ORIGINAL ARTICLE

Adenosine stress myocardial perfusion imaging in octogenarians: Safety, tolerability, and long-term prognostic implications of hemodynamic response and SPECT-related variables

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Background. Evaluation of tolerability, safety, and prognostic implications of adenosine stress myocardial perfusion imaging (MPI) in octogenarians.

Methods. 370 octogenarians (49% known coronary artery disease) were studied. Hemodynamic response, MPI-related data, and rest-left ventricular ejection fraction (LVEF) based on echocardiography were registered per patient, and prospective follow-up was performed to document all-cause death (ACD), cardiac death (CD), myocardial infarction (MI), and late revascularization.

Results. No deaths or MIs were observed during adenosine infusion or the short-term post-infusion period. 86% of patients were able to tolerate a 6-minute infusion. All side effects terminated spontaneously after infusion cessation, except for one case of pulmonary oedema. After 9.3 years, there were 124 ACDs, 62 CDs, 16 MIs, and 35 revascularizations. Differences between survival curves of summed stress score (SSS)-based risk groups were significant for all end points ($P < .001$). SSS and LVEF were independent predictors of all end points ($P \leq .01$) and lung uptake of cardiac end points. ΔHR <10 bpm (OR = 1.78, $P = .004$) and inability to increase HR by >10 bpm and decrease systolic blood pressure by >10 mmHg (OR = 2, $P = .02$) during adenosine infusion were independent predictors of ACD and CD, respectively. Hemodynamic response variables, SSS, and lung uptake provided incremental prognostic value over pre-test data for ACD and CD.

Conclusions. In octogenarians, adenosine stress MPI is well tolerated and provides effective long-term risk stratification. (J Nucl Cardiol 2019;26:250–62.)

Key Words: Octogenarians • adenosine • myocardial perfusion imaging • risk stratification • safety

Abbreviations

MPI	Myocardial perfusion imaging
SBP	Systolic blood pressure
HR	Heart rate
SSS	Summed stress score
SRS	Summed rest score
SDS	Summed difference score
TID	Transient ischemic left ventricular dilation
LHR	Lung to heart ratio
ACD	All-cause death
CD	Cardiac death

INTRODUCTION

Adenosine stress myocardial perfusion imaging (MPI) is a time-honored non-invasive imaging modality with a wealth of accumulated data regarding both diagnosis and risk stratification of patients with coronary artery disease (CAD). Its prognostic utility has been established by several large studies in the general population and has also been documented in various specific patients subgroups.[1] The same holds true for its safety profile.[2-6] However, since aging of the population will become a virtually universal phenomenon during the twenty-first century,[7] the elderly for the new millennium should be defined as patients ≥75 years old, and in these ''older old'' patients data regarding side effects and long-term prognostic role of adenosine stress MPI remain limited. Hence, we attempted to evaluate these issues in a cohort study of octogenarians, which represent the fastest growing segment of the elderly population.[7]

METHODS

Raw data from the ONassis Cardiac Surgery Center Elderly RIsk Stratification (ONERIS) Registry were used as the initial patient's pool. The registry has been described previously.[8] In this registry, stress, rest, and single-photon emission computed tomography (SPECT)-related data of all patients aged ≥75 years who have undergone MPI at our institution are registered and combined with respective left ventricular ejection fraction (LVEF) measurements from echocardiographic studies performed within 1 month from MPI. For the purpose of the present study, registered patients were scanned according to the following criteria: adenosine stress testing without concomitant low-level exercise of any form, 1 day stress-rest, single isotope (^{201}Tl or ^{99m}Tc) protocol, age 80-89 years, date of testing after 1st January 2000, suspected or known CAD, systolic blood pressure (SBP) ≥100 mmHg before testing and absence of significant valvular, congenital and non-ischemic cardiomyopathic disease or

acute myocardial infarction (MI) within 15 days from MPI. The severity of valve disease was determined by echocardiography, in accordance with the 2014 ACC/AHA Guidelines for the management of patients with valvular heart diseases.[9] Standard adenosine stress MPI was performed according to the American Society of Nuclear Cardiology (ASNC) Guidelines with regards to radiopharmaceutical dosing, timing of radioisotope injection, interval between stress and rest study, image acquisition and processing.[10] All patients were instructed to fast for 8 hours before the study and to avoid products or drugs containing methylxanthines for 24 hours before testing, while discontinuation of antianginal medications was left at the referring physician's discretion. Adenosine (Adenocor, Sanofi-Aventis) was infused at 140 $\mu g \cdot kg^{-1} \cdot minute^{-1}$, using an accurate infusion pump over 6 minutes, and 3 minutes after initiation of the infusion the radiotracer (^{201}Tl or ^{99m}Tc) was injected. Indications for early termination of adenosine infusion were in accordance with ASNC Guidelines.[10] In case of increasing intensity side effects not included in indications for early termination, an effort was made by the supervising physician to complete a 4 minutes infusion, with tracer injection taking place at 2 minutes in this case. During the infusion, heart rate (HR), blood pressure, and 12-lead ECG were recorded at baseline and every minute thereafter for the whole duration of the infusion and at least 2 minutes in the recovery phase. ECG was monitored continuously (leads aVF, V1, and V5) for arrhythmia or ischemic ST-segment deviation. For comparison with previous studies,[11] peak HR and peak SBP were defined as the HR and SBP at the end of adenosine infusion (not the maximal HR and SBP during infusion). Stress imaging started 45-60 (for ^{99m}Tc) or 10-15 (for ^{201}Tl) minutes after the completion of adenosine infusion and was performed with either a Millennium VG (GE Medical Systems, Milwaukee, USA) or an ORBITER 400 (Siemens AG, Erlangen, Germany) gamma camera with the step and shoot method and an 180° arc rotation. Rest imaging took place after a radioisotope-dependent interval, according to the ASNC Guidelines.[10] Imaging performed with the use of ^{201}Tl was not gated to the ECG. ^{99m}Tc studies were ECG gated, however the LVEF figures registered for these patients were the ones obtained by echocardiography for homogeneity reasons. SPECT images were reconstructed using filtered back-projection without attenuation or scatter correction. SPECT images interpretation was performed during daily reading sessions by two experienced readers (AT, MK), using the ASNC standardized 17-segment model and a five-point regional perfusion scoring system (4 = absent uptake to 0 = normal uptake), as previously described.[8] Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS = SSS − SRS) were calculated, and SSS risk categories were formed as following: low risk (0-3), medium risk (4-12), and high risk (>12). The presence of transient ischemic LV dilation (TID) was classified subjectively (i.e., no specific transient dilation ratio was calculated) from planar anterior images, by comparing the computer-derived LV area on the stress and rest images. Increased lung uptake was considered present when the quantified ratio of mean counts/pixel in the lung region of interest divided by the mean counts/pixel in the

