The Safety and Clinical Utility of Dobutamine Stress Echocardiography among Octogenarians

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ABSTRACT

Background: Increasing numbers of octogenarians are being referred for investigation of chest pain. While dobutamine stress echocardiography (DSE) has been shown to be useful in younger patients, its role among octogenarians remains unclear. This investigation aimed to investigate the safety and prognostic utility of DSE on cardiac events and total mortality in octogenarians.

Methods: 550 consecutive patients aged ≥80 years underwent DSE for suspected cardiac chest pain. All subjects were followed-up prospectively until March 2011 and the study end points were a major cardiac event and total mortality.

Results: One hundred and eighty three (33%) patients had a positive DSE result, 271 (49%) had a normal study, and 164 (30%) had fixed wall motion abnormalities. During a mean follow-up of 2.14±1.13 years, there were 217 (39%) cardiac events and 63 (11%) deaths, of which 46 (73%) were cardiac. The absolute risk of cardiac events increased with burden of ischaemia on DSE, from 13%/year (none), to 26%/year (1-3 ischaemic left ventricular [LV] segments) and 38%/year (>3 ischaemic LV segments), $p<0.001$. Any ischaemia was associated with an additional 13 cardiac events per 100 person years. In multivariate analysis, compared with non-ischaemic patients, the relative hazard of cardiac events for 1-3 and >3 ischaemic LV segments were 1.34 (95% CI, 1.13–1.29) and 1.86 (95% CI, 1.16–2.98), respectively. Addition of echocardiographic parameters to basic models improved the C statistic from 0.77 to 0.89 ($p<0.001$).

Conclusions: Among octogenarians referred with suspected cardiac chest pain, DSE is safe and importantly identifies a subset at high risk of cardiac events.

What is already known about this subject?

The prognostic value of dobutamine stress echocardiography has been previously reported in large studies in patients with various pre-test probabilities.

What does this study add?

Dobutamine stress echocardiography is safe in octogenarians and importantly identifies a subset at high risk of cardiac events in this population.

How might this impact on clinical practice?

The results demonstrate that ischaemia and particularly high ischaemic burden in octogenarians not only accurately predicts significant coronary artery disease, therefore avoiding unnecessary invasive tests among those with a negative dobutamine stress test, but also is associated with future cardiac events. Importantly revascularization did not attenuate this risk. The authors believe the study adds important information regarding the risk stratification of octogenarians with suspected cardiac chest pain.

INTRODUCTION

Increasing life expectancy will exact an increasing economic burden on health services. It is estimated that by 2050 the number of individual's ≥80 years of age living in the United States (US) will increase to approximately 25 million.[1] Much of the burden on chronic disease in ageing populations will be in the form of coronary artery disease (CAD). Despite significant advances in diagnostic and therapeutic interventions, CAD remains the most common cause of morbidity and mortality in the elderly.[2] In the US, octogenarians comprise 5% of the total population and account for more than 20% of all hospital admissions for myocardial infarction (MI) and one third of all MI related hospital deaths.[2] An increase in the prevalence and severity of CAD is observed with increasing age,[3] necessitating the development of techniques which are both safe and which reliably provide prognostic information, given the higher rate of complications with invasive techniques among this age group.[4]

The early diagnosis and treatment of suspected CAD is a particular challenge in the elderly as patients often have atypical symptoms, limited exercise capacity, and a higher frequency of co-morbidity.[5] This may result in lower utilisation of stress tests and coronary angiography by physicians.[6] Additionally, a well-known elderly paradox exists whereby higher risk populations receive less evidence based care.[7] Dobutamine stress echocardiography (DSE) has been shown to be well tolerated and an extremely useful tool for predicting all-cause mortality and cardiac events in the general and largely younger populations [8, 9] but its utility among those ≥80 years of age remains unclear. The aim of this study was to investigate the feasibility of

DSE in this cohort and to assess whether a positive DSE reliably predicted angiographic disease and cardiac events among octogenarians.

METHODS

Study Design and Patients

The study population consisted of 568 consecutive patients from a single centre undergoing DSE for the evaluation of angina pectoris between June 2006 to March 2010 in the outpatient setting. Exclusion criteria included patients referred for viability assessment only, asymptomatic patients awaiting non-cardiac surgery, and patients with severe valve disease. DSE test results were interpreted by 2 readers with more than 5-years of experience. The majority of DSE requests (76.9%) resulted as a consequence of the subject being unable to perform an exercise treadmill test and the remainder were due to physician choice. Clinical characteristics were recorded at the time of DSE. Follow-up data was collated by contacting patients or a family member, general practitioners, and reviewing hospital records to inquire about interim hospital admissions, outpatient diagnosis of cardiovascular events, and deaths. The date of the last review or consultation was used to calculate the duration of follow-up through to March 2011.

