Myocardial perfusion imaging and cardiac events in asymptomatic patients with diabetes

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Abstract

Myocardial perfusion single-photon emission computed tomography (MP-SPECT) has become essential for screening diabetic patients at high risk of silent myocardial ischemia. The combined use of pharmacological and exercise stress, together with the generalization of gated studies has increased both the sensitivity and the specificity of MP-SPECT, leading to a better identification of balanced coronary artery disease, of coronary artery disease with normal coronary angiography, and artifacts. In addition, the incremental prognostic value of gated MP-SPECT over myocardial perfusion and clinical data has been demonstrated. However, the selection of those asymptomatic diabetic patients who will benefit from screening remains an open question. A more refined estimation of cardiovascular risk factors is required.

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Introduction

Projections indicate that the worldwide prevalence of diabetes is likely to increase from about 200 million today to more than 300 million in 2025 [1]. This dramatic increase, and the association between diabetes and coronary artery disease (CAD), constitute a major public health problem in developed countries.

Patients with diabetes are at a 2–4-fold greater risk of cardiovascular mortality and are both more likely to have silent ischemia and less likely to survive a myocardial infarction than non diabetic individuals. In the population of patients with diabetes, most experience in the clinical setting for the assessment of ischemia has been obtained with myocardial perfusion single-photon emission computed tomography (MP-SPECT). Gated stress–rest MP-SPECT not only provides information about the physiological significance of flow-limiting CAD, but also assesses several independent risk factors for subsequent cardiac events (extent of scarring, global left ventricular ejection fraction, end-systolic volume, ventricular remodeling, transient ischemic dilatation). The risk of cardiac death, myocardial infarction, or need for revascularization after non fatal myocardial infarction is more than 7-fold greater in diabetic patients with myocardial perfusion defects than in diabetic patients for whom scintigraphic data are normal [2,3]. However, although occult CAD is a common finding in asymptomatic patients with diabetes, the prevalence of occult coronary disease differs widely among the various published results, ranging from 20% to 60% [4]. This discrepancy most probably reflects differences in the diabetic populations included in the studies, thus indicating the need for a more refined selection of those patients who would benefit from screening for occult CAD.

This article will focus on three points. First, it will consider the improvement in accuracy of myocardial

perfusion scintigraphy that has resulted from the development of pharmacological stress procedures and gated studies. Secondly, the overall accuracy of MP-SPECT will be discussed, in comparison with coronary angiography, for the specific case of asymptomatic diabetic patients. Hypotheses to explain the so-called 'false positive' findings of MP-SPECT will be considered. Thirdly, the limits of the guidelines for CAD screening in patients with diabetes will be reviewed and discussed.

Recent improvements in MP-SPECT

Although myocardial perfusion imaging has been available in routine clinical settings since the 1970s, the development of gated SPECT over the past two decades has made possible a combined assessment of myocardial perfusion and left ventricular function (*Figure 1*). This additional information on ventricular function has proven to be useful for both the diagnosis and prognosis of CAD. Using gated studies, the quantification of post-stress wall motion abnormalities or ejection fraction increases the sensitivity of stress–rest MP-SPECT, especially in patients with three-vessel CAD, in whom a diffuse decrease in subendocardial blood flow may cause an impairment of ventricular function without focal perfusion defects [5,6]. Moreover, quantification of wall motion is a powerful tool with which to differentiate actual scars from attenuation artifacts, thus leading to better specificity of gated MP-SPECT compared with non gated studies [7]. Finally, post-stress left ventricular ejection fractions and end-systolic volumes measured by gated MP-SPECT are independent predictors of cardiovascular events and have incremental prognostic values over myocardial perfusion and clinical data in predicting cardiac death [8].

