Refining risk in diabetes and CAD with SPECT MPI: New insights and future challenges

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Diabetes mellitus (DM) is an expanding global epidemic. Estimates of a global prevalence of 415 million people and total health expenditure of 673 billion US dollars have been reported.[1] The prevalence of individuals between 20 and 79 years with diabetes is predicted to rise to 642 million by 2040.[1] Assessment of morbid risk of diabetes is of substantial importance in the allocation of resources to address the human and financial burdens of this growing global health threat. Epidemiological studies have demonstrated that diabetes places patients at an elevated risk for developing coronary artery disease (CAD).[2,3] A large meta-analysis of 102 studies confirmed a two-fold excess risk for vascular disease in DM.[4] Since the landmark study by Haffner first reported the equivalence of risk of diabetes and CAD,[5] widespread controversy has ensued with several studies, which have supported[6-10] or challenged[11-17] the concept of risk equivalent of DM and CAD.

The substantial incremental risk assessment of radionuclide SPECT MPI compared to the exercise ECG and echocardiography reported in referred populations suggests its role to refine the heterogeneity of risk in patient populations with CAD and/or DM.[18-20] The DIAD study reported that 22% of asymptomatic diabetic patients had myocardial ischemia on adenosine Tc-99 m SPECT MPI,[18] and subsequent COURAGE, INSPIRE, and BARI-2D trials confirmed the powerful incremental risk assessment with SPECT MPI as well as favorable effects of optimal medical therapy in patients with CAD and/or DM.[21-23]

In the current issue of the Journal of Nuclear Cardiology, Morales et al. report a large retrospective analysis of 17,499 patients undergoing SPECT MPI at a single tertiary center from 1996 to 2006.[24] The study explores the interaction of risks of subsequent hard coronary events identified by diabetes mellitus, history of CAD, and the presence of greater than mild stress perfusion defect (SSS $\geq$ 4)[24] equivalent to a 6% total stress LV perfusion defect score. Patients were divided into four groups based on CAD and DM status at the time of initial imaging: non-DM patients without CAD ($N = 9133$), non-DM patients with CAD ($N = 3906$), DM patients without CAD ($N = 2768$), and DM patients with CAD ($N = 1692$). These four groups were further divided based on summed stress score (SSS) < 4 or ≥ 4 to classify normal and abnormal perfusion, respectively. Yearly event rate for the composite end point of cardiac death or non-fatal myocardial infarction (MI) was calculated over a mean follow-up of 2.4 ± 1.5 years with a maximum of 5 years.

As expected, SPECT MPI did contribute incremental risk assessment to patients with CAD and/or DM. Although the rates of events in patients with diabetes without CAD and those with CAD without diabetes were similar by inter-group comparison, robust

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survival analysis demonstrated that the incidence of adverse cardiac event rate was slightly lower among DM subjects without CAD compared to non-diabetic subjects with CAD (5.5% vs 7.1%, respectively, $P < 0.001$). The greatest risk of cardiac death and non-fatal MI was observed in DM subjects with CAD {HR 3.7 (95% CI 3.02-4.50) $P < 0.001$}. Within these diabetic patients with CAD, the presence or absence of SPECT perfusion defects (SSS $\geq$ 4) identified a nearly 3-fold difference in event rate: 6.6% vs 2.3%. In patients without diabetes or CAD, the presence or absence of SPECT perfusion defects identified a 4.5-fold difference in events. A normal SPECT MPI was associated with a hard event rate of well under 1% (0.6%) in the groups of non-diabetic patients without CAD. Normal SPECT studies identified patients with more than 1% hard events in patients with CAD (1.4%) or with DM (1.6%), which were similar. Abnormal perfusion by SPECT identified the same 3.5% event rate in non-diabetic patients with CAD and Diabetic patients without CAD.