This investigation conformed to the Declaration of Helsinki principles. All patients provided informed consent before testing and the local research ethics committee approved the study.

DSE

All patients recruited underwent DSE. The image quality obtained was interpretable in all patients (104 [18.9%] requiring contrast) and the entire cohort was used in data analysis. DSE

was performed according to a standard protocol [10] with dobutamine infusion starting at and increasing every 3-minutes with 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to a maximum of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (stage 4). If no end-point was reached, atropine (in doses 0.25 mg up to a maximum of 2 mg) was used. Mean dobutamine dose was 31.6±4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 178 (32.4%) patients required atropine (1±0.3 mg) to achieve target heart rate. Transthoracic echo images of the heart were acquired in standard parasternal long- and short-axis and apical 2-, 3-, 4-chamber views at baseline and during stepwise infusion of dobutamine. Baseline, low-dose (heart rate 10-15 beats above baseline), peak and recovery (10-minutes post drug infusion) stage images were acquired as digital full cardiac cycle loops in a quad screen format and stored for off-line analysis. The left ventricle (LV) was divided into a 17-segment model for qualitative analysis [11] and wall motion was scored on a 4-point scale (1, normal wall motion; 2, hypokinesis; 3, akinetic; and 4, dyskinetic) as is standard.[10] In patients with resting akinetic segments a biphasic response was used to indicate ischaemia. LV ejection fraction was calculated using biplane Simpson's technique. Results were classified as a normal response with an overall increase in wall motion or abnormal response. An abnormal response was described as the occurrence under stress of hypokinesia, akinesia or dyskinesia in one or more resting normal segments and/or worsening of wall motion in one or more resting hypokinetic segments.[12] In this way patients were categorised as non-ischaemic or ischaemic. The extent and location of inducible ischaemia were evaluated and a wall motion score index (WMSI) was calculated, both at rest and during stress. Patients were further categorised with low (1-3 ischaemic LV segments) or high (>3 ischaemic LV segments) ischaemic burden.[13] Non-viable myocardium was defined as resting akinetic or dyskinetic LV segment without improvement during DSE [14] and referred to as fixed wall motion abnormalities (WMA).

End Point Definition

The principle end-point of interest for this analysis was major cardiac event and secondarily death from any cause, with patients censored at the time of event or at the last follow-up. A major cardiac event was defined as cardiac death (due to MI, cardiac arrhythmias, or congestive heart failure) or non-fatal MI (NFMI). NFMI was defined by the standard criteria of ischaemic chest pain associated with an elevation of cardiac enzymes with or without electrocardiographic changes. Revascularization procedures were also recorded and patients were censored at the date of their procedure. For patients with multiple events, only the first event was considered.

Statistical Analysis

Continuous variables were expressed as mean±SD and categorical variables as n (%). Group comparisons were based on 2-sample *t* test and one-way analysis of variance tests for continuous variables and χ^2 test was used for group comparisons among categorical variables. To describe the frequency of cardiac events according to time since dobutamine stress test, Kaplan-Meier cumulative event curves were constructed and compared using the log-rank test with a *P* value <0.05 considered statistically significant. The data were stratified according to A) ischaemic and non-ischaemic patients; B) non-ischaemic (0 segments), low ischaemic burden (1-3 ischaemic LV segments) and high ischaemic burden (>3 ischaemic LV segments) patients; and C) ischaemic patients with or without subsequent cardiac revascularization. Event rates were calculated and expressed as % per year. The relationship between baseline clinical characteristics, DSE results and clinical outcomes were assessed using unadjusted and

multivariable Cox regression analyses. All models were adjusted for age, gender, presence or absence of hypertension, diabetes, hypercholesterolaemia, revascularization and smoking history and use or non-use of anti-hypertensive or lipid-lowering therapies. All other variables that reached statistical significance were entered into the multivariable model. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) are reported. We then calculated the C statistic as a measure of the incremental value of DSE. All analyses were conducted using the statistical package for social sciences (SPSS 17 release version of SPSS for Windows; SPSS Inc., Chicago IL, USA).