myocardial region of interest [lung to heart ratio (LHR)] on anterior planar images exceeded 50%. Lung uptake and TID were registered for both isotopes, using the same thresholds.

The Ethics Committee of our institution approved the study and prospective follow-up was performed by dedicated research personnel using scripted and blinded telephone interviews and review of hospital records and death certificates to document adverse events. All patients gave informed consent for their data to be included in the study. Adverse cardiac events, i.e., all-cause death (ACD), cardiac death (CD), MI, and revascularization, were defined as previously described.[8] Revascularization was further classified as early or late, with early revascularization being defined as revascularization performed within 3 months from the MPI. Revascularization was used to censor follow-up in survival analysis regarding ACD, CD and CD, MI. For analysis of the CD, MI or late revascularization (LR) composite, patients with early revascularization were excluded and LR was used as an end point. In case that a patient experienced more than one non-fatal events during follow-up (MI or revascularization), only the first event was considered as an end point.

Statistical Analysis

Continuous and normally distributed variables are presented as mean ± standard deviation with range values while continuous variables with asymmetric distribution as median with range values. The normality assumption for continuous variables was evaluated by the Kolmogorov-Smirnov test. Categorical data are presented as counts and percentages. Cox proportional hazard analysis was used to evaluate the association between covariates of interest and survival free of ACD, CD, CD or MI and CD, MI or LR. Initially, univariate analysis was performed, with candidate variables being selected based on clinical judgment (step 1, Table 3). Subsequently, the statistically significant univariate predictors along with on-going beta-blocker use during MPI were entered in a stepwise forward fashion in multivariable models with a threshold of $P = .05$ (Wald test) for variable entry and $P = .10$ for variable removal from the model (step 2). To assess the incremental value of hemodynamic, SPECT- and function-related variables, additional multivariate models were constructed for each end point, based on sequential increases in global χ^2 values and using the variables described in Figure 2 (step 3). Finally, Kaplan-Meier curves were generated to compute event-free survival by SSS risk groups and the log-rank test was used to determine the significance of event-free survival differences. Analyses were performed with the SPSS version 17 software; all tests were two-tailed, and a value of $P = .05$ was considered indicative of statistical significance.

RESULTS

Upon registry scan completion, 388 eligible patients were identified, as seen in the CONSORT diagram of the study (Figure 1). 18 Patients were lost to follow-up, leaving 370 patients as the study's population. The characteristics of these patients are presented in Table 1.

Regarding patients who were under chronic treatment with beta blockers, 44% did not discontinue these medications before testing. In addition, MPI was performed with the on-going use of dihydropyridine-type calcium channel blockers, non-dihydropyridine-type calcium channel blockers and long-acting nitrates in 29, 3, and 41 patients, respectively. Indication for testing in asymptomatic patients was the risk assessment: (a) post-revascularization (42 patients), (b) before extra-cardiac operation in patients with poor functional capacity (8 patients), and (c) in patients with high CAD risk (41 patients).

Results of the adenosine stress MPI are presented in Table 2. The radioisotope used was ^{201}Tl in 311 patients (84%) and ^{99m}Tc-tetrofosmin in the remainder. 84% of patients were able to complete a full 6 minutes protocol with intolerable angina-like symptoms being the most frequent cause for premature discontinuation of the protocol. 99% of the patients studied were able to tolerate at least 3 minutes of adenosine infusion and no dose lowering was used to extent the duration of infusion in patients who reported adenosine-related side effects. There were no deaths, MIs, sustained ventricular arrhythmias or episodes of advanced (i.e., more severe than second degree type I) atrio-ventricular block observed during the infusion or the short-term post-infusion period. There was one case of pulmonary oedema which required O_2, intravenous aminophylline and loop diuretics for reversal. All other side effects ceased within a few minutes from the termination of the infusion. Patients were watched for 5-8 hours after the infusion, depending on the time required for completion of the imaging sequence.

After a median follow-up duration of 9.3 years, there were 124 ACDs, 62 CDs, 16 MIs, and 35 revascularizations [12 with coronary artery by-pass graft surgery (CABG) and 23 with percutaneous coronary intervention (PCI)], with 23 of the latter being performed within 3 months from MPI. Five patients underwent revascularization for acute MI, and one patient experienced both MI and revascularization at different time points during follow-up. Three patients who were not able to tolerate at least 3 minutes of adenosine infusion were excluded from statistical analysis, and according to the study's design, there were 109 ACDs, 50 CDs, 56 CDs or MIs, and 63 CDs, MIs, or LRs available for survival analyses.

