Coronary artery disease

ORIGINAL ARTICLE

The clinical efficacy and long-term prognostic value of stress echocardiography in octogenarians

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ABSTRACT

Introduction  Although stress echocardiography (SE) is invaluable in younger populations, its prognostic value may be attenuated in the elderly due to shorter life expectancy and the frequent presence of severe comorbidities. This study sought to evaluate the clinical effectiveness of SE in octogenarians, particularly its prognostic value over clinical variables, in predicting hard events.

Methods  A total of 374 consecutive octogenarians who underwent SE for evaluation of coronary artery disease (CAD) were assessed for feasibility, diagnostic accuracy and safety of the test, and followed up for hard outcomes (all-cause mortality, cardiovascular (CV) deaths and non-fatal myocardial infarction (NFMII)). Cox regression analysis was performed to identify predictors of outcome.

Results  Of the 374 tests, 360 (96.3%) were diagnostic. Of the 50 patients with inducible ischaemia, 33 patients (66%) proceeded to angiography of which 27 (82%) patients had significant CAD. During long-term follow-up of 4.0±2.0 years, there were 127 deaths and 36 NFMIs. The annualised mortality, NFMII and combined mortality/NFMII rates were 8.1%, 1.8% and 9.4% for patients with a normal SE and 12.1%, 5.5% and 14.1% for those with an abnormal SE, respectively. Predictors of NFMII on multivariate analysis were prior CAD (HR 2.89, CI 1.03 to 8.15, p=0.045), peripheral vascular disease (HR 3.33, CI 1.18 to 9.45, p=0.02), and inducible ischaemia (HR 3.97, CI 1.49 to 10.55, p=0.006). In patients without prior history of CAD, inducible ischaemia was the only independent predictor of NFMII (HR 8.72, CI 1.46 to 52.2, p=0.018). The larger the extent of ischaemia, the greater the incidence of NFMII. The independent predictors of CV events (NFMII or CV mortality) were PAD (HR 2.81, CI 1.21 to 6.52, p=0.016) and peak wall motion score index (HR 5.71, CI 1.67 to 19.6, p=0.006). Although inducible ischaemia predicted all-cause mortality on unadjusted analysis, it did not on multivariate analysis.

Conclusions  In octogenarians, SE demonstrated excellent feasibility, safety and diagnostic accuracy. SE parameters were independent predictors of NFMII and CV events, and the presence of inducible ischaemia was associated with a 50% increase in all-cause mortality.

INTRODUCTION

Coronary artery disease (CAD) represents a major burden of chronic illness in the elderly population. The prevalence and severity of CAD increases markedly with age and is the leading cause of mortality and morbidity.1 In the USA and EU, although patients aged 80 years or above comprise 5% of the population, 20% of myocardial infarctions (MI) and one third of MI fatalities occur in octogenarians.2

Given the impact of CAD, and the higher complication rate of invasive angiography in the elderly,3 safe and robust non-invasive testing is essential to guide decision-making. Stress echocardiography (SE) is well established in various settings with clear prognostic value,4,5 and with recent advances in harmonic imaging and newer contrast agents, it remains a cornerstone of clinical practice.

There are several challenges to non-invasive testing in octogenarians. The limited life expectancy and the prevalence of severe comorbidities may potentially negate the benign prognosis associated with a negative test seen in younger populations. Drug intolerances, restricted exercise capacity and comorbidities may also impact on the feasibility of functional testing. Resting wall motion abnormalities occur in up to one third of elderly patients,6 and require more advanced testing protocols and experienced operators and interpretation.

Previous studies of SE in octogenarians have been limited by modest event rates and short follow-up duration.8,9 Diagnostic techniques must be rigorously assessed against long-term outcomes in order to forecast future health care costs and plan resource allocation. The role of this study was to evaluate the feasibility, safety, diagnostic accuracy and prognostic value of SE in octogenarians during long-term follow-up.

METHODS

Consecutive patients aged 80 years or above from two centres undergoing SE for the evaluation of known or suspected CAD between April 2007 and April 2013 formed the study population. Exclusion criteria included patients referred for viability assessment only, severe valvular disease and cardiomyopathy. The study was approved by the institutional review board. Clinical characteristics and follow-up data were collated by reviewing hospital records, contacting patients or a family member, and contacting general practitioners. A national mortality database was used to identify deceased patients. The date of the last review or consultation was used to calculate the duration of follow-up up to 1 January 2016.