These recent advances in MP-SPECT have been enhanced by improvements in the stress procedure used, especially for patients with diabetes, who are less likely to achieve peak stress using conventional procedures than are non diabetic patients. It has been shown that the combined use of a vasodilator-induced pharmacological stress (intravenous dipyridamole or adenosine) and submaximal exercise on a treadmill or bicycle reduces the non cardiac side effects of vasodilatation and arrhythmias while producing

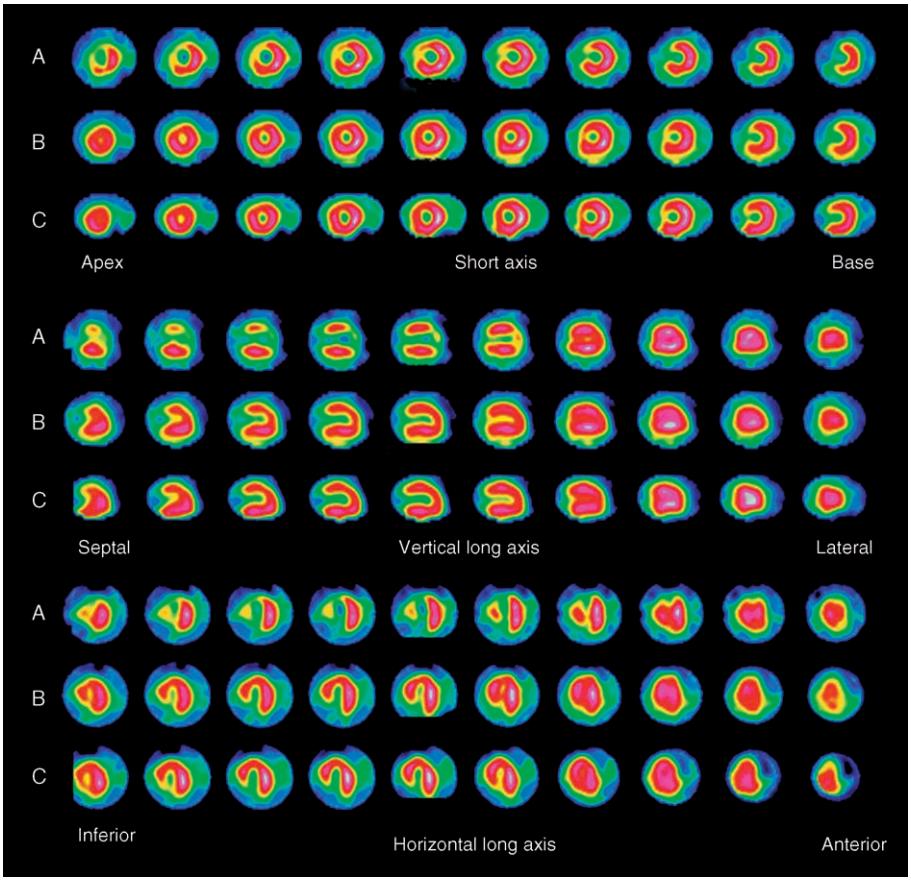

Figure 1. Stress- (lines A) and rest- (lines B) gated myocardial perfusion single-photon emission computed tomography (MP-SPECT) performed during a screening test for silent myocardial ischemia in a 45-year-old woman with type 2 diabetes with two cardiovascular risk factors. The scintigraphic data were consistent with reversible septal and apical ischemia. Six months after percutaneous coronary intervention, stress MP-SPECT was performed again to eliminate a thrombosis of the stent (lines C). The scintigraphic data confirmed a normal stress perfusion.

images that are similar to that produced when maximal exercise is achieved [9]. In the case of obstructive airways disease, dobutamine can be used as an alternative to vasodilator agents, so that an optimal stress–rest MP-SPECT is usually possible, even with patients who cannot perform maximal exercise.