The univariate predictors of the prespecified end points are presented in Table 3. All scintigraphic variables and LVEF were highly significant predictors of all evaluated end points. The inability to increase HR by more than 10 bpm, either as an isolated finding or in combination with the inability to decrease SBP by more than 10 mmHg, was a significant predictor of all the end
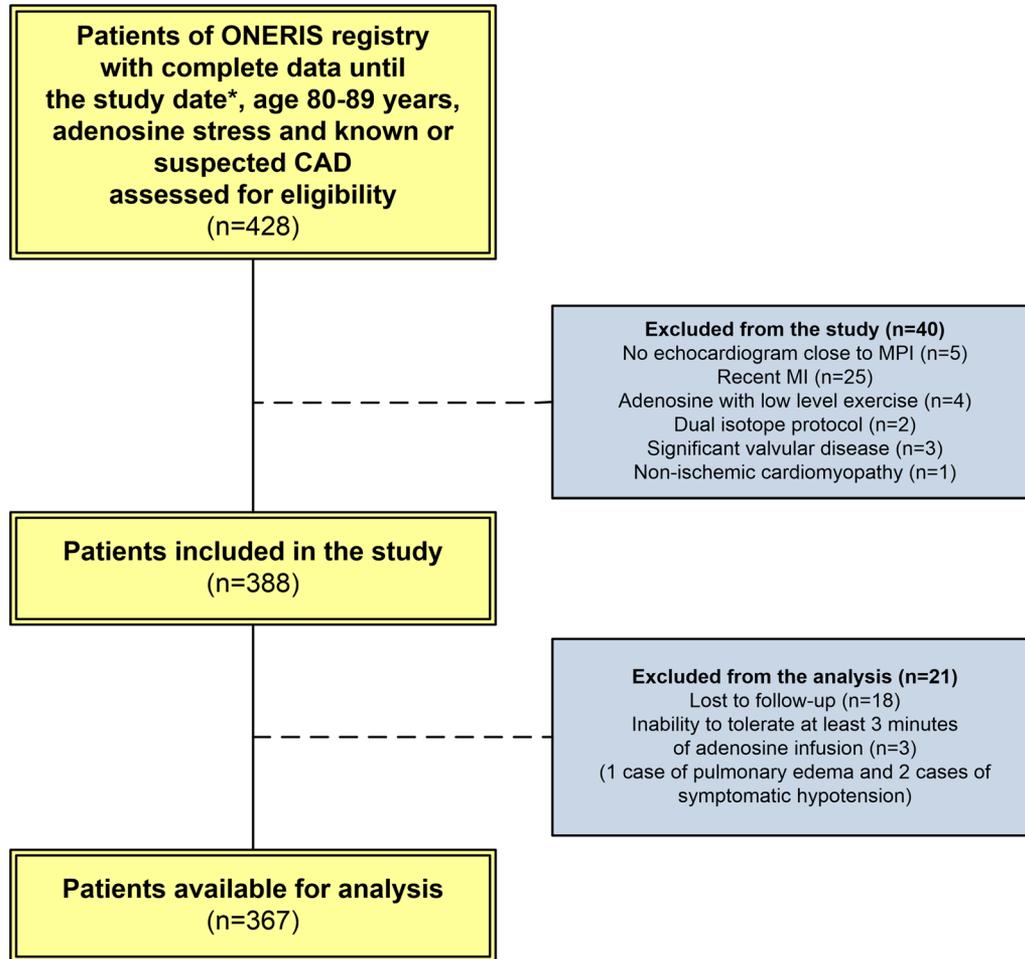
**Patients of ONERIS registry
with complete data until
the study date*, age 80-89 years,
adenosine stress and known or
suspected CAD
assessed for eligibility
(n=428)**

Excluded from the study (n=40)
No echocardiogram close to MPI (n=5)
Recent MI (n=25)
Adenosine with low level exercise (n=4)
Dual isotope protocol (n=2)
Significant valvular disease (n=3)
Non-ischemic cardiomyopathy (n=1)

**Patients included in the study
(n=388)**

Excluded from the analysis (n=21)
Lost to follow-up (n=18)
Inability to tolerate at least 3 minutes
of adenosine infusion (n=3)
(1 case of pulmonary edema and 2 cases of
symptomatic hypotension)

**Patients available for analysis
(n=367)**

Figure 1. CONSORT diagram of the study. *Demographic, clinical and MPI-related data were collected at study entrance (January 1st, 2000 to April 23rd, 2011), while follow-up data were collected in the second half of 2015.

points of the study. With regards to the rest of the hemodynamic variables evaluated, only HR ratio and baseline HR were of prognostic value, and this value was confined to ACD. Clinical data were also prognostically useful, with exertional dyspnea as a pre-test symptom being a significant predictor of ACD.

When the significant univariate predictors of each end point were entered in the respective multivariate model, SSS and LVEF were identified as independent predictors of all end points. In addition, hemodynamic response and non-perfusion-related SPECT variables were identified as independent predictors of cardiac end points, with different components of these variables being predictive of different cardiac end points. Predictors that remained significant after adjustment are presented in details in Table 4.

Furthermore, over a core set of clinical and historical information available before the test (history of MI

or revascularization, current cigarette smoking and pre-test symptoms of exertional dyspnea or typical angina), selected post-test acquired information (hemodynamic response, SPECT-related variables) and LVEF provided incremental prognostic value (Figure 2).

Finally, the three classically used SSS-based risk groups had a highly significant ($P < .001$), overall difference in event-free survival in Kaplan-Meier analysis, as shown in Figure 3. For all evaluated end points, in pairwise comparisons, the difference was significant ($P < .001$) only for the low vs high and the low vs medium group comparisons.

