

# Adenosine MPS in octogenarians: Looking safely into the future

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Back in 2002, a commendable Editorial piece by RJ Gibbons concluded with a word of advice: "...more studies are needed to define the role of noninvasive testing [...] in the management of elderly patients. Such studies should be a high priority of the nuclear cardiology research community, given the growing number of elderly patients."<sup>1</sup> Fifteen years later, the number of studies remains relatively small, while the proportion of elderly citizens continues to grow. It is a fact that we are living longer. In the USA, life expectancy has been rising over the last 30 years, and by 2015 the life expectancy at age 65 was 19.4 years.<sup>2</sup> In the UK, the population aged 65 and over has increased by 21% since mid-2005, while the population aged 85 and over has increased by an astounding 31%.<sup>3</sup> This is a cause for celebration with a caveat; as age increases so does the likelihood of developing clinically significant atherosclerosis and obstructive coronary artery disease (CAD). Although there has been a decline in cardiovascular mortality rates in recent years, the risk of an adverse outcome remains high in older individuals compared to their younger counterparts. Indeed, CAD is one of the leading causes of death in the elderly.<sup>3</sup> This is a growing population for whom there is a paucity of evidence to guide management decisions, and there are even less data on the impact of investigations and

subsequent interventions on long-term prognosis. It has therefore become imperative to identify the optimal pathway for diagnosing and treating obstructive CAD in older patients, who are often underrepresented in clinical studies. In this regard, radionuclide myocardial perfusion scintigraphy (MPS) continues to play a major role in the non-invasive detection of obstructive CAD, and evidence of its efficacy and cost-effectiveness supports the use of MPS as first-line test for the diagnostic and prognostic assessment of patients with suspected CAD.<sup>4</sup>

One of the advantages of MPS is that it can be combined with any of the stress modalities currently available without inconvenience and without compromising diagnostic accuracy. While exercise is the modality of choice, pharmacological agents are preferred in patients who are unable to exercise adequately. There is clearly an even greater role for pharmacological stress MPS in the elderly because comorbidities that impair physical capacity and limit the scope of the exercise test are particularly prevalent in this age group. In this issue of the *Journal*, the article by Katsikis et al. presents the results of a study evaluating the tolerability, safety, and prognostic value of adenosine MPS in 370 patients aged 80–89 years.<sup>5</sup> As the authors rightly pointed out, tolerability to adenosine stress was similar to that reported in a previous series of younger subjects with a slightly larger proportion of octogenarians completing a full 6-minute adenosine infusion protocol (84% vs. 80%).<sup>6</sup> This finding is not surprising. In general, the frequency of any vasodilator-related symptom appears to be lower in older patients regardless of the agent used,<sup>7</sup> although ischemia may manifest more often given the higher prevalence of significant CAD in the elderly. Indeed, angina-like-symptoms were the commonest reason for discontinuing the adenosine infusion in the study of Katsikis et al. The relation between these and ischemic ECG changes was not documented but it is very likely that some of these symptoms were the result

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of true myocardial ischemia. Despite the potential risk for stress-induced ischemia, there were no major adverse events with only one patient developing pulmonary edema that resolved after medical therapy. These results support the excellent safety profile of adenosine stress, even in the very elderly.

There are a couple of aspects of the study by Katsikis et al. that deserve further attention. First, the safety and tolerability of vasodilator stress in this selected cohort may be similar to that described in younger patients but differences do become apparent in clinical practice. These are mainly determined by the presence of comorbidities that carry a potential risk for stress intolerance and vasodilator-related events such as significant aortic valve stenosis and bradyarrhythmias, which are common in the elderly. When any of these are known or suspected, decision to proceed with vasodilator stress requires careful consideration of benefits vs. risks. Patients with significant valve disease were not included in the study of Katsikis et al. This might be partly due to referral bias since only three patients were excluded as per study design. There are currently few data available on the safety of vasodilator stress in this important patient group despite the increasing number of elderly patients presenting with clinically significant valve disease. The growing availability of safe and effective percutaneous therapeutic procedures and the need to assess concurrent CAD have the potential for increasing further the volume of patients with severe valve disease referred for stress imaging. To fill the gap between evidence and practice, Hussain et al. recently investigated the safety of vasodilator MPS in 95 patients (average age, 79 years) with severe aortic stenosis (mean aortic valve area,  $0.79 \text{ cm}^2$ ).<sup>8</sup> They showed that dipyridamole, adenosine, and regadenoson had comparable safety profiles with no occurrence of major adverse events or serious complications. Although patients with valve disease were nearly twice as likely to experience a marked reduction ( $>20 \text{ mmHg}$ ) in systolic blood pressure as patients without disease, none experienced symptomatic hypotension. These observations are reassuring but more evidence is needed to document the safety of vasodilator stress in the very elderly with significant valve disease.

