Echocardiographic Predictors of Late Mortality in Elderly Patients with Acute Coronary Syndromes

Avinoam Shiran MD, Salim Adawi MD, Idit Dobrecky-Mery MD, David A. Halon MB ChB and Basil S. Lewis MD FRCP

Department of Cardiovascular Medicine, Lady Davis Carmel Medical Center, Haifa, Israel
Affiliated to Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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Abstract

Background: Echocardiographic ventricular function predicts prognosis and guides management in patients with acute coronary syndromes. In elderly patients, interpretation of echocardiographic measurements may be difficult, especially regarding assessment of diastolic left ventricular function.

Objectives: To examine the usefulness of echocardiographic systolic and echocardiographic diastolic LV function measurements as predictors of long-term outcome in elderly patients with ACS.

Methods: We studied 142 consecutive elderly patients (≥ 70 years old, mean age 80 ± 6 years) with ACS who had an echocardiogram at the index hospitalization and were in sinus rhythm. LV ejection fraction and diastolic mitral inflow pattern were examined as predictors of survival and repeat hospitalization over a period of 18–24 months.

Results: During the 2 year mean follow-up period 35/142 patients died (25%). Survival was lower in patients with EF < 40% (n=42) as compared to EF ≥ 40% (n=100) (2 year survival rate 61% vs. 81%, *P* = 0.038). Patients with severe diastolic dysfunction (a restrictive LV filling pattern, n=7) had a lower survival rate than those without (43 vs. 76%, *P* = 0.009). The most powerful independent predictor of mortality was a restrictive filling pattern (hazard ratio 4.6, 95% confidence interval 1.6–13.5), followed by a clinical diagnosis of heart failure on admission and older age. Rate of survival free of repeat hospitalization was low (33% at 18 months) but repeat hospitalization was not predicted either by EF or by a restrictive filling pattern.

Conclusions: As in the young, echocardiographic measurements of systolic and diastolic LV function predicted long-term survival in elderly patients with ACS. A restrictive filling pattern was the strongest independent predictor of mortality.

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Elderly patients with acute coronary syndromes have a poor outcome and increased mortality [1]. The risk of percutaneous coronary intervention and coronary artery bypass surgery increases with age [2,3], and for this reason myocardial revascularization is performed less frequently in the elderly. While echocardiographic systolic and diastolic left ventricular function measurements predict outcome in patients with ischemic heart disease, acute myocardial infarction and congestive heart failure [4-7], there is little information regarding elderly patients, who have different baseline standards and norms regarding echocardiographic measurements. The purpose of this study was to examine echocardiographic measurements of systolic and diastolic LV function as predictors of outcome in elderly patients with ACS.

LV = left ventricular
ACS = acute coronary syndromes
EF = ejection fraction

Patients and Methods

Patient sample

Consecutive patients ≥ 70 years of age hospitalized during one calendar year with an admission diagnosis of ACS in the cardiology or internal medicine departments of a single medical center were entered into the Lady Davis Carmel Medical Center geriatric cardiovascular registry. The registry included 449 consecutive patients, and has been described in detail [8]. The diagnosis of ACS included all patients with acute or rapidly worsening symptoms thought to be due to coronary artery disease at the time of hospitalization and included patients with acute ST elevation myocardial infarction, non-ST elevation myocardial infarction, and patients with unstable angina. Myocardial infarction was diagnosed when total creatine phosphokinase was more than twice the upper limit of normal. Unstable angina was diagnosed when study criteria for myocardial infarction were lacking but patient complaints suggested ACS. In the majority of patients in whom unstable angina was diagnosed, total creatine phosphokinase was elevated to less than twice the normal rate, or there was historical or angiographic evidence of coronary artery disease (72 of 94, 77%). The present study included all 142 registry patients who had an echocardiogram performed during the index hospitalization and who were in sinus rhythm at that time (echo group).

Record was made of interventional procedures and in-hospital outcomes. Repeat hospitalization was assessed at 17 ± 4 months and survival at 24 ± 4 months. Survival status was obtained for all patients through government records or direct patient inquiry by a structured telephone interview. Repeat hospitalizations in internal medicine, cardiology or cardiac surgery departments were recorded from the administrative databases of health insurance funds. These databases included > 90% of all hospitalizations. Records of the repeat hospitalizations were reviewed, and the reason for the hospital admission recorded.

The study endpoints were the identification of echocardiographic univariate and multivariate predictors of 2 year survival and 1.5 year survival free of a repeat hospitalization.

Echocardiography

Echocardiography was performed 5 ± 5 days after admission using a commercially available echocardiograph (Sonos 2500 or Sonos 5500, Agilent Technologies, Palo Alto, CA, USA) and 2.5 MHZ or 1–3 MHZ broadband transducer. A complete echocardiographic study was performed using standard views and techniques. LV and left atrial dimensions were measured from two-dimensional images. Valvular stenosis and regurgitation was graded mild, moderate or severe using Doppler echocardiography. LVEF was visually estimated from multiple 2D views [9]. Transmitral pulsed-wave Doppler flow velocity was recorded from the apical four-chamber view. The sample volume was placed at the mitral valve tips with the ultrasound beam aligned with the mitral inflow, and peak E and A-wave velocities and E-wave deceleration time were recorded. Severe diastolic dysfunction (grade ≥ 3) was defined as restrictive filling pattern with E/A > 2 and deceleration time < 160 msec [10].