RESULTS

Of the 568 patients referred for DSE, 18 were excluded from our final analysis (Figure 1). The remaining 550 patients (305 caucasian, 229 Indian Asian, 15 black, and 1 Chinese) are the subjects of this report. Online supplementary table I details the characteristics of all patients, event free patients, cardiac event patients and all-cause mortality patients. The patients' mean age was 84±3.7 years (range 80-92 years) with an almost equal male to female ratio. The prevalence of hypertension, hypercholesterolaemia and diabetes were 66.4%, 53.6% and 22.2% respectively with unsurprisingly 42.4% of patients having a prior history of revascularisation and 14.4% a prior MI. Eight (1.5%) patients were current smokers and 117 (21.3%) ex-smokers. Five (0.9%) patients had pacemaker implantation, 12 (2.2%) had atrial fibrillation at baseline, and 14 (2.5%) had left bundle branch block. Atrial fibrillation induced by DSE occurred in 12 (2.2%) patients and non-sustained ventricular tachycardia in 1 (0.2%) patient, which resolved within 3-minutes of recovery. None of the patients required intravenous beta-blocker to reverse the effects of dobutamine or treat arrhythmias. The Canadian Cardiovascular Society angina classification was similar in all groups. The majority of patients were treated with anti-hypertensive (angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, and calcium antagonists), anti-platelet (aspirin), and lipid-lowering therapies.

DSE and Detection of Significant CAD

DSE was completed in all patients and the level of agreement; kappa between the two sonographers was 0.82. Consensus was obtained in discordant cases. In total 9350 left ventricular

segments were analysed. Two hundred and seventy one patients (49.3%) had a normal DSE study, 183 (33.3%) developed a new or worsening WMA and 164 (29.8%) had fixed WMA's. Of the patients with fixed WMA's, 68 (41.5%) developed a new or worsening WMA during DSE.

One hundred and sixty one (88%) patients who developed a new or worsening WMA during DSE underwent coronary angiography within 30±1.2 days. Of these patients, 40 (24.8%) had fixed WMA's. In total, 146 patients (79.8%) who developed a new or worsening WMA had significant CAD (defined as ≥70% coronary lumen stenosis by visual determination), of which 31 (21.2%) had significant triple vessel disease, 49 (33.6%) had significant double vessel disease and 66 (45.2%) had significant single vessel disease. Fifteen patients (9.3%) with a positive DSE result did not have significant obstructive CAD on visual coronary angiography. However, none of these patients had angiographic normal arteries, with 9-patients having moderate disease (defined as 50% - 69% coronary lumen stenosis) and 6 mild disease (defined as ≥20% - 49% coronary lumen stenosis). One hundred and seven patients (29.2%) who did not have ischaemia on DSE underwent coronary angiography within 30±1.6 days due to continued clinical investigation of symptoms. Of these patients, eleven (10.3%) had angiographic evidence of CAD, of whom 1 had significant single vessel disease, 3 had moderate double vessel disease, 5 had mild double vessel disease and 2 had moderate single vessel disease. The resulting sensitivity, specificity, positive and negative predictive values for DSE in detecting significant CAD were 93%, 86.5%, 90.7%, and 89.7% respectively.

During follow-up, 63 patients underwent revascularization before any cardiac event and were censored at the time of their procedure. Of these patients, 47 (74.6%) had ischaemia by DSE and

19 (30.2%) had fixed WMA's. These 63 patients had a higher baseline WMSI (1.13±0.15 versus 1.08±0.16, p=0.006) and higher WMSI at peak stress (1.26±0.18 versus 1.12±0.18, p<0.001) compared to the rest of the study population.

Clinical Outcomes

During the mean follow-up period of 2.14±1.13 years, the composite endpoint of cardiac death or NFMI occurred in 217 (39.5%) patients, reflecting 46 cardiac deaths and 171 NFMI's. There were also 17 non-cardiac deaths. The clinical characteristics of subjects who experienced a cardiac event and those who did not are shown in table 1. Briefly, subjects experiencing a cardiac event were more likely to have hypertension, hypercholesterolaemia and have a previous MI or coronary revascularization.

Table 1. Characteristics of Patients According to Cardiac Event or No Cardiac Event.

