EDITORIAL

Myocardial perfusion imaging in very elderly patients with suspected coronary artery disease: Never too late!

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Increasing longevity and declining fertility are the factors mainly responsible for the rapid growth of geriatric population in Western countries during the past few decades. Subjects born during the post-World War II baby boom are now starting to reach geriatric age, expanding the demographic group of the elderly. In the United States, the proportion of the population in the senior age group ($\geq$65 years) is expected to peak at just over 20% in 2030, while in the time interval from the years 2000-2030, the absolute number of the very old (>85 years of age) will double from 9.3 to 19.5 million.[1,2] This will result in a sizeable increase in coronary artery disease (CAD) prevalence, since aging is a significant cardiovascular risk factor.[3,4] CAD is the most common cause of death in the elderly, but its diagnosis and management may be particularly challenging in aged patients. In fact, due to age-related changes in the cardiovascular system, reduced multi-system organ reserve as well cardiovascular and non-cardiovascular comorbidities, clinical presentation can be misleading in aged patients.

Despite evidence of higher benefit of pharmacologic and revascularization therapies in older compared to younger patients, community practice patterns continue to indicate a limited use in elderly patients.[5] At

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least, in part, this is due to the concern that elderly are generally more vulnerable to the adverse effects of drugs used in CAD, as well as the procedural complications of revascularization, and to the fact that only few randomized clinical trials verified the efficacy of treatment strategies of CAD in elderly patients.[6]

Yet, there is no doubt that revascularization improves prognosis in high-risk old patients. The Trial of Invasive Versus Medical Therapy in Elderly Patients (TIME) study enrolled patients over 75 years of age with stable angina and randomly assigned them to a conservative strategy (optimal medical therapy) or an invasive strategy (coronary angiography and revascularization when appropriate).[7] At short-term follow-up (6 months), the conservative strategy was associated with less favorable results on angina severity and quality of life, with an increased risk of major adverse cardiac events (49% vs 19%, $P < .001$). In further analyses involving the TIME population, the invasive strategy remained associated with a significantly better prognosis at 1-year follow-up, but longer observations revealed a similar survival in the two groups.[8,9]

In a sub-group analysis of the Clinical Outcomes Utilizing and Aggressive Drug Evaluation (COURAGE) study focusing on patients aged $\geq$65, the addition of percutaneous coronary intervention (PCI) to optimal medical therapy did not impact on clinical outcomes in the whole cohort of elderly patients during a median 4.6-year follow-up.[10] The nuclear sub-study of COURAGE indicated that significant reduction in risk of death or myocardial infarction is observed in patients with $\geq$5% reduction in myocardial ischemia with no interaction of age.[11]

The diagnostic and prognostic values of single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) have been clearly established during the last three decades, with the extent and severity of myocardial hypoperfusion shown to be independent predictors of prognosis in patients with known or suspected CAD.[12-14] However, only a minority of the clinical studies conducted with SPECT MPI so far have been focused on elderly patients.[15] Diagnostic accuracy seems to be preserved and, at least at the short-term follow-up, normal or mildly abnormal SPECT MPI

appears to identify elderly patients at low risk of major adverse cardiac events. Even less investigated is the role of stress myocardial SPECT MPI for the diagnostic and prognostic evaluations of CAD in very old patients. Isolated reports conducted in small groups of patients indicated that even in very old patients, a negative SPECT MPI study is associated with a relatively low risk of subsequent cardiac events.[16]

In this issue of the Journal, Nair et al[17] describe the prognostic value of SPECT MPI in very old patients with suspected CAD. They reported a retrospective evaluation of 1,093 patients ≥80 years of age out of a total population of 8,864 consecutive patients with suspected CAD aged 50 years and older. Patients with evidence of CAD were excluded. The study cohort was categorized into three age groups: middle-aged (50-64 years of age), elderly (65-79 years of age), and very elderly (≥80 years of age). In each age category, the results of SPECT MPI were reported using the summed stress score (SSS) and the summed difference score (SDS). After the SPECT MPI study, major adverse cardiac events (cardiac death and non-fatal myocardial infarction) were recorded during a mean follow-up of 1.9 ± .9 years. SPECT MPI results were made available to the referring physician and contributed to select management strategy in each patient.