DISCUSSION

In this study, we describe the long-term prognostic value, safety, and tolerability of adenosine stress MPI specifically in octogenarians. To the best of our

Table 1. Patients' characteristics

Variables	Median (min-max) n (%)
Age (years)	82 (80-89)
Gender	
Male	232 (63)
Risk factors for CAD	
Current cigarette smoking	116 (31)
Diabetes	101 (27)
Hypertension	284 (77)
Hypercholesterolemia	195 (53)
Family history of CAD	84 (23)
Known atherosclerotic cardiovascular disease	
MI	108 (29)
Revascularization	133 (36)
PCI	73 (20)
CABG	74 (20)
MI or revascularization	181 (49)
Stroke	15 (4)
Atrial fibrillation	
All forms	63 (17)
Paroxysmal	19 (5)
Persistent-chronic	44 (12)
Resting ST abnormalities	
All forms	55 (15)
LBBB-related	19 (5)
RBBB-related	8 (2)
Pacemaker rhythm-related	10 (3)
Non-specific ST depression	14 (4)
LVH-related	1 (0)
Digoxin-related	3 (1)
Pacemaker	23 (6)
Medications	
Beta blockers	215 (58)
Long-acting nitrates	162 (44)
Calcium channel blockers	132 (36)
ACEI or AT-II*	244 (66)
Statins	166 (45)
Digoxin	13 (3)
No antianginal medications during test	136 (37)
Myocardial function	
LVEF (%)	55 (20-79)
LVEF $\geq$50%	270 (73)
LVEF 31-49%	79 (21)
LVEF $\leq$30%	21 (6)
Pre-test symptoms	
Typical angina	66 (18)
Exertional dyspnea	93 (25)

Table 1. continued

Variables	Median (min-max) n (%)
Atypical angina	39 (10)
Atypical chest pain	28 (7)
Unstable angina	9 (2)
Asymptomatic	91 (24)
Fatigue	34 (9)
Atypical symptoms**	10 (3)

* Angiotensin converting enzyme inhibitors or angiotensin receptor blockers, ** including palpitations, syncope or pre-syncope

knowledge, this is the first study of this kind in this population. The results are of particular importance for the practicing physician nowadays since octogenarians have both increased prevalence of and mortality from CAD compared to other age groups[12] and are increasingly referred for CAD-related imaging studies in developed countries.

The type and frequency of adenosine-related side effects have been comprehensively described in the Adenoscan Multicenter Trial Registry.[6] Adenosine was documented as a safe mean for vasodilator stress with relatively well-tolerated side effects, although older patients had relatively increased side effects frequency. A few studies reported later on the safety and adverse events of adenosine specifically in the elderly,[13-17] but used a substantially lower age threshold to define the elderly population, compared to our study. Older patients are less likely to report adverse events than younger patients,[6,18] but the reasons for this tolerance difference remain speculative. Whether this difference translates into lower rates of premature discontinuation of adenosine infusion in older vs younger patients has not been specifically studied. We demonstrated that adenosine-MPI is both safe and relatively well tolerated in very elderly patients, with 99% of the patients being able to tolerate at least 3 minutes of adenosine infusion. The 16% premature discontinuation rate compares favorably with the figures observed in Adenoscan trial, where mean patient's age was 65 ± 11 years, and infusion was terminated early in 7% of the patients due to intolerable side effects, with another 13% of patients requiring dose lowering to complete the 6 minutes infusion. In contrast to previous studies, we report the premature termination of the infusion-related side effects, not the overall incidence of adverse events observed during adenosine infusion, which has been extensively studied[2,6] and is beyond the scope of this study.

Table 2. Test-related variables

Variables	Median (min-max) n (%)	
Myocardial perfusion: ischemia scores		
SSS	*4 (0-15)**	
SRS	*0 (0-6)**	
SDS	*1 (0-8)**	
Myocardial perfusion: SSS category		
Medium	92 (25)	
Low	177 (48)	
High	101 (27)	
Myocardial perfusion: other parameters		
TID	90 (24)	
Lung uptake	10 (3)	
Fixed defect	125 (34)	
Hemodynamic variables		
Peak/rest HR	1.1 (0.8-2)	
SBP baseline (mmHg)	*140 (100-220)*	
SBP peak (mmHg)	*130 (80-230)*	
DBP baseline (mmHg)	*80 (60-110)*	
DBP peak (mmHg)	*80 (48-100)*	
HR baseline (bpm)	*68 (45-128)*	
HR peak (bpm)	*80 (47-140)*	
Hemodynamic response subsets		
ΔSBP $<-$10 mmHg	130	35
ΔSBP $-$10 to 0 mmHg	213	57
ΔSBP $>$0 mmHg	27	7
ΔHR $>$10 bpm	180	48
ΔHR 0 to 10 bpm	156	42
ΔHR $<$0 bpm	34	9
Adenosine-induced ST depression		
Total	18	5
In patients with SSS $<$4	7	2
Adenosine infusion duration (minutes)		
6	310	84
4 to $<$6	38	10
$<$4	22	6
$<$3	3	$<$1%
Arrhythmias during adenosine infusion		
Second degree atrio-ventricular block	1	0.3
Ventricular extra-systoles	37	10
Atrial fibrillation	7	3
Non-sustained VT	2	0.5
Reason for termination		
Six minutes protocol completion	310	84
Angina-like chest, throat, neck or upper extremity pain or discomfort	27	7
Flushing**	10	3
Dyspnea***	9	2
Light headedness: hypotension	8	2
Arrhythmia	6	2

VT, ventricular tachycardia; Δ, change in variable during adenosine infusion; *DBP*, diastolic blood pressure
* Figures in italics represent medians with minimum and maximum values, except for ischemia scores where medians with 25th and 75th percentiles are presented, ** when the reason for termination was flushing, minimum adenosine infusion duration of at least 4 minutes had been achieved in all cases, *** including one case of pulmonary oedema