Characteristics		Cardiac Events (n=217)	No Cardiac Events (n=333)	P Value
Demographics				
	Age, yrs	84.4±2.9	83.9±3.1	0.50
	Men	122 (56.2)	165 (49.5)	0.10
History				
	Hypertension	154 (71)	211 (63.4)	0.04
	Diabetes mellitus	53 (24.4)	69 (20.7)	0.25
	Hypercholesterolaemia	130 (59.9)	165 (49.5)	0.01
	Family history of CVD	24 (11.1)	29 (8.7)	0.29
	Prior myocardial infarction	43 (19.8)	36 (10.8)	<0.01
	PCI	80 (36.9)	61 (18.3)	<0.001
	CABGS	47 (21.7)	45 (13.5)	0.01
	Smoking history			0.06
	Never smoked	157 (72.4)	268 (80.5)	
	Ex-smoker	55 (25.3)	62 (18.6)	
	Current smoker	5 (2.3)	3 (0.9)	
Canadian Cardiovascular Society angina classification				0.18
	Class I	81 (37.3)	148 (44.4)	
	Class II	115 (53)	151 (45.3)	
	Class III	20 (9.2)	34 (10.2)	
Long term cardiac medication				
	ACEI	129 (59.4)	140 (42)	<0.001
	Angiotensin II receptor antagonist	49 (22.6)	84 (25.2)	0.51

Table 1. Characteristics of Patients According to Cardiac Event or No Cardiac Event continued.				
	Aspirin	147 (67.7)	191 (57.4)	0.01
	Beta Blockers	108 (49.8)	160 (48)	0.63
	Calcium antagonists	82 (37.8)	134 (40.2)	0.66
	Diuretic	89 (41)	122 (36.6)	0.27
	Lipid-lowering agents	121 (55.8)	180 (54.1)	0.01
	Nitrates	34 (15.7)	54 (16.2)	0.89
	Warfarin	23 (10.6)	42 (12.6)	0.56
Baseline Echocardiography Data				
	LVESD (cm)	3.3±0.9	2.7±0.7	0.01
	LVEDD (cm)	5.1±1.2	4.5±0.9	0.01
	LVEF (%)	52.3±11.6	55.5±8.5	<0.001
	Maximal LVEDD WT (cm)	1.25±0.54	1.22±0.61	0.30
	LA size (mm)	44±12	42±15	0.10
	Mitral E/A	1.12±0.61	1.08±0.53	0.60
	Mitral E Deceleration (ms)	223±98	206±62	0.30
	Mitral E/Ea	13.2±5.9	12.6±4.3	0.70
	Mitral Annular Calcification	13 (6)	32 (9.6)	0.14
	Mitral Regurgitation	57 (26.3)	60 (18)	0.02
	Mild Mitral Regurgitation	40 (18.4)	51 (15.3)	0.34
	Moderate Mitral Regurgitation	22 (10.1)	4 (1.2)	<0.001
	Aortic Stenosis	15 (6.9)	14 (4.2)	0.30
	Mild Aortic Stenosis	11 (5.1)	10 (3)	0.30
	Moderate Aortic Stenosis	4 (1.8)	4 (1.2)	0.61
	Aortic Regurgitation	11 (11.5)	24 (3)	0.20
	Mild Aortic Regurgitation	9 (4.1)	20 (6)	0.23
	Moderate Aortic Regurgitation	2 (0.9)	4 (1.2)	0.66
Dobutamine stress echocardiography test				
	Baseline heart rate ($b \cdot min^{-1}$)	69.5±14.3	71.4±13.3	0.11
	Peak heart rate ($b \cdot min^{-1}$)	127±20.8	131±19.2	0.02
	Target heart rate achieved	167 (77)	282 (84.7)	0.18
	Baseline sBP (mmHg)	139±26.6	136±25	0.31
	Peak sBP (mmHg)	146±31.2	143±31.6	0.28
	Baseline dBP (mmHg)	67.8±16.3	67±15.8	0.71
	Peak dBP (mmHg)	70.5±16.3	67.9±16.1	<0.01
	Resting wall motion score index	1.11±0.18	1.05±0.13	<0.001
	Peak wall motion score index	1.2±0.2	1.1±0.16	<0.001
	Fixed wall motion abnormality	90 (41.5)	74 (22.2)	<0.001
	New wall motion abnormality	111 (51.2)	72 (21.6)	<0.001
Number of ischaemic LV segments				<0.001
	0 LV segments	104 (47.9)	263 (79)	
	1-3 LV segments	76 (35)	61 (18.3)	
	>3 LV segments	37 (17.1)	9 (2.7)	

Note: Values are mean ± SD or n (%); CVD = cardiovascular disease; PCI = percutaneous coronary intervention; CABGS = coronary artery bypass graft surgery; ACEI = angiotensin converting enzyme inhibitor; LVESD = left ventricular end systolic diameter; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; Maximal LVEDD WT = maximal left ventricular end diastolic diameter wall thickness; LA = left atrial; sBP = systolic blood pressure; dBP = diastolic blood pressure; LV = left ventricle.

