguanidine (MIBG) imaging in diabetic patients is well studied, and findings from several studies in this field suggest that impaired heart-to-mediastinum (H/M) ratio and washout rate (WR) of MIBG correlate well with the presence or absence of clinical autonomic neuropathy in diabetic patients.[8,9] Similar data assessing the relationship of cardiac MIBG activity to cardiac autonomic neuropathy in pre-diabetes is very limited. The only major previous study employing I-123 MIBG and assessing it as a reliable tool for evaluating the sympathetic arm of cardiac autonomic function in pre-diabetes was reported by Diakakis et al.[10]

In the present study, Asghar and associates tested the prevalence of cardiac autonomic neuropathy in patients with IGT using conventional methods of cardiac autonomic reflex testing as well as cardiac adrenergic innervation using imaging with I-123 MIBG. Their study concludes that there is no difference in cardiac autonomic function or cardiac sympathetic innervation among 15 controls and 15 subjects with IGT.

The study is well designed, and the method of selection of patients with IGT (serum glucose at 2-hour post oral challenge 7.8-11.1 mmol/L or 140-200 mg/dL) is in accordance with the standards recommended by American Diabetes Association and American College of Endocrinology for diagnosis of IGT.[11] Nevertheless,

Reprint requests: Myron C. Gerson, MD, Division of Cardiovascular Health and Disease, Department of Internal Medicine, University of Cincinnati College of Medicine, P.O. Box 670542, Cincinnati, OH 45267-0542; *myron.gerson@uc.edu*
J Nucl Cardiol 2015;22:1269–72.
1071-3581/$34.00

the most recent guidelines place substantial emphasis on a moderately elevated hemoglobin A1C in a range of 5.5%-6.0% as a strong predictor of future overt diabetes and cardiovascular risk, and as an equally reliable method of screening for pre-diabetes. This raises a question of whether any members of the control group in the Asghar study might have had pre-diabetes by hemoglobin A1c but not by post oral glucose challenge criteria, given the fact that the data analysis did not show a statistically significant difference in mean hemoglobin A1C between the two groups. This in turn might have resulted in unsuspected cardiac autonomic dysfunction in members of the control group, potentially explaining the lower mean control late H/M ratio reported in the Asghar study compared to the previously reported normal values in the Diakakis study and referenced in the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study.[12]

In attempting to understand whether the IGT patients studied by Asghar and associates are comparable to those studied by Diakakis et al, there are several limitations. Unfortunately, the level of hemoglobin A1c was not reported in the Diakakis study. On the other hand, the very high prevalence of a family history of diabetes (77%) in the IGT group compared to controls in the Diakakis study (25%, $P < .001$) suggests selection of a high-risk pre-diabetic group. Family history of diabetes was not reported in the present study. Hypertension and left ventricular hypertrophy clearly influence the I-123 MIBG H/M ratio. Puzzling trends in the present study are that the controls tended to have a higher echocardiographic mass index than subjects with IGT, whereas the IGT group tended to have a higher systolic and diastolic blood pressure. Does the trend toward higher left ventricular mass in the controls have any bearing on the lack of difference in late H/M ratios between the two study groups? On the other hand, one wonders whether the lower late H/M ratio in glucose intolerant subjects (1.60 ± 0.14) compared to controls (2.85 ± 0.42, $P < .001$) in the Diakakis study was influenced by the presence of significantly higher diastolic blood pressure (82.3 ± 3.0 mm Hg) in IGT subjects vs controls (74.7 ± 5.3, $P < .001$).