In this study, several types of stress were used as indicated by the referring physician.[17] This resulted in significant differences between age groups, with vasodilator stress testing more frequently used in the very elderly than in elderly and middle-aged patients (63% vs 35% and 20%, respectively; $P < .001$). In contrast, exercise stress testing was less commonly applied in the elderly than in the other age category (10% vs 34% and 56%, respectively; $P < .001$). The preference in the very elderly for non-exercise stress protocols has been already reported in other studies and appears to be a direct consequence of the reduced ability to exercise because of functional limitation or comorbidities.[18] As a consequence, the applied type of stress may already select patient populations with different levels of risk (generally higher in the group undergoing pharmacological stress SPECT MPI), as demonstrated by the very low event rate (.7% per year) observed in the study for patients who were able to exercise and who had a negative MPI. This outcome was more favorable than observed in the entire cohort of elderly patients with a negative MPI (1.8% per year).[17]

As expected, a higher rate of cardiac events was observed in the very elderly as compared to other age categories.[17] Using Cox regression in the very elderly patients, SSS was identified as a significant multivariable predictor of adverse cardiac events (HR 1.090, 95% CI 1.047-1.135, $P < .001$). In addition, Cox proportional-hazards modeling revealed that the inclusion of the variable SSS added to traditional clinical and stress-ECG data, increases the ability to predict adverse cardiac events in very elderly patients. These data are of extreme relevance since they fill the considerable gap existing in the evidence base supporting the value of SPECT MPI for prognostic stratification in elderly patients.

Hachamovitch et al[19] published the principal study so far available investigating the prognostic value of SPECT MPI in the elderly. The study included 5,200 consecutive patients with 75 years of age or older undergoing rest thallium-201/stress technetium-99 m sestamibi dual-isotope SPECT MPI with exercise (42%) or adenosine (58%) stress and principally referred for CAD diagnosis. The fact that over 70% of the included patients had resting ECG abnormalities, leading to the impossibility of using stress-induced ECG changes for CAD diagnosis, emphasizes the value of SPECT MPI in this category of patients (44% of the very elderly patients had resting ECG abnormalities in Nair et al[17]).

In the case of a normal SPECT MPI, Hachamovitch et al reported an unadjusted, annualized cardiac death rate of 1.0% per year in the 75-84-year group and of 3.3% per year in the ≥85-year-old age group (about one-third lower than the age-adjusted rate in the general population) over a mean follow-up of 2.8 ± 1.7 years. In addition, an interaction between early treatment strategy and ischemia was detected in a sub-group of 684 patients with extended follow-up (6.2 ± 2.9 years), suggesting that a high degree of ischemia was associated with increasing survival with early revascularization, whereas in the setting of little or no ischemia by SPECT MPI, medical therapy had improved outcomes. These findings are consistent with the results of the nuclear sub-study of the COURAGE Trial.[11] In the study conducted by Nair et al[17] in this issue of the Journal, very elderly patients showed a significant increase in early (≤60 days after SPECT MPI results) cardiac catheterization and revascularization as a function of severity of myocardial ischemia on SPECT MPI. Interestingly, even though the very elderly showed a higher severity of myocardial ischemia, a clear propensity toward a conservative approach was observed when compared with younger patients. Compared with patients in the elderly and middle-age categories, the very elderly with severe ischemia (SDS > 7) were referred less frequently for early cardiac catheterization (41% vs 57% and 59%, respectively; $P < .001$) as well as for early revascularization (26% vs 45% and 40%, respectively; $P < .001$). Yet, it is also of concern that >40% of younger patients with high-risk SPECT MPI did not undergo invasive evaluation.

Increasing use of drug-eluting stents, transradial access, and more accurate prevention of renal function

impairment is expanding the use of PCI in very old patients. In a Scottish registry collecting 31,758 non-emergency PCIs, the proportion of elderly patients (age ≥ 75 years) went from 8.7% in 2000 to 13.9% in 2007 although, when compared with younger patients, the elderly demonstrated a significantly higher risk of major cardiovascular events at an early follow-up.[20] Similarly, a cohort study conducted in Denmark demonstrated that the annual proportion of patients ≥80 years of age undergoing PCI for any reason almost doubled (from 5.4% to 10.2%) during the period between 2000 and 2007.[21] In the same time period, progress in the care of patients undergoing coronary artery bypass graft (CABG) surgery led to improved outcomes in elderly patients, thereby reducing perioperative complications.[22,23]

Thus, effective risk stratification in the elderly is, and will increasingly be, much needed, and the study from Nair et al[17] represents an important contribution to the delineation of the prognostic value of SPECT MPI in this setting of patients. The findings of this study should hopefully foster prospective multicenter trials to assess whether MPI-assisted management of elderly patients with suspected CAD will ultimately translate in a cost-effective outcome benefit in this population.

Conflict of interest

Drs Perrone-Filardi, Cuocolo, and Dellegrottaglie have no disclosures to report.

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