In unadjusted analysis, several echocardiographic parameters were associated with cardiac events (Table 1) including several measures of ischaemia (resting and peak WMSI, new WMA, fixed WMA, and the number of ischaemic LV segments; all $p<0.001$). Table 2 illustrates the differences between 3-groups according to the ischaemic burden on DSE (none, 1-3 ischaemic LV segments, and >3 ischaemic LV segments). Use of medications was broadly similar across groups and only varied significantly with respect to use of calcium antagonists and warfarin. Of the other demographics, hypertension, hypercholesterolaemia, smoking history and previous coronary artery bypass graft surgery significantly differed between the groups. The Kaplan-Meier curves for the cumulative survival and freedom from cardiac events are presented in Figure 2 dichotomized according to myocardial ischaemia (A), number of ischaemic LV segments (B) and ischaemic patients with or without subsequent cardiac revascularization (C). The cardiac event rate for patients with a normal DSE study was 13% per year, increasing to 26% for patients with resting WMA's, 28% for ischaemic patients and highest amongst those with ischaemia and resting WMA's (32% per year). In further analysis, the cardiac event rate was 26% per year for those with 1-3 ischaemic LV segments and highest among those with >3 ischaemic LV segments (38% per year). A positive DSE was associated with 13 extra cardiac events per 100 person years of follow-up. The event rate for ischaemic patients who did not undergo coronary revascularization was 24.4% per year compared to an event rate of 34.8% per year in those who underwent coronary revascularization. In those patients without ischaemia on DSE and who had cardiac events during follow-up, the baseline LVEF and proportion with a history of previous MI was not significantly different to those with no ischaemia and no cardiac events.

Table 2. Selected Characteristics of the Population According to the number of Ischaemic LV Segments.

Characteristics			Number of Ischaemic LV Segments			
			0 segments (n=367)	1-3 Segments (n=137)	>3 segment (n=46)	P Value
Demographics						
	Age, yrs		82.5±2.3	83.6±2.3	83.7±2.4	0.90
	Men		179 (48.8)	81 (59.1)	27 (58.7)	0.06
History						
	Hypertension		228 (62.1)	101 (73.7)	36 (78.3)	0.01
	Diabetes mellitus		71 (19.3)	39 (28.5)	12 (26.1)	0.09
	Hypercholesterolaemia		184 (50.1)	90 (65.7)	21 (45.7)	0.01
	Family history of CVD		31 (8.4)	19 (13.9)	3 (6.5)	0.10
	Prior myocardial infarction		47 (12.8)	26 (19)	6 (13)	0.30
	PCI		90 (24.5)	40 (29.2)	11 (23.9)	0.58
	CABGS		50 (13.6)	36 (26.3)	6 (13)	<0.01
	Smoking history					0.02
		Never smoked	298 (81.2)	97 (70.8)	30 (65.2)	
		Ex-smoker	64 (17.4)	37 (27)	16 (34.8)	
		Current smoker	5 (1.4)	3 (2.2)	0 (0)	
Canadian Cardiovascular Society angina classification						0.56
	Class I		153 (41.7)	55 (40.1)	21 (45.7)	
	Class II		176 (48)	71 (51.8)	19 (41.3)	
	Class III		38 (10.4)	11 (8)	6 (13)	
Long term cardiac medication						
	ACEI		169 (46)	79 (57.7)	21 (45.7)	0.08
	Angiotensin II receptor antagonist		88 (24)	32 (23.4)	13 (28.3)	0.68
	Aspirin		216 (58.9)	96 (70.1)	26 (56.5)	0.08
	Beta Blockers		171 (46.6)	75 (54.7)	22 (47.8)	0.28
	Calcium antagonists		161 (43.9)	42 (30.7)	13 (28.3)	0.01
	Diuretic		134 (36.5)	58 (42.3)	19 (41.3)	0.41
	Lipid-lowering agents		200 (54.5)	74 (54)	27 (58.7)	0.65
	Nitrates		51 (13.9)	26 (19)	11 (23.9)	0.09
	Warfarin		32 (8.7)	26 (19)	7 (15.2)	<0.01

Note: Values are mean ± SD or n (%); LV = left ventricular; CVD = cardiovascular disease; PCI = percutaneous coronary intervention; CABGS = coronary artery bypass graft surgery; ACEI = angiotensin converting enzyme inhibitor.

