EDITORIAL

The relative nature of a ''normal'' myocardial perfusion SPECT

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See related article, pp. 999–1008

> The farther backward you can look, the farther forward you can see.
>
> Winston Churchill

With an array of non-invasive imaging modalities available to diagnose and risk stratify individuals with suspected coronary artery disease (CAD), myocardial perfusion SPECT (MPS) has distinguished itself from others owing to its wealth of prognostic data. This is not only true for patients with greater extent, severity, and reversibility of MPS abnormalities, but also for those with normal MPS findings.[1] The salutatory prognosis of those with a normal MPS test has lead to the implication of a ''warranty period'' following a normal SPECT stress test.

While tempting to generalize this ''warranty period'' to all patients undergoing MPS, rates of freedom from adverse cardiac events differ significantly for patients with normal exercise MPS as compared to patients with normal pharmacological MPS.[2] The reasons for these observed differences based on the method of hyperemia induction may seem intuitive; patients who undergo pharmacological MPS tend toward older age, greater numbers of CAD risk factors, increased non-cardiac co-morbidities and reduced functional status, a known powerful predictor of mortality.[3]

Nevertheless, because prior studies comparing those undergoing exercise vs pharmacological MPS have not accounted for these clinical differences, it remains unknown whether the prognostic ability of a normal MPS also differs for individuals who can against cannot exercise. To address this question, Rozanski et al[4] undertook an important study evaluating the prognostic differences between normal exercise and normal pharmacological MPS—as defined by a summed stress score ≤3—among patients with similar clinical profiles.

The authors followed 6,069 patients without known CAD for 10.2 ± 1.7 years for rates of all-cause mortality. By propensity score analysis accounting for age, gender, angina typicality, CAD risk factors, medications, and baseline findings at the time of MPS testing (including heart rate, blood pressure, and presence of left ventricular hypertrophy), the authors further compared 1,125 patients with normal exercise MPS (defined by summed stress score ≤ 3) matched to 1,125 patients with normal pharmacological MPS for long-term all-cause mortality, as well as short-term 2.6 ± 2.1 years cardiac death and non-fatal myocardial infarction.

Within propensity-matched groups manifesting normal MPS findings, individuals undergoing pharmacological MPS still experienced an annualized mortality rate that was almost twofold that of their exercising counterparts (3.9% vs 1.6%, $P < .0001$), a relationship consistently observed across all age groups and independent of smoking status, diabetic state, body mass index, presence of left ventricular hypertrophy, or history of peripheral vascular disease. Even more divergent differences were observed for short-term cardiac outcomes between propensity-matched patients manifesting normal exercise vs normal pharmacological MPS, with a nearly sixfold higher annualized rate of cardiac events (1.1% vs 0.2%, $P < .0001$) and a sevenfold higher annualized rate of cardiac death (0.7% vs 0.1%, $P = .0002$). After partitioning individuals undergoing exercise MPS by Bruce treadmill protocol duration, rates of all-cause mortality for individuals undergoing pharmacological MPS were found to be similar to those in the lowest functioning exercise category, that is, exercising <3 min (3.9% vs 3.4%, $P = .65$).

This study represents the latest in an important series of studies published by this group examining the essential clinical and test characteristics that influence the prognostic features of MPS findings. In this study, examining matched patients with normal exercise vs normal pharmacological MPS, the study cohort was large, the follow-up period long, and the study analytics appropriate. A particularly illustrative finding was that

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patients exhibiting normal pharmacological MPS experienced similar mortality rates to their normal counterparts who could exercise less than 3 min of the Bruce protocol, modified Bruce protocol, or ''adenowalk'' protocol. This article does not provide a breakdown of frequencies for individuals undergoing each of these protocols, nor does it provide a breakdown of exercise time as stratified by gender or age. Nevertheless, it can be estimated that for the lowest exercise cohort—by Bruce or modified Bruce protocol—the average expected metabolic equivalents (METs) ranged from less than 2.9 to 4.7.

As prior studies examining exercise capacity and mortality among individuals referred for exercise testing have generally focused on <5 METs as a ''basement'' comparator group, this study extends prior findings by identifying a group of patients with even lower functional capacity and very high risk of cardiac and non-cardiac mortalities despite apparently normal MPS findings. Indeed, the functional capacity of the lowest exercise MPS group translates barely to the ability to perform common daily household chores (3-4 METs) or walking at a brisk pace (3-5 METs), whereas those individuals with apparently normal pharmacological MPS would be expected to be able to perform even less.

Further, this study adds to our understanding by a carefully performed matching of individuals undergoing exercise vs pharmacological MPS. Prior studies have not accounted for differences in age, gender, CAD risk factors, non-cardiac co-morbidities, and functional capacity. This study accounted for most—but not all of these factors—notably non-cardiac co-morbidities, which were not analyzed nor accounted for during propensity matching. It thus remains unknown whether non-cardiac causes of death may be able to fully explain the overall long-term mortality differences between normal exercise and normal pharmacological MPS groups, although this seems less likely given the short-term differences in noted between groups for cardiac-specific events and cardiac-specific death.

The present results emphasize the need for remembrance of clinical findings at the time of MPS performance—in particular, the inability to exercise—as highly important and additive prognostic indicators that are an integral part of even apparently ''normal'' MPS studies. While tempting to examine perfusion findings in isolation, the inability of individuals undergoing pharmacological MPS to perform activities that most of us take for granted renders them a high-risk population irrespective of other characteristics. These data encourage us to assimilate the totality of prognostic data from MPS testing for optimization of prognostic risk assessment even in patients with apparently normal MPS studies, and remind us that while the test may be normal, the patient may still be at risk.

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