Stress echocardiography

All SE studies were performed using either treadmill exercise or pharmacological (dobutamine-atropine)
stress as we have previously described. In summary, exercise stress was the preferred modality, and in patients unsuitable for exercise, dobutamine was infused in 3 min dose increments, starting from 10 μg/kg/min and increasing to 20, 30 and 40 μg/kg/min if there were no resting wall motion abnormalities, otherwise a viability protocol was used commencing at 5 μg/kg/min. Parasternal long axis, short axis and apical 4-chamber, 2-chamber and 3-chamber images were obtained at rest and peak stress (IE33 Philips Medical Systems, Eindhoven, the Netherlands). In patients in whom the endocardial borders of ≥2 contiguous segments were not visualised, the ultrasound contrast agent Sonovue (Bracco, Milan, Italy) was given by intravenous bolus injection (0.3 mL) and flushed with saline. SE was performed by multiple operators (n = 12) but the final result was based on the interpretation of the expert cardiologist (RS) who reported all SEs at both sites.

The SEs were reported as normal (normal wall thickening at rest and stress), abnormal ischaemic (inducible wall thickening abnormality in more than one segment at peak stress or presence of biphasic response in patients with resting wall thickening abnormalities during low and high doses of dobutamine), or abnormal non-ischaemic (which included patients with resting wall thickening abnormality in more than one segment with no change or improvement during stress). SE was considered inconclusive when terminated before target heart rate was achieved (eg, side effects from dobutamine or maximum dose of dobutamine-atropine given) or when images were uninterpretable.

**Endpoint definition**

The principal endpoints of interest for this analysis were death from any cause, cardiovascular (CV) death (due to MI, cardiac arrhythmias or heart failure) and non-fatal MI (NFMI), with patients censored at the time of event or at the last follow-up. NFMI was defined by the standard criteria of ischaemic chest pain associated with an elevation of cardiac enzymes with or without electrocardiographic changes. For patients with multiple events, only the first event was considered.

**Management after SE**

Patients with a normal SE were discharged. Patients with an abnormal SE were managed by the attending cardiologist, who was responsible for decisions on coronary angiography and revascularisation. At angiography, significant CAD was defined as ≥50% narrowing in ≥1 of the 3 epicardial coronary arteries or their major branches.11

**STATISTICS**

Categorical variables are expressed as percentages and continuous variables as mean±SD. Categorical variables were compared by use of the χ² test. Cox regression analysis was performed to assess the prognostic impact of clinical variables and SE parameters on the time to a hard event. Patients without a hard event were censored at the time of last follow-up. Both univariable and multivariable regression analyses were performed. Only those variables with a value of p < 0.2 in the univariable analysis were entered into the multivariable model. For all tests, a value of p < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS V23.0 (IBM Corp, Armonk, New York, USA).

**RESULTS**

Table 1 illustrates the patient demography of the 374 patients who underwent SE. The mean age was 83.6±3.0 years and 173 (47%) patients were male. Chronic kidney disease (CKD), peripheral vascular disease (PVD), current AF and left bundle branch block (LBBB) occurred in 87 (23%), 38 (10%), 85 (23%) and 39 (10%) patients, respectively. The mean left ventricular ejection fraction (LVEF) was 53±6% with 44 (12%) patients demonstrating LV dysfunction (LVEF <50%). An abnormal ischaemic and abnormal non-ischaemic SE was present in 50 (13%) and 63 (17%) patients, respectively. The characteristics of patients with normal and abnormal SE are shown in table 2.

**Feasibility of SE**

Of 374 octogenarians who underwent SE, 343 (92%) patients underwent dobutamine SE with the remainder undergoing exercise SE. Nearly two thirds of patients (65%) received contrast...
Diagnostic value of SE

The diagnostic value of SE was assessed in the 360 patients with conclusive studies. Of the 50 patients with inducible ischaemia, 33 patients (66%) proceeded to angiography of which 27 (82%) patients had significant CAD; 4 patients had 3-vessel, 10 had 2-vessel and 13 had single-vessel disease. The positive predictive value for flow-limiting CAD was 82%. Of the 33 patients with inducible ischaemia who underwent angiography, 16 (48.5%) underwent early revascularisation, within 6 months of the SE.