Following multivariable adjustment (Table 3), ischaemia parameters significantly associated with risk were new WMA (HR 1.6; 95% CI, 1.02–1.61), peak WMSI (HR 3.6; 95% CI, 1.75–6.77) and the number of ischaemic LV segments (HR for 1-3 ischaemic LV segments was 1.34; 95% CI, 1.13–1.29; and HR for >3 ischaemic LV segments was 1.86; 95% CI, 1.16–2.98). In addition, peak diastolic blood pressure was also independently associated with risk of cardiac

events (HR 1.98; 95% CI, 1.97–1.99). The C statistic for the basic model without DSE parameters was 0.77, which improved significantly to 0.89 (p<0.001) indicating an improvement in discrimination.

Table 3. Multivariate Predictors of Cardiac Events.

Characteristics		Hazard Ratio (95% CI)	P Value
Demographics			
	Age, y	0.99 (0.96 - 1.03)	0.66
	Gender	1.21 (0.97 - 1.76)	0.08
History			
	Hypertension	0.96 (0.45 - 2.02)	0.82
	Diabetes mellitus	0.84 (0.62 - 1.13)	0.25
	Hypercholesterolaemia	0.98 (0.95 - 1.03)	0.59
	Prior myocardial infarction	1.32 (0.54 - 3.21)	0.67
	PCI	1.12 (0.55 - 2.28)	0.73
	CABGS	1.01 (1.00 - 1.01)	0.19
	Smoking history		0.21
	Never smoked	1 (Reference)	
	Ex-smoker	1.56 (0.41 -1.77)	
	Current smoker	1.75 (0.73 - 4.22)	
Long term cardiac medication			
	ACEI	1.04 (0.99 - 1.11)	0.09
	Angiotensin II receptor antagonist	0.87 (0.60 - 1.26)	0.45
	Aspirin	0.98 (0.97 - 1.01)	0.53
	Beta Blocker	1.06 (0.80 -1.39)	0.68
	Calcium Antagonists	0.94 (0.71 - 1.25)	0.69
	Diuretic	1.20 (0.88 - 1.63)	0.26
	Lipid-lowering agents	0.99 (0.98 - 1.00)	0.11
	Nitrates	0.84 (0.54 -1.28)	0.41
Baseline Echocardiography Data			
	LVESD (cm)	0.97 (0.77 - 1.20)	0.66
	LVEDD (cm)	0.97 (0.74 - 1.31)	0.69
	LVEF (%)	1.40 (0.99 - 4.01)	0.07
	Mitral Regurgitation	1.69 (0.73 - 3.92)	0.09
Dobutamine stress echocardiography test			
	Peak heart rate ($b \cdot min^{-1}$)	1.13 (0.59 - 2.75)	0.41
	Peak dBP (mmHg)	1.98 (1.97 - 1.99)	0.01
	Resting wall motion score index	1.11 (0.62 - 2.61)	0.07
	Peak wall motion score index	3.60 (1.75 - 6.77)	<0.001
	Fixed wall motion abnormality	2.31 (0.99 - 5.32)	0.6
	New wall motion abnormality	1.60 (1.02 - 1.61)	<0.01
Number of ischaemic LV segments			<0.001
	0 LV segments	1 (Reference)	
	1-3 LV segments	1.34 (1.13 - 1.29)	
	>3 LV segments	1.86 (1.16 - 2.98)	

Note: CI denotes confidence interval; PCI = percutaneous coronary intervention; CABGS = coronary artery bypass graft surgery, ACEI = angiotensin converting enzyme inhibitor; LVESD = left ventricular end systolic diameter;

LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; dBP = diastolic blood pressure; LV = left ventricle.