Table 3. Univariate predictors of end points

Variables	ACD (n = 109)		CD (n = 50)		CD or MI (n = 56)		CD, MI or late revascularization (n = 63)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Risk factors								
Age	1.07 (0.99-1.16)	.07	1 (0.9-1.1)	.9	1 (0.8-1.1)	.7	0.9 (0.8-1.05)	.3
Current cigarette smoking	1.2 (0.8-1.8)	.3	1.4 (0.8-2.6)	.2	1.4 (0.8-2.4)	.2	1.4 (0.9-2.4)	.1
Diabetes	1.2 (0.8-1.8)	.3	1.4 (0.8-2.6)	.2	1.4 (0.8-2.4)	.2	1.6 (0.9-2.7)	.06
Hypertension	0.9 (0.6-1.4)	.7	0.9 (0.5-1.8)	.8	0.8 (0.4-1.6)	.6	0.7 (0.4-1.2)	.2
Hypercholesterolemia	0.7 (0.5-1.1)	.1	0.8 (0.4-1.3)	.4	0.7 (0.4-1.3)	.3	0.9 (0.5-1.5)	.7
Body mass index	0.9 (0.9-1.01)	.1	0.9 (0.8-1.03)	.2	0.9 (0.90-1.05)	.4	1 (0.9-1.05)	.5
History of cardiovascular disease								
Stroke	2.6 (1.3-5.5)	.01	2 (0.6-6.4)	.2	1.7 (0.5-5.5)	.3	1.5 (0.5-5)	.4
Previous revascularization (all types)	1.2 (0.8-1.8)	.2	1.2 (0.7-2.1)	.5	1.2 (0.7-2.1)	.4	1.3 (0.8-2.1)	.3
MI	1.3 (0.9-1.9)	.1	1.4 (0.8-2.5)	.2	1.6 (0.9-2.8)	.06	1.7 (1.03-2.8)	.04
Atrial fibrillation (all forms)	1.2 (0.7-1.9)	.4	1.4 (0.7-2.7)	.3	1.2 (0.6-2.3)	.5	1.1 (0.6-2.1)	.6
ECG variables								
LBBB in resting ECG	1.7 (0.9-3.5)	.1	0.8 (0.2-3.2)	.7	0.7 (0.1-2.8)	.6	0.6 (0.1-2.5)	.5
Resting ST abnormalities	1.1 (0.6-1.9)	.6	1 (0.4-2.3)	.9	0.9 (0.4-1.9)	.8	1.2 (0.6-2.3)	.6
ST depression during adenosine infusion	1.2 (0.4-3.4)	.6	1.8 (0.6-5.1)	.2	2.1 (0.8-5.2)	.1	1.7 (0.7-4.4)	.2
On beta blockers during test	1.3 (0.9-2)	.1	1.4 (0.8-2.5)	.2	1.4 (0.8-2.4)	.2	1.3 (0.8-2.2)	.2
Pre-test symptoms								
Exertional dyspnea	1.6 (1.07-2.3)	.02	1.7 (0.9-3)	.07	1.6 (0.9-2.8)	.08	1.2 (0.9-1.5)	.1
Typical angina	1.1 (0.7-1.8)	.7	1.5 (0.8-3)	.1	1.3 (0.7-2.6)	.3	1.2 (0.9-1.6)	.1
Asymptomatic	1.04 (0.6-1.6)	.8	1.2 (0.6-2.2)	.6	1.2 (0.6-2.2)	.5	1 (0.7-1.3)	.9
Hemodynamic variables								
Baseline HR	1.01 (1.00-1.03)	.04	1.01 (0.99-1.03)	.1	1.01 (1.00-1.03)	.1	1.01 (0.99-1.03)	.2
Baseline SBP	1 (0.99-1.01)	.6	1 (0.99-1.01)	.8	1 (0.99-1.01)	.8	1 (0.99-1.01)	.7
HR ratio	0.1 (0.03-0.5)	.002	0.1 (0.02-1.1)	.07	0.2 (0.05-1.6)	.1	0.7 (0.1-3.3)	.7
ΔSBP	1 (0.98-1.01)	.3	1 (0.97-1.01)	.4	0.99 (0.98-1.01)	.5	1 (0.98-1.01)	.7
ΔHR $\leq$+10 bpm	1.8 (1.2-2.6)	.004	2 (1.1-3.5)	.02	1.8 (1.05-3.1)	.03	1.5 (0.9-2.5)	.1
Non SBP dippers and tachycardics*	1.5 (1.04-2.2)	.03	2.2 (1.3-3.9)	.01	2.1 (1.2-3.5)	.01	1.9 (0.1-3.2)	.01
SPECT variables								
SSS	1.04 (1.02-1.06)	<.001	1.06 (1.04-1.09)	<.001	1.05 (1.03-1.08)	<.001	1.06 (1.04-1.08)	<.001
SRS	1.05 (1.03-1.08)	<.001	1.07 (1.03-1.1)	<.001	1.06 (1.03-1.09)	<.001	1.06 (1.03-1.09)	<.001
SDS	1.03 (1.00-1.06)	.02	1.06 (1.03-1.1)	<.001	1.05 (1.02-1.09)	.002	1.06 (1.03-1.1)	<.001

Table 3. Univariate predictors of end points

Variables	ACD (n = 109)		CD (n = 50)		CD or MI (n = 56)		CD, MI or late revascularization (n = 63)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
TID	1.5 (1.00-2.26)	.05	1.9 (1.08-3.4)	.03	1.7 (0.99-3)	.06	1.8 (1.1-3)	.02
Lung uptake	4.8 (1.5-15.6)	.01	8.4 (2.5-28.2)	.001	7.3 (2.2-24.5)	.001	2.8 (1.7-4.8)	<.001
Echocardiographic variables								
LVEF	0.96 (0.94-0.98)	<.001	0.93 (0.91-0.96)	<.001	0.94 (0.92-0.97)	<.001	0.94 (0.92-0.96)	<.001

OR, odds ratio, CI, confidence intervals
* Inability to increase HR by >10 bpm and decrease SBP by >10 mmHg

Pertinent to the issue of adenosine tolerability is the discussion about the cut-off limits of infusion duration that were used for including a study in the statistical analysis. The minimum duration of an abbreviated adenosine infusion protocol that is recognized by the ASNC is 4 minutes,[4] and it has been shown recently that the abbreviated protocols cause significantly less coronary flow reserve than the standard 6 minutes protocol.[5] However, two studies have provided proof of concept that a diagnostic test can still be achieved with a 3 minutes infusion,[6,7] and this option is also acknowledged in the recent MPI guidelines of the European Association of Nuclear Medicine.[8] Furthermore the degree of coronary flow increase is not a major determinant of the diagnostic and prognostic value of a SPECT-MPI study using conventional radioisotopes, since these variables are equivalent for pharmacologic stress and exercise, despite the fact that vasodilators increase coronary flow to a greater degree than exercise.[9,10] Hence, we excluded only patients who were not able to tolerate at least 3 minutes of adenosine infusion.