Safety of SE

In this high-risk population where 45% had a history of CAD, 63 patients (17%) demonstrated resting WMA, 44 patients (12%) had LVEF<50% and 92% underwent dobutamine SE with contrast agent usage in 65%, there were no major complications during SE. Specifically, no patients developed serious ventricular arrhythmias, acute MI or death.

Follow-up

Of the 360 patients with conclusive tests, 11 patients were lost to follow-up (see figure 1). A total of 349 patients were followed up for a mean interval of 4.0±2.0 years. In total, there were 127 (36%) deaths and 36 NFMI (10%). Table 2 shows that patients with a normal SE had significantly lower mortality, NFMI and combined mortality and NFMI than those with abnormal SE. The annualised mortality, NFMI and combined mortality/NFMI rates were 8.1%, 1.8% and 9.4% for patients with a normal SE and 12.1%, 5.5% and 14.1% for those with an abnormal SE, respectively. During follow-up, 34 (9.4%) patients underwent revascularisation. Of the 50 patients with myocardial ischaemia, 19 (38%) underwent revascularisation during the 4-year follow-up versus 15 (5%) out of 299 patients without myocardial ischaemia (p<0.0001).

Cox regression analyses were performed after excluding patients who underwent revascularisation (n=34), since revascularisation may influence outcomes, either positively if relieving myocardial ischaemia or negatively if the procedure results in an adverse event (eg, AMI or death). A total of 315 patients were entered into the analysis.

On univariate cox regression analysis, age, male gender, CKD, AF, LBBB, PVD, LVEF <50%, WMSIpeak WMSIrest and the presence of inducible ischaemia all predicted all-cause mortality. However, on multivariate analysis, predictors of all-cause mortality were age (HR 1.11, CI 1.05 to 1.17, p=0.001), CKD (HR 1.48, CI 1.68 to 3.67, p<0.001) and AF (HR 1.78, CI 1.9 to 2.66, p=0.009) (see table 3).

Predictors of NFMI on multivariate analysis were prior CAD (HR 2.89, CI 1.03 to 8.15, p=0.045), PVD (HR 3.33, CI 1.18 to 9.45, p=0.02) and inducible ischaemia (HR 3.97, CI 1.49 to 10.55, p=0.006) (table 4). The larger the extent of ischaemia, the greater the incidence of MI. Figures 2 and 3 demonstrate the Kaplan-Meier curves for freedom from NFMI for the entire duration of follow-up (a) in the presence of myocardial ischaemia and (b) according to number of ischaemic segments. The presence of inducible ischaemia on SE was the strongest predictor of NFMI. When patients who underwent revascularisation were included in the analysis, the presence of inducible ischaemia was the only independent predictor of NFMI (HR 4.90, CI 2.45 to 9.82, p<0.001). Revascularisation did not influence outcome. When patients who underwent exercise SE were removed from the analysis, the findings were unchanged for the prediction of both all-cause mortality and NFMI.

Cox regression analysis was also performed on the 177(56%) patients without CAD. In this analysis, age (HR 1.15, CI 1.06 to 1.25, p=0.001), CKD (HR 2.72, CI 1.56 to 4.76, p=0.001), AF (HR 2.28, CI 1.36 to 3.84, p=0.002) and LV function (HR 2.41, CI 1.14 to 5.12, p=0.021) were independent predictors of mortality. Inducible ischaemia was the only independent predictor of NFMI (HR 8.72, CI 1.46 to 52.2, p=0.018).

Since a large number of patients would have suffered non-cardiac deaths, the analysis was repeated for CV events (the composite endpoint of NFMI and CV deaths). Cause of death was established in 93/110 (85%) patients of which CV death occurred in 21 patients. For the purposes of this analysis, the 17 patients with unknown cause were treated as non-CV deaths. Independent predictors of CV events were PVD (HR 2.81, CI 1.21 to 6.52, p=0.016) and WMSI (stress) (HR 5.71, CI 1.67 to 19.6, p=0.006).