When the components of the composite endpoint were further evaluated, we found that after multivariable adjustment, the only DSE parameters associated with cardiac death were LV ejection fraction (HR 1.21; 95% CI, 1.13–8.64; p=0.03) and mitral regurgitation (HR 1.3; 95% CI, 1.27–1.93; p=0.03). The C statistic for this basic model without DSE parameters was 0.74 improving to 0.77 after the addition of DSE findings (p=0.34). When the endpoint of NFMI was assessed in multivariable models the parameters associated with NFMI were new WMA (HR 2.77; 95% CI, 1.32–5.9; p=0.01) and the number of ischaemic LV segments (HR for 1-3 ischaemic LV segments was 1.31; 95% CI, 1.14–1.41; for patients with >3 ischaemic LV segments the HR was 1.73; 95% CI, 1.27– 1.76; p<0.001). The C statistic for this basic model without DSE parameters was 0.76 improving to 0.83 after the addition of DSE findings (p<0.001).

After multivariable adjustment, DSE parameters significantly associated with all-cause mortality were, LV ejection fraction (HR 1.13; 95% CI, 1.04–2.31; p=0.03) and fixed WMA's (HR 1.08; 95% CI, 1.02–1.81; p=0.02). The presence of ischaemia however was not significantly associated with all cause mortality. The C statistic for this basic model without DSE parameters was 0.56 improving to 0.71 after the addition of DSE findings (p=0.02).

DISCUSSION

Prior studies of DSE in octogenarians have reported on a total of 88 (14.7% of total combined population) cardiovascular events.[15, 16] This is largest study to date assessing the safety and prognostic utility of DSE among octogenarian patients (average age 84±3.7 years) reporting on 217 (39.5%) events, which increases the evidence base 2.5 fold. Of note prior studies evaluating the role of DSE with known or suspected CAD have largely excluded subjects greater than 80 years of age.[8, 17, 18] Importantly, DSE was safe in this older population with no serious adverse complications. The procedure was well tolerated with only 12 (2.2%) patients experiencing dobutamine induced atrial fibrillation and 1-patient (0.2%) experiencing non-sustained ventricular tachycardia. None of the patients required intravenous beta-blocker to reverse the effects of dobutamine or treat arrhythmias. The sensitivity, specificity, positive and negative predictive values of DSE in detecting significant CAD were 93%, 86.5%, 90.7%, and 89.7% respectively, suggesting that DSE is a robust non-invasive test for CAD among octogenarians. However, it must be noted that coronary angiography was based on clinical decisions and not performed on all patients, which may impact the predictive value of DSE in this study.

Importantly, ischaemia was a strong and independent predictor of cardiac events. The risk of cardiac events was associated with the burden of ischaemia, as assessed by peak WMSI and the number of ischaemic segments during DSE, with event rates increasing from 13% per year, for those with no ischaemic segments to 26% per year for 1-3 segments and highest among those with >3 segments (38% per year). These event rates are higher than reported for DSE in younger

populations, reflecting the fact that these octogenarian patients are high risk. In relative terms, those subjects with the greatest ischaemic burden (>3 ischaemic segments) were at 86% increased risk compared to those without any ischaemia. The addition of DSE to models for risk prediction increased the C statistic from 0.77 to 0.89, an order of magnitude that is considerably greater than that achieved by most blood based biomarkers in general populations and comparable to that observed with coronary calcium scoring in younger populations.[19] Peak dBP was an independent predictor of cardiac events, in keeping with prior work [20] and LV ejection fraction predicted total and cardiac mortality but not NFMI. In our analysis, non-viable myocardium was only a univariate predictor of cardiac events.

The overall cardiac event rate was 39.5% over a mean follow-up of 2.14 years, representing an event rate of 18.4% per year. This is much higher than that documented in younger patients,[8] demonstrating the very high morbidity and mortality of this patient group and the potential unmet clinical need for tests which can safely provide a clinical diagnosis of CAD and improve risk prediction. In the present study the prognostic utility of a positive DSE was largely driven by its association with NFMI rather than death from cardiac causes. This may reflect in part the relatively fewer cardiac deaths (n=46) recorded compared to NFMI (n=171) resulting in less power. Additionally, ischaemia on DSE is more likely to be associated with coronary deaths rather than non-coronary or “other” cardiac deaths (arrhythmias, heart failure). The relative contributions of other types of cardiac death to overall cardiac deaths was unavailable in the present study and the use of cardiac rather than coronary death may have diluted any potential association between ischaemia on DSE and coronary death. In future, further studies with a larger sample size and a greater number with cardiac deaths should explore this relationship

further to more reliably assess any potential association. Cardiac event rate in patients with a normal DSE result was higher than studies in younger patients, suggesting that the octogenarians referred for DSE were a sicker patient group. Despite this and in contrast to younger patients [8, 21], ischaemia on DSE did not predict total mortality among octogenarians but rather non-fatal coronary events.