The short-term prognostic value of perfusion SPECT variables during vasodilator stress MPI in elderly patients (>75 years old) has been specifically evaluated in two large studies. In an all-comers study which included patients with exercise and adenosine stress, Hachamovitch et al[19] studied 3042 patients >75 years old (58% of the total study population) with known or suspected CAD, regardless of LVEF, who underwent adenosine stress MPI. Follow-up duration was 1.9 ± 0.9 years, but the study also included a subgroup of 684 patients with extended follow-up (6.2 ± 2.9 years) who underwent gated MPI. For the short-term follow-up patients undergoing adenosine stress, there was no LVEF information, while for the long-term follow-up group, results were not presented separately by stress type. Curtis et al[20] studied 439 octogenarians who underwent vasodilator stress, non-gated MPI, and were followed up for a mean period of 2.5 years. These studies formed the body of evidence supporting the role of scintigraphic variables during vasodilator stress MPI in the risk stratification of very elderly patients for cardiac[19] and all-cause[20] mortality. Another all-comers study[21] with relatively short follow-up (2.8 ± 1.7 years) has included a large arm of octogenarians without known CAD or LV systolic dysfunction undergoing adenosine stress MPI, but did not report separately on the results of these patients. The present study confirms the results of previous studies regarding the risk stratification ability of vasodilator stress MPI in very elderly patients and makes a significant step forward. The prognostic value of perfusion-related SPECT variables applies to all commonly used clinical end points and is maintained during long-

Table 4. Multivariate models: independent prognostic value

| End points	Variables	OR (95% CI)	P
ACD	SSS	1.03 (1.01–1.05)	.01
	LVEF	0.97 (0.95–0.99)	.004
	ΔHR <10 bpm	1.8 (1.2–2.6)	.004
	Pre-test symptoms = exertional dyspnea	1.6 (1.07–2.3)	.02
CD	SSS	1.05 (1.02–1.07)	.001
	LVEF	0.96 (0.93–0.98)	.001
	Lung uptake	4.3 (1.2–15.5)	.02
	Non SBP dippers and tachycardics	2 (1.1–3.5)	.02
CD or MI	SSS	1.04 (1.01–1.07)	.01
	LVEF	0.96 (0.94–0.99)	.01
	Lung uptake	4.3 (1.2–14.9)	.02
	Non SBP dippers and tachycardics	1.8 (1.05–3.06)	.03
CD, MI, or late revascularization	SSS	1.04 (1.02–1.07)	<.001
	LVEF	0.96 (0.94–0.99)	.004
	Lung uptake	2.2 (1.2–3.8)	.005
	Non SBP dippers and tachycardics	1.7 (1.05–2.9)	.03
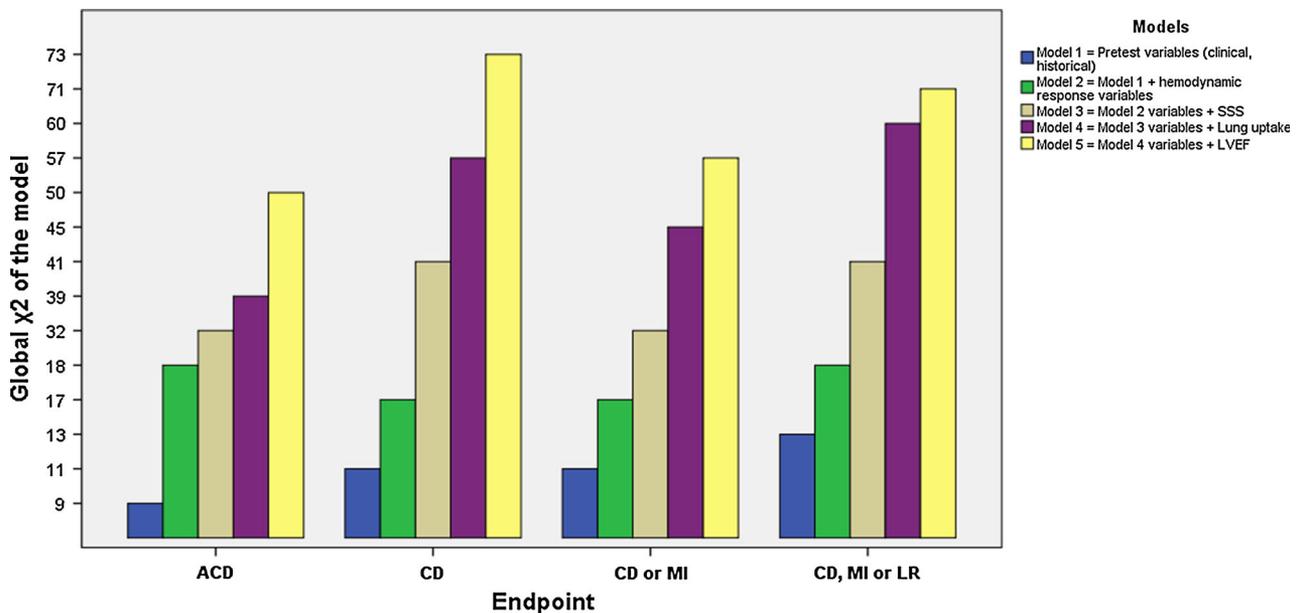
Figure 2. Global χ^2 values of the multivariate models for each end point. The individual components of each model are described in the right part of the figure. Hemodynamic variables included ΔHR $\leq$+10 bpm for ACD and ''Non SBP dippers & tachycardics'' for the rest of the end points. All stepwise increases in global χ^2 from Model 1 to Model 5 were significant at $P < .05$ for all end points with the exceptions of change from Model 1 to Model 2 for the CD or MI and CD, MI or late revascularization (LR) end points.