DISCUSSION

This retrospective study has examined the clinical value of contemporary SE performed by multiple operators in octogenarians presenting for evaluation for CAD. Our results suggest that SE was safe and demonstrated excellent feasibility with a diagnostic test achieved in 96% of cases. Furthermore, patients who underwent coronary arteriography following demonstration of myocardial ischaemia showed obstructive CAD in over 80% of...
patients. An abnormal ischaemic SE predicted all-cause mortality on unadjusted analysis and was the strongest independent predictor of NFMI during long-term follow-up. WMSI (peak) was the strongest independent predictor of CV events. There was a 50% increase in mortality in patients with an abnormal SE, over patients with a normal SE.

Although the presence of inducible ischaemia and resting LV impairment were able to predict higher all-cause mortality, clinical and demographic variables were the only independent predictors of all-cause mortality. These findings are in contrast to SE studies performed in younger populations. Although CKD is highly prevalent in elderly populations (23% of our population) and forebodes worse outcomes, with predialysis patients having nine times higher death rates in comparison to population controls. This is the first study to report on CKD in this population. AF is likely to be a surrogate marker of more advanced structural heart disease including diastolic heart failure in the elderly, and is also a strong independent risk factor for stroke in octogenarians.

The presence of inducible ischaemia was the strongest independent predictor of NFMI with the burden of ischaemia correlating with event rate, but this relationship persisted during long-term follow-up. With many MIs occurring in patients who are elderly and patients aged 80 years or above accounting for one third of fatalities, the ability to predict MI is important for considering potentially prognostic therapies such as revascularisation and drug therapy. Although this study did not show any benefit in outcome following ischaemia-driven revascularisation, this is likely to be because only 40% of ischaemic patients underwent revascularisation.

The association between WMSI (peak) and CV events (NFMI and CV death) further extends the long-term prognostic value of SE in this population. Since the majority of CV deaths were due to fatal MI and ‘pump failure’ this association is not surprising since WMSI (peak) is a composite score dependent on resting LV function, and the presence of inducible ischaemia.

Comparison to previous studies
Contrary to prior studies in octogenarians, we have found that SE is able to risk stratify patients for all-cause mortality; although not independently. In view of the frequency and severity of other comorbid conditions in octogenarians, it was unsurprisingly not an independent predictor of all-cause mortality. However, since stress-induced ischaemia and resting LV function are markers of

Figure 1  Study flow diagram.
cardiac reserve, which is fundamentally important in critically unwell patients, they would intuitively contribute to non-cardiac deaths, which is why wall motion index at rest and with stress were associated with all-cause mortality. In line with previous studies, we have found that SE independently predicts NFMI, but our study extends the results of previous studies by demonstrating that it does so also in patients without prior CAD, and during long-term follow-up. Diagnostic techniques need to be rigorously assessed against long-term outcomes to forecast future healthcare costs and plan resource allocation.

The high frequency of current AF, CKD, LBBB and the low number of exercise echocardiograms performed suggest that our population was frailer with more concurrent medical conditions in comparison to previous studies. The high feasibility achieved, despite the presence of factors that may lower diagnostic yield (eg, AF, LBBB, previous bypass surgery), may be attributable to

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<th>Multivariable analysis</th>
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<td>HR 95% CI p Value</td>
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<td>Nitrate</td>
<td>1.12 0.74 to 1.70 0.58</td>
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CAD, coronary artery disease; CKD, chronic kidney disease.

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<td>WMSI (Peak)</td>
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<td>Nitrate</td>
<td>3.31 1.34 to 8.15 0.009</td>
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CAD, coronary artery disease; CKD, chronic kidney disease.
the use of contrast in two thirds of our patients. Previous studies have not commented on contrast use, which is associated with improved accuracy for the detection of CAD. In addition, other studies have used other pharmacological stressors (eg, dipyridamole) to assess wall motion.9

Clinical implications
As the average life expectancy continues to increase, patients aged 80 years or above will be encountered more frequently in clinical practice. We have demonstrated the excellent feasibility and safety of SE in octogenarians. Approximately 96% of patients had conclusive SE results, which is important since inconclusive tests result in additional investigations, which can affect morbidity and even mortality in this frail population, and also impact on downstream costs. In terms of safety, although 25% of patients had abnormal SE, no patients developed serious side effects. Our results also suggest that SE appropriately influences the use of coronary angiography and subsequent revascularisation. Of the 33 patients with inducible ischaemia that underwent angiography, flow-limiting CAD was present in over 80%. Almost 40% of patients with ischaemia demonstrated on SE underwent revascularisation compared with only 5% in the group with no inducible ischaemia (n=299) where angiography was not clinically indicated following the SE result.