While coronary angiography remains the gold standard for CAD diagnosis, a number of investigations are available for risk stratifying patients with CAD. Few studies have assessed the effectiveness of these tools in octogenarians. Exercise treadmill testing is safe with no major complications in carefully selected octogenarians,[22] but is impractical for patients with poor mobility. Myocardial perfusion imaging [23] is both feasible and predicts outcome as shown in a study of 162 octogenarians. In a healthier and more selected cohort of octogenarians, DSE successfully risk stratified patients, but this was based on only 54 events (16%).[15] Additionally, one-third of patients performed exercise stress echocardiography suggesting a better functional capacity and the ability of DSE to improve prediction over conventional parameters was not reported. In a recent meta-analysis of 13,304 patients, Rai et al [24] demonstrated that stress myocardial perfusion imaging and stress echocardiography accurately predicted cardiac events, whereas exercise treadmill alone did not. However, the age cut off for this population was >65 years. Therefore, the present study extends the results of prior studies and supports the prognostic role of DSE in octogenarians with suspected angina.

The clinical management of older patients with ischaemic heart disease is a double-edged sword as both the risk of cardiac events and the risk of complications from invasive tests and

revascularization are high. For instance, for elective percutaneous coronary intervention procedures, octogenarian mortality varied nearly 10-fold compared to younger counterparts, which was strongly influenced by co-morbidities.[4] Moreover, there was a two to fourfold higher risk and 5-9% lower procedural success compared to younger patients.[4, 25] Given the risks of an invasive strategy in an otherwise stable cohort in an outpatient setting, the present study demonstrates that DSE has a high accuracy for diagnosing CAD as well as predicting future cardiac events. Interestingly, in the present study use of revascularization for those with significant ischaemia on DSE was not associated with a lower risk of subsequent clinical events, in keeping with data from randomised trials such as COURAGE or meta-analyses.[26, 27] Furthermore, use of evidence-based treatments was similar in those patients with low and high ischaemic burden. Taken together, the data suggest that while ischaemia on DSE identifies a high-risk group, it may not be useful by itself for guiding a revascularization strategy, similar to recent findings.[28] Indeed, such elderly patients may benefit from optimal medical treatment rather than percutaneous coronary intervention.[29] Nevertheless, risk stratification following DSE might help clinicians optimise medical management for symptom relief and perhaps improve the intensity of cardiovascular risk factor control as a potential means to reduce CVD risk in line with clinical trials, as the elderly often get less evidence based care. The follow-up trial to COURAGE is assessing revascularization vs medical therapy based on ischaemic burden [13] and it will be interesting to see whether the observational data reported here are replicated in a trial setting among older patients with respect to event rates and lack of benefit from revascularization.

Limitations

This is an observational study from a single centre. Patients recruited into our study were referred for a clinically indicated DSE and there is the potential for referral bias and high pre-test probability related to a higher prevalence of co-morbidities and symptoms. The proportion with atrial fibrillation, pacemaker implantation and left bundle branch block was also low. These abnormalities are known to reduce the sensitivity of DSE. Coronary angiography was only performed in about a third of people with negative DSE, so the false negative rate for CAD is unclear. While the present data may not be applicable to general unselected populations it does provide "real world" clinical information, suggesting that those with a negative DSE are at a relatively low risk of future cardiac events. While we had detailed medical and echocardiographic records and adjusted for a number of variables, we cannot exclude the possibility of residual confounding despite multivariable adjustment. Furthermore, medication listed refers to treatment at time of DSE and changes in medication over the follow-up period were not taken into account. Notwithstanding these limitations, the present study is consistent with earlier work and extends our knowledge of elderly populations.

Conclusion

DSE is safe and well tolerated among octogenarians with a high positive predictive power for diagnosing CAD and similar to those reported in younger patients. A positive DSE result improves risk prediction and in particular ischaemic burden appears to be a strong and independent predictor of cardiac events.

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Figure legends

Figure 1: Study flow diagram.

Figure 2: Kaplan-Meier hazard curves for the cumulative survival and freedom from cardiac events.

Kaplan-Meier hazard curves dichotomized according to myocardial ischaemia (A), number of ischaemic LV segments (B), and ischaemic patients with and without subsequent cardiac revascularization (C).