term follow-up and after adjustment for LVEF, the most important predictor of long-term survival in patients with CAD, regardless of its extent and severity.[22] Furthermore, this study demonstrated that overall the most potent, post-MPI survival predictor in octogenarians is SSS, a marker reflecting both reversible and fixed ischemic defects. This is in accordance with observations in the general population, where the extent and severity of stress perfusion defects are the predominant predictors of most post-MPI outcomes.[23]
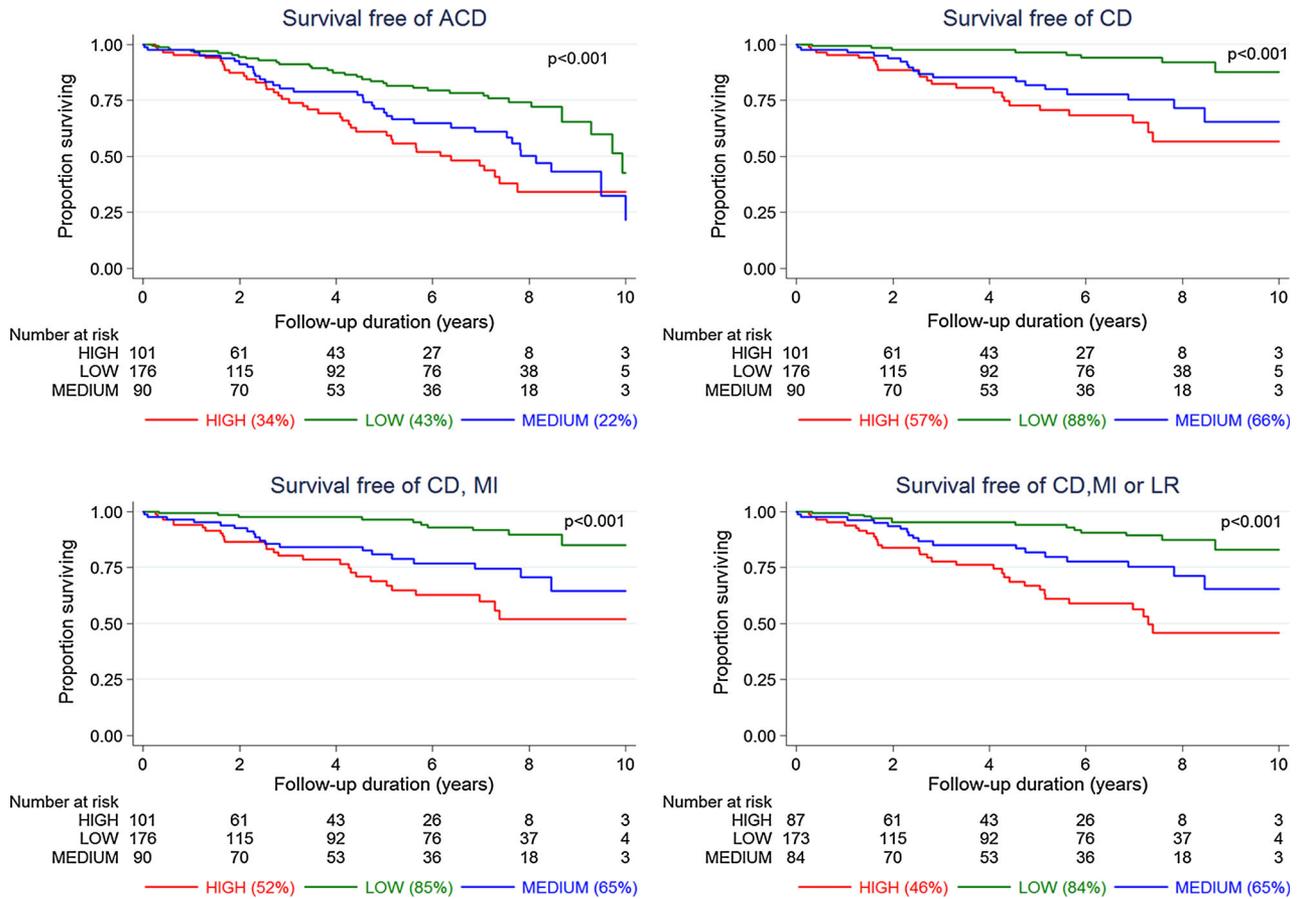
Figure 3. Kaplan-Meier plots of estimated 10-year survival free of adverse events by SSS-based risk groups. High, low and medium risk groups are represented by red, green and blue lines, respectively, with % of patients surviving at the end of follow-up demonstrated at the bottom of each diagram. *P* values of statistical significance are demonstrated for the overall comparison (*top right*). *LR* late revascularization.

Reversible ischemia has been shown in large, registry-based studies to be the best predictor of survival after MPI results-driven revascularization,[24,25] but the present study was not designed to address this issue.