Accuracy of MP-SPECT

A meta-analysis published in 2004 [10] confirmed the high sensitivity of MP-SPECT for the detection of a critical stenosis in patients with known or suspected CAD (the range of sensitivity was 85–90%). In diabetic patients, objective data are lacking; only one study has reported a similar accuracy of MP-SPECT in diabetic and non diabetic patients [11]. However, there is growing evidence that MP-SPECT may be more sensitive than coronary angiography to detect critical stenosis in patients with diabetes. Given that patients with diabetes and no evidence of CAD have a risk of myocardial infarction similar to that of patients with a history of myocardial infarction [12], the finding of a reversible myocardial perfusion defect in a diabetic patient without obstructive CAD may reflect anomalies in the coronary vasodilator function induced by diabetes [13]. The development of positron emission tomography (PET) myocardial imaging has provided insight into the specificities of endothelial function in patients with diabetes. Using [^{13}N]ammonia to measure the coronary blood flow, it was shown that non insulin-dependent diabetic patients without evidence of epicardial CAD had an impaired increase in coronary blood flow after infusion of dipyridamole. This dysfunction was reversed by infusion of an angiotensin-converting enzyme inhibitor [14]. Another PET tracer, [^{11}C]meta-hydroxyephedrine, was used to associate a sympathetic dysfunction in patients with type 1 diabetes with an impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation [15,16]. This latter finding is consistent with those reported in the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects study, in which the strongest predictor of an abnormal MP-SPECT scan was the Valsalva heart rate ratio, a marker of autonomic dysfunction [17]. These results need to be confirmed by larger clinical trials, but they are consistent with the interest in the use of MP-SPECT in the assessment of cardiovascular risk in diabetic patients with normal coronary angiography.

Which diabetic patients should be screened for silent myocardial ischemia?

Diabetic patients have a high incidence of occult CAD, ranging from 20% to nearly 60%, depending on the patient populations included in the various studies [5,18]. Moreover, a meta-analysis involving patients with normal MP-SPECT [19] demonstrated that the median annual rate of cardiac death or non fatal myocardial infarction is much smaller in non diabetic patients (0.6%) than in diabetic populations, in whom published rates have ranged from 1.6 to 3.3% [2,3]. This highly variable prevalence, together with the fact that a normal MP-SPECT is associated with a greater cardiovascular risk in diabetic patients, points to the need for additional clinical or imaging data to select the patients who will actually benefit from a screening procedure for occult CAD.

The European and American guidelines recommend screening asymptomatic diabetic patients with evidence of peripheral or carotid occlusive arterial disease, microvascular disease (proliferative retinopathy, nephropathy), or at least two cardiovascular risk factors (diabetic dyslipidemia, hypertension, smoking, family history of premature CAD) [20–22]. Although the emerging evidence supports the appropriateness of testing patients with vascular disease [18], recent studies have reported a similar frequency of abnormal MP-SPECT studies in asymptomatic diabetic patients with and without two or more cardiovascular risk factors [17,23]. These results indicate the need for a more refined estimation of cardiovascular risk factors, especially in countries where the prevalence of CAD is relatively low [24]. This may necessitate further clinical studies to assess the individual cardiovascular risk factor of an asymptomatic diabetic patient as a continuous variable, accounting for both the presence and severity of cardiovascular risk factors, which probably should include age and sex, in addition to markers of atherosclerosis [25] and autonomic dysfunction [17].

Summary

The risk of cardiac death, myocardial infarction, or revascularization is more than 7-fold greater in diabetic patients with myocardial perfusion defects than in diabetic patients with normal scintigraphic data. Although complementary studies are needed to test whether the treatment of silent ischemia will influence outcome, MP-SPECT has become an essential diagnostic tool in the management of patients with diabetes. However, the prevalence of occult CAD depends largely on the severity of the diabetes, and diabetic patients with a normal MP-SPECT still present a greater cardiovascular risk than non diabetic patients. This indicates the need for a more refined selection of those patients with diabetes who are likely to benefit from scintigraphic screening for occult CAD. There is consistent evidence that diabetic patients with peripheral or carotid occlusive

arterial disease or microvascular disease must be screened. Further clinical studies are needed to assess more accurately the individual cardiovascular risk factor of an asymptomatic diabetic patient as a continuous variable accounting for both the presence and severity of risk factors, including age and sex, in addition to markers of autonomic dysfunction and atherosclerosis. ■

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