Potentially the most important distinction between the present study and the previous study by Diakakis is that the present study excluded subjects with peripheral neuropathy. Recent data suggest that an association exists between peripheral and autonomic neuropathy in all hyperglycemic states. One recent study reported that patients with peripheral neuropathy are at 15 times higher risk of developing cardiac autonomic neuropathy and that both conditions frequently coexist.[13] Another study looked at the prevalence of somatic and autonomic neuropathy in patients with diabetes and pre-diabetes and noted that as many as half of the patients with somatic neuropathy had concurrent autonomic neuropathy.[14] This is also supported by similar pathological precursors and pathways known to cause peripheral neuropathy as well as cardiac parasympathetic and sympathetic nervous dysfunction.[15] Exclusion of patients with peripheral neuropathy from the present study may have identified a unique subgroup of pre-diabetic subjects with minimal or no cardiac autonomic neuropathy. Previous studies have also noted that the incidence of cardiac autonomic neuropathy correlates strongly with the duration of hyperglycemic state in both type 1 and 2 diabetes.[6,16] This may also apply to the pre-diabetic state. The authors rightly pointed out toward the end of their discussion that longitudinal studies may be required to assess the prevalence or absence of autonomic dysfunction in pre-diabetes.

Different results between the present study and the previous study by Diakakis et al may also relate to technical considerations. The present authors used a cardiac region of interest including the entire heart for calculation of the H/M ratio, as recommended by the European Association of Nuclear Medicine Cardiovascular Committee and the European Council of Nuclear Cardiology,[17] and as employed in the ADMIRE-HF phase III clinical trial.[18] In addition to being more widely accepted, the whole heart region of interest was shown to provide more reproducible H/M ratios[19] compared to limited region methods like that used in the earlier study by Diakakis et al. The cardiovascular reflex testing using heart rate variability (HRV) employed in the present study is according to recommended autonomic cardiovascular indices outlined in the Toronto Consensus Panel which are now accepted as most standardized and highly specific methods to screen for cardiac autonomic neuropathy. Lastly, the authors used a more robust method of excluding ischemic cardiac disease, using cardiac magnetic resonance imaging, compared to previous similar studies.

FUTURE DIRECTIONS

The capability of I-123 MIBG to stratify risk of death, heart failure progression, and life-threatening cardiac arrhythmias[20] is well established in patients with heart failure,[18,21] including diabetic patients with heart failure.[22] Abnormality of cardiac sympathetic nerve function in diabetic subjects in the absence of clinical heart failure has also been well documented.[23,24] If the differences between the present study and the previous study by Diakakis are related to differences in the populations of pre-diabetics studied, then a prognostic role and a role in guiding therapy may exist in some pre-diabetic subjects. This will require larger studies with

more clearly defined levels of pre-diabetes and longitudinal follow-up. If a subset of pre-diabetics can be identified with cardiac autonomic neuropathy, then a practical question will be whether the level of cardiac sympathetic function, as measured by I-123 MIBG, has prognostic implications for the development of overt diabetes mellitus, for the development of heart failure and for survival. If there is a subgroup of pre-diabetic subjects with autonomic dysfunction, could those subjects who are obese gain specific outcome benefits from bariatric surgery, as well as by dietary and medical weight reduction and physical exercise? In addition to these considerations, future cardiac autonomic nervous system studies in pre-diabetics may include novel cardiac parasympathetic imaging tools.[25] This may prove informative in pre-diabetics as parasympathetic autonomic dysfunction is known to precede sympathetic dysfunction.[3] Finally, modalities for assessment of cardiac autonomic innervation like imaging with I-123 MIBG have the potential to quantify autonomic function more precisely than the current standard methods. One thing that is clear is that the prevalence of pre-diabetes and obesity is increasing dramatically. Assessment of cardiac autonomic dysfunction has demonstrated potential to predict outcomes in diabetic subjects, but much more research will be needed to clarify its potential role in pre-diabetics.

Acknowledgments

Myron Gerson received grant support from GE Healthcare related to the ADMIRE-HF study and subsequent sub-studies.