Study limitations should be recognized which may have contributed to the observed rates of events between the diabetic and CAD groups. Table 1 in the article identifies major differences of inter-group use of statins, aspirin, beta-blockers and ACE inhibitors. More prevalent use of statins and use of intensive statin therapy recommended by current 2013 lipid guidelines in the diabetic patients without CAD in the current era might influence inter-group differences. In this study, the categorization of diabetes was based on self-reporting of patients; thus, unknown differences in the duration and severity of DM assessed by A1C may have influenced results. This consideration is important because 25% of acute MI patients in the era of this study (1996-2006) had unrecognized T2DM.[25] The distinction of Type I and Type II DM was not made in this study, and a recurring question of the risk and treatment response of these diabetic groups persists. BMI was higher in the DM groups, and neither attenuation correction nor parallel hole CZT SPECT MPI was used, which enhances diagnostic accuracy for detection of angiographic stenosis in obese patients.[26]

The findings of this landmark Morales study support the concept of CAD risk equivalence of diabetes and CAD in a population more than seven times larger than that studied in the original Haffner East West study.[5] They also support AHA guidelines which recommend treating CAD risk factors in DM patients without CAD as aggressively as in non-diabetic patients with CAD.[27] The study firmly establishes the role of SPECT MPI to refine incremental risk assessment in patients with diabetes and/or CAD and has implications for envisioning further research to personalize strategies for optimal therapy in these patients.

RISK ASSESSMENT BEYOND SPECT PERFUSION

Data for the Morales study began more than two decades ago. Has it underestimated the robust risk assessment afforded by routine contemporary techniques of nuclear cardiology, including ECG-gated post-stress LVEF and LV volume indices by gender,[28] transient ischemic dilation,[29] quantitative flow reserve by PET[30-32] or CZT SPECT now commercially available, I-123-MIBG, and TTR cardiac amyloid assessments with Tc-99 m pyrophosphate[33] in our aging population, and assessment of cardiac dyssynchrony with single injection SPECT MPI?[34] These techniques may provide substantial opportunities for incremental risk assessment in the growing worldwide epidemics of diabetes mellitus, ischemic heart disease, and heart failure.

A major lesson we learned from the DIAD (Detection of Ischemia in Asymptomatic Diabetes) is that routine screening of asymptomatic patients with diabetes and normal resting electrocardiograms is not justified, because of the relatively low yield of significant abnormalities, the low overall cardiac event rate with contemporary medical therapy, and the lack of clinical impact of screening on events in patients receiving routine, goal-directed medical therapy. However, DIAD reported a simple clinical bedside testing of autonomic dysfunction measured by a Valsalva test to quantify that heart rate variability in the clinic was highly predictive of myocardial ischemia in the 22% of patients found to have ischemia by adenosine Tc-99 m SPECT MPI in DIAD. Whether a simple, rapid inexpensive clinical assessment of autonomic dysfunction with heart rate variability can identify a very low-risk group of diabetic patients alone or in combination with coronary calcium scoring, and stress only SPECT MPI and delay of routine goal directed medical therapy remains an important hypothesis for further research.

A major trend of imaged populations has been the declining pretest risk and prevalence of events in tested populations,[35] ironically reflecting improved prevention and treatment strategies of clinically defined populations as our imaging techniques over time have improved. Concurrently, as our population over time becomes older, fatter, and more insulin resistant, the rate of decline of cardiac morbidity will probably decrease. Although goal-directed medical therapy such as routine statin use provides populations of patients with diabetes favorable outcomes, a substantial minority of patients do not tolerate or want high-intensity statin therapy if they do not require it. Can a personalized medicine approach help identify the substantial minority of very low-risk patients in whom intensive statin therapy can be safely delayed or avoided, reduce adverse medications effects, and improve quality of life? Is the widely reported 10%

LV ischemia burden threshold associated with improved outcome with revascularization[36] the same or different in CAD patients with or without DM?

With the burgeoning global epidemics of diabetes and CAD, the field of nuclear cardiology is challenged to stay on track with patient-centered appropriate use testing[37] and to define patient-centered strategies of risk assessment and management that deliver better outcomes in diabetes and ischemic heart disease than that provided by routine goal-directed medical therapies for these conditions. The best interests of public health are indebted to the substantial historic study of Morales, which has positioned the field of nuclear cardiology on a large scale to evaluate these challenges to optimize cost effective health care and patient satisfaction outcomes in the 21st century.

Disclosure

Dr. Syed Y. Naqvi reports no industry relationships. Dr. Steven D. Wittlin reports he is on the speakers bureau of Medtronics. Dr. Ronald G. Schwartz reports he is on the speakers bureau of Astellas.

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