Second, only a very small proportion of octogenarians from the target population underwent adenosine stress combined with exercise. It is already well known that supplemental low-level exercise improves vasodilator stress tolerability by reducing the frequency of symptoms such as flushing and hypotension,<sup>9</sup> which indeed were two of the reasons for discontinuing the adenosine infusion in the studied cohort. Although the addition of dynamic exercise may not be feasible in the frail elderly patient, isometric exercise (e.g. handgrip)

can also be used to improve stress tolerability.<sup>10</sup> Adjuvant exercise also decreases the incidence of adenosine-induced bradyarrhythmias including AV block.<sup>9</sup> In this regard, it is important to note that the reported incidence of sinoatrial and AV block in the study of Katsikis et al. was relatively low compared with the previously published data and anecdotal experience;<sup>6,11</sup> second-degree AV block occurred in only 1 patient, and no episodes of third-degree AV block were reported. The cause for this is likely multifactorial with referral bias, pacing, differences in population risks for developing bradyarrhythmias, and premature discontinuation of the infusion in some patients as potential explanations.

The study of Katsikis et al. also provides valuable evidence on the predictive value of adenosine MPS in octogenarians. In this regard, the authors are to be congratulated for investigating the risk stratification capability of MPS in the long term ( $\sim 9$ -year follow-up). They demonstrated that perfusion and non-perfusion MPS markers as well as resting LVEF (measured by echocardiography) were predictors of all-cause death, hard cardiac events (i.e., cardiac death and non-fatal myocardial infarction), and late revascularization. In multivariate analysis, the extent and depth of adenosine-induced perfusion abnormality and LVEF remained independent predictors of all-cause death and adverse cardiac outcomes, while increased lung tracer uptake retained its power as predictor of cardiac events. Of note, a blunted hemodynamic response to adenosine was also an independent predictor of all-cause death as well as cardiac events. Importantly, the study of Katsikis et al. also demonstrated the incremental prognostic value of stress and scintigraphic parameters over clinical variables in the very elderly. Previous studies investigating the prognostic value of stress imaging in patients aged 70 years and over have shown similar findings although the predictive power of imaging variables and their value relative to other markers of risk differ between studies.<sup>12-14</sup> Patient's ability to exercise appears to be an important determinant of these differences. In the very elderly patient with CAD, physical capacity is likely to have wider prognostic implications because of its relation to biological aging and frailty. In recent years, frailty has been found to be a powerful adverse prognostic factor in patients with cardiovascular disease, outweighing conventional risk factors and clinical markers of poor outcome.<sup>15,16</sup> Currently, establishing the level of frailty involves the assessment of physiological functions as well as psychological status using instruments with varying levels of complexity. Although there is still uncertainty about the best method for measuring frailty and its components,<sup>16</sup> it would be highly informative to document the level of physical capacity and if possible the frailty status of elderly

cohorts, and to investigate the contribution of these variables to risk assessment. Systematic assessment of frailty in the elderly is gathering support and this should be considered when evaluating the prognostic power of diagnostic testing in older patients with known or suspected CAD.<sup>16</sup>

Taking all these into account, it is reassuring to observe that stress MPS remains a safe and reliable tool for risk-stratifying the very elderly according to their likelihood of an adverse outcome in the long term. As demonstrated by Katsikis et al., the risk of major adverse events remains high in this patient population. Medical progress and the rapid rise in living standards mean that, more than ever before, our senior citizens are likely to benefit from a comprehensive diagnostic assessment and a management pathway that cares for both their present symptoms and quality of life as well as their future.

## Disclosure

*No conflicts of interest to declare.*

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