References

1. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553-79.
2. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:1578-84.
3. Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes 2014;5:17-39.
4. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, et al. Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: Clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011;27:639-53.
5. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285-93.
6. Vinik AI, Freeman R, Erbas T. Diabetic autonomic neuropathy. Semin Neurol 2003;23:365-72.
7. Vinik AI. Diagnosis and management of diabetic neuropathy. Clin Geriatr Med 1999;15:293-320.
8. Nagamachi S, Jinnouchi S, Nakahara H, Flores LG 2nd, Ohnishi T, Hoshi H, et al. 123I-MIBG myocardial scintigraphy in diabetic patients: Relationship to autonomic neuropathy. Nucl Med Commun 1996;17:621-32.
9. Hattori N, Rihl J, Bengel FM, Nekolla SG, Standl E, Schwaiger M, et al. Cardiac autonomic dysinnervation and myocardial blood flow in long-term Type 1 diabetic patients. Diabet Med 2003;20:375-81.
10. Diakakis GF, Parthenakis FI, Patrianakos AP, Koukouraki SI, Stathaki MI, Karkavitsas NS, et al. Myocardial sympathetic innervation in patients with impaired glucose tolerance: Relationship to subclinical inflammation. Cardiovasc Pathol 2008;17:172-7.
11. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37:S81-90.
12. Jacobson AF, Lombard J, Banerjee G, Camici PG. I-123 mIBG scintigraphy to predict risk for adverse cardiac outcomes in heart failure patients: Design of two prospective multicenter international trials. J Nucl Cardiol 2009;16:113-21.
13. Moţăţăianu A, Bălaşa R, Voidăzan S, Bajkó Z. Cardiovascular autonomic neuropathy in context of other complications of type 2 diabetes mellitus. Biomed Res Int 2013;18:507216.
14. Hsu WC, Yen AM, Liou HH, Wang HC, Chen TH. Prevalence and risk factors of somatic and autonomic neuropathy in prediabetic and diabetic patients. Neuroepidemiology 2009;33:344-9.
15. Tomlinson DR, Gardiner NJ. Glucose neurotoxicity. Nat Rev Neurosci 2008;9:36-45.
16. Pop-Busui R, Low PA, Waberski BH, Martin CL, Albers JW, Feldman EL, et al. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). Circulation 2009;119:2886-93.
17. Flotats A, Carrió I, Agostini D, Le Guludec D, Marcassa C, Schäfers M, et al. EANM Cardiovascular Committee; European Council of Nuclear Cardiology. Proposal for standardization of 123I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging 2010;37:1802-12.
18. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol 2010;55:2212-21.
19. Somsen GA, Verberne HJ, Fleury E, Righetti A. J Nucl Cardiol 2004;11:126-33.
20. Waqar F, Dunlap SH, Gerson MC. What will be the role of I-123 MIBG in improving the outcome of medically treated heart failure patients? J Nucl Cardiol 2012;19:1198-205.
21. Nakata T, Nakajima K, Yamashina S, Yamada T, Momose M, Kasama S, et al. A pooled analysis of multicenter cohort studies of (123)I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. JACC Cardiovasc Imaging 2013;6:772-84.
22. Gerson MC, Caldwell JH, Ananthasubramaniam K, Clements IP, Henzlova MJ, Amanullah A, et al. Influence of diabetes mellitus on prognostic utility of imaging of myocardial sympathetic innervation in heart failure patients. Circ Cardiovasc Imaging 2011;4:87-93.

23. Yufu K, Takahashi N, Okada N, Shinohara T, Nakagawa M, Hara M, et al. Cardiac iodine-123 metaiodobenzylguanidine (123I-MIBG) scintigraphy parameter predicts cardiac and cerebrovascular events in type 2 diabetic patients without structural heart disease. Circ J 2012;76:399-404.
24. Sugiyama T, Kurata C, Tawarahara K, Nakano T. Is abnormal iodine-123-MIBG kinetics associated with left ventricular dysfunction in patients with diabetes mellitus? J Nucl Cardiol 2000;7:562-8.
25. Delforge J, Le Guludec D, Syrota A, Bendriem B, Crouzel Slama M, et al. Quantification of myocardial muscarinic receptors with PET in humans. J Nucl Med 1993;34:981-91.