Comparison with other modalities
Few non-invasive diagnostic techniques have been investigated in octogenarians. Although treadmill testing is safe in selected octogenarians,18 most are unable to exercise, and in our institution where exercise stress is the preferred modality, only 8% could exercise. Recently, the role of myocardial perfusion imaging in octogenarians able to undergo exercise testing was able to predict CV events and late revascularisation.19 Stress cardiovascular magnetic resonance is safe and feasible in the elderly population,20 but has not been evaluated in octogenarians specifically to our knowledge. CT coronary angiography (CTCA) is problematic in patients with AF, renal failure, those unable to hold their breath for >10 s and those with contraindications to β-blockers. The diagnostic accuracy for CTCA is reduced in the presence of significant coronary artery calcium, or coronary stents <3 mm in diameter. All of the above circumstances are far more common in the elderly.

Strengths and limitations
Our study is unique in several ways from previous studies. First, our study has examined hard outcomes during long-term follow-up, with over twice the average follow-up duration of other studies. The high number of events (10.4% per year) increases the statistical power of the study. Second, we have included common adversely prognostic clinical variables into our analysis, which were not examined in previous studies, and not the presence of inducible ischaemia in relative isolation. Third, there was high contrast usage in our study, and therefore image quality was inadequate in only four patients. This may explain the superior clinical capabilities of SE seen here. Fourth, SE was performed in this study by 12 different independent operators with excellent feasibility, suggesting that SE is a reproducible and reliable technique even in such a challenging population.

This is a retrospective study. Fifteen patients were lost to follow-up who may have experienced events that would have not been captured affecting the results. Additionally, there is a possibility of referral bias where some patients who are elderly may have undergone alternative functional testing or coronary angiography, and only patients that would benefit from SE investigation would be included. However, given the aforementioned frailty of our population, it is likely that any selection bias would have disadvantaged the performance of SE here.

CONCLUSION
SE had excellent safety and feasibility in the octogenarian population, and had excellent positive predictive value for flow-limiting CAD and influenced subsequent revascularisation. During long-term follow-up, SE parameters were the strongest independent predictors of NFMI and CV events, and an abnormal SE was associated with a 50% increase in mortality.
Coronary artery disease

Key messages

What is already known on this subject?
The prognostic value of stress echocardiography (SE) has been previously reported in large studies in younger populations. During short-term follow-up, SE in octogenarians predicts cardiac events.

What might this study add?
We have shown SE to be safe in octogenarians, with excellent feasibility and diagnostic accuracy for predicting flow-limiting coronary artery disease. During long-term follow-up, SE parameters independently predict non-fatal myocardial infarction and cardiovascular (CV) events, and are associated with increased all-cause mortality even in the presence of significant comorbidities. A higher ischaemic burden predicts worse outcomes. Diagnostic techniques need to be rigorously assessed against long-term outcomes to forecast future health care costs and plan resource allocation.

How might this impact on clinical practice?
In view of our findings, SE, which can be performed at the bedside, should be the first-line functional test in octogenarians due to excellent safety, feasibility and diagnostic accuracy. SE also identifies patients who are at high risk of hard events.

Contributors
RS and BNS conceived the idea for the study and AA wrote the rst draft of the manuscript, which was critically appraised and edited by all coauthors. RS is the corresponding author and guarantor.

Competing interests
Regarding conicts of interest, RS has previously received honoraria from Bracco (Milan, Italy) and Philips Healthcare (Eindhoven, Netherlands).

Ethics approval
Research & Development department London North West Hospitals NHS Trust.

Provenance and peer review
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