Regarding non-perfusion SPECT variables, it is known that TID during vasodilator stress MPI is a strong predictor of cardiac end points in the general population,[26] but has not been studied in the very elderly. Furthermore, the data for the prognostic role of the LHR in patients undergoing vasodilator stress MPI are scarce, regardless of patients age,[26] the prognostic role of lung uptake has been described predominantly for ^{201}Tl and the cut-off limit with ^{99m}Tc-based tracers is not well defined. However, there are a few studies evaluating the prognostic role of the LHR in conjunction with ^{99m}Tc-based tracers,[27,28] one of them demonstrating that LHR was significantly elevated (0.39 for both exercise and adenosine stress) in the presence of multivessel disease.[28] In our cohort of elderly patients, non-perfusion variables

were associated with all end points, but most important, increased lung uptake provided incremental prognostic value over clinical, hemodynamic and perfusion-related variables. It should be noted that we used the same LHR cut-off limit for documenting increased lung uptake for both radioisotopes, as according to some experts the LHR is rarely useful with ^{99m}Tc tracers, except when the ratio is much higher with stress than at rest.[26]

Beyond scintigraphic variables, it has long been reported that hemodynamic variables can provide important risk stratification information in patients undergoing adenosine stress MPI. The Cedars-Senai Medical Group demonstrated in 2003 that assessment of the hemodynamic response to adenosine adds incremental prognostic value to MPI results.[11] A few years later, the same group[29] derived and validated a prognostic adenosine score in 5873 patients who underwent non-gated SPECT and were followed for a mean duration of 2.2 ± 1.1 years. This score, which

included rest and peak HR as essential components, further risk stratified patients with respect to CD in all categories of SPECT abnormality. The typical hemodynamic response to adenosine infusion is a modest reduction in SBP (10-15 mmHg) with a compensatory increase in HR (10-15 bpm).[6,18] Severe hypotension or paradoxical hypertension is infrequent.[6] Using the cut-off values introduced by Amanullah et al,[30] as surrogate markers of significant peripheral hemodynamic effects of adenosine (10 bpm for HR, 10 mmHg for SBP), we demonstrated that two hemodynamic subsets were independent predictors of hard adverse events. Increase in HR by ≤10 bpm during adenosine infusion had independent and incremental prognostic value for ACD and the combination of no significant drop in SBP and no significant increase in HR for CD. In contrast, no isolated SBP-related variables were identified as significant predictors of adverse events. The latter observation is in agreement with two previous large studies[11,31] regarding adenosine-induced SBP changes, but discordant with the aforementioned studies with regards to baseline SBP. To our knowledge, this is the first study to report that hemodynamic variables during adenosine-MPI have independent prognostic value in a multivariate model which includes both SPECT and function-related variables and involves extended follow-up. This statement holds true regardless of the highly selected population on which this observation was made. The prognostic role of HR-response during vasodilator stress has been explored in numerous studies with other agents.[26] It should be noted, however, that although all agents used for vasodilator stress studies act by stimulating the adenosine receptors, they have different pharmacokinetic properties, and specific studies are needed to characterize ideal cut-offs tailored for each reagent.[32]

One might argue that the non-homogenous use of beta blockers can obscure the interpretation of our observations; however, both hemodynamic and scintigraphic variables remained significant after adjustments for on-going use of beta blockers. Hence, the significant proportion of patients undergoing adenosine stress without prior discontinuation of beta blockers serves to generalize the prognostic significance of hemodynamic variables regardless of treatment status, an issue which remained unclear when the prognostic implications of these variables were initially described.[11]

NEW KNOWLEDGE GAINED

Octogenarians have significant prevalence of and mortality from CAD. Furthermore, because of their limited exercise capacity and susceptibility to complications during invasive imaging, pharmacologic stress testing is the most frequently used method for their risk stratification. However, long-term prognostic data for adenosine stress MPI in this extreme age group remain limited. The present study demonstrates in a comprehensive manner the feasibility and prognostic utility of this non-invasive imaging method, specifically for octogenarians.

LIMITATIONS

The sample size of the study should be considered moderate, and no sample size calculations were performed. A larger sample size might allow for the identification of additional independent predictors of cardiac end points. A ratio of the number of individuals with the outcome event to the number of candidate predictors (referred to as events per variable or EPV) of 10 is widely advocated as a rough rule of thumb for Cox regression analyses. This rule was violated in the case of cardiac end points analysis. However, Vittinghoff and McCulloch[33] have shown that the worst instances of each problem that model overfitting causes are not severe with 5-9 EPV and usually comparable to those with 10-16 EPV. The population studied was very specific, limiting the generalizability of the findings to the overall elderly population, which by current standards includes patients older than 75 years old. Patients with both known and suspected CAD were studied and no subgroup analysis was performed to assess the effect of known CAD in the results of the study. Also, no comparison with data from a younger cohort was performed. Although all data were collected and entered prospectively, the study qualifies as a single-centre, retrospective cohort study. The setting of the study was a large, reference nuclear medicine laboratory, and there was no way to control for referral bias. Another limitation of the study is the potential bias introduced by the exclusion of patients who underwent combined adenosine with low-level stress, as such patients might be perceived to be at high risk of bradyarrhythmias. This effect, however, if present, would not be expected to be significant, as only four such patients were identified in our registry. Furthermore, because of the mixing of the radioisotopes used, we cannot elucidate the relative merit of each isotope in the observed prognostic value of increased lung uptake, while the thresholds used for documenting TID and increased lung uptake limit their prognostic utility in cohorts using the same standards as the present study.

Finally, LVEF figures were derived from echocardiography instead of gated SPECT imaging. This fact limits the conclusions regarding the prognostic value of MPI in this patients group to the perfusion arm of the study since functional information based on nuclear medicine methods was not evaluated. Gated SPECT would further improve the

prognostic value of the study. However, for homogeneity reasons, echocardiography was chosen for the estimation of LVEF instead of ECG gated SPECT, which was introduced to our department in 2005 and is not applied in ^{201}Tl studies. Although gated ^{201}Tl studies can be performed, they have lower accuracy and reliability compared to studies using ^{99m}Tc-labeled tracers and require significantly longer acquisition time.[34,35] Hence, given the fact that in 84% of the studies the isotope used was ^{201}Tl, this limitation is significantly attenuated. Furthermore, in MPI, while functional information serves as an important supplement to perfusion information, this information has never been acquired when the primary study objective is to assess ventricular function.[36] Indeed, when the main goal of LVEF evaluation is the assessment of prognosis, most relevant studies have been performed using echocardiography. Hence, it is interesting to see how perfusion and non-perfusion variables of an MPI study compare to LVEF when the latter is determined by the golden standard method for its evaluation with regards to prognosis.

Disclosures

No conflicts of interest to disclose.

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