Statistical methods

Baseline characteristics in the two groups were examined and compared using 2 × 2 tables and chi-square tests for categorical variables and Student's *t*-test for continuous variables. Difference in time-to-event distributions was examined using Kaplan-Meier curves and tested using the log-rank test. Hazard ratios were estimated using the Cox proportional hazards model. Binary outcomes were examined by logistic regression. Results were summarized using hazard ratios and 95% confidence intervals. Independent predictors of outcome were sought using multivariate models including significant univariate predictors of outcome. A two-tailed probability of < 0.05 was considered statistically significant.

Results

Patient characteristics

Compared with the total registry, patients in the echo group (n=142) were older (mean age 80 ± 6 vs. 79 ± 6 years, $P = 0.01$), more likely to have heart failure (28% vs. 19%, $P = 0.035$) and infarction (34 vs. 19%, $P = 0.001$) during the index hospitalization, and left main or triple-vessel coronary artery disease (27% vs. 17%, $P = 0.008$). There was no difference in the prevalence of diabetes mellitus, systemic hypertension, serum cholesterol, or in the history of previous revascularization, previous cerebrovascular events or renal failure.

Echocardiographic predictors of survival

During the 2 year follow-up period 35 patients (25%) in the echo group died as compared to 105 (23%) in the total registry ($P = 0.8$). Patients who died had a lower EF than patients who survived (44 ± 15% vs. 53 ± 15%, $P = 0.006$) [Table 1]. Estimated 2 year survival was 61% for patients with EF < 40% vs. 81% for those with EF ≥ 40% ($P = 0.038$) [Figure 1A]. There was no significant difference between survivors and non-survivors with regard to LV or left atrial dimensions, LV wall thickness, presence of significant valve disease, or estimated systolic pulmonary artery pressure. There was no difference in E/A ratio or E-wave deceleration time between survivors and non-survivors. A restrictive filling pattern was relatively rare (5% of patients), but patients who died were more likely to have a restrictive filling pattern than patients who survived (11.4% vs. 2.9%, $P = 0.046$). Similarly, patients with severe diastolic dysfunction (a restrictive filling

Table 1. Echocardiographic predictors of survival

	Alive (n=107)	Dead (n=35)	*P*
Ejection fraction (%)	53 ± 15	44 ± 15	0.006
Peak E-wave velocity (cm/sec)	81 ± 31	88 ± 34	0.2
Peak A-wave velocity (cm/sec)	79 ± 23	84 ± 32	0.4
E/A ratio	1.09 ± 0.69	1.1 ± 0.74	0.7
E-wave deceleration time (msec)	237 ± 85	231 ± 79	0.7
Restrictive filling pattern	3/104 (2.9%)	4 (11.4%)	0.046
LVEDD (cm)	4.9 ± 0.7	4.9 ± 0.6	0.9
LVESD (cm)	3.4 ± 0.9	3.6 ± 0.9	0.3
Interventricular septum width (cm)	1.1 ± 0.2	1.1 ± 0.2	0.9
Posterior wall width (cm)	1.0 ± 0.2	1.0 ± 0.2	0.8
Left atrium diameter (cm)	4.2 ± 0.51	4.3 ± 0.5	0.2
Systolic pulmonary artery pressure (mmHg)	37 ± 10	41 ± 12	0.13
Aortic stenosis (moderate/severe)	8 (8%)	7 (20%)	0.09
Aortic regurgitation (moderate)	4 (4%)	3 (9%)	0.5
Mitral regurgitation (moderate/severe)	17 (16%)	11 (31%)	0.09
Tricuspid regurgitation (moderate)	9 (9%)	3 (9%)	1.0

LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter

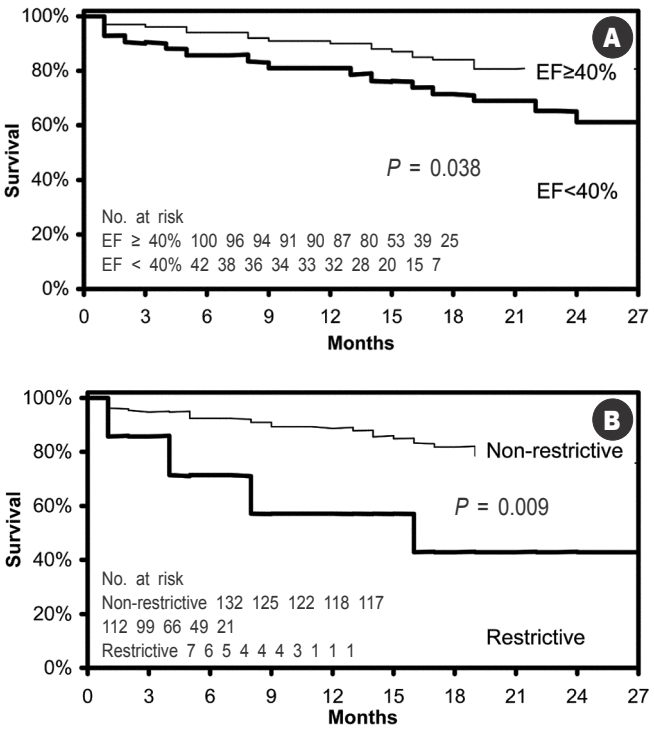

Figure 1. Survival of elderly patients with acute coronary syndrome and LVEF < or ≥ 40% **[A]**. Survival in relation to presence or absence of a restrictive filling pattern **[B]**.

pattern) had significantly worse survival than patients without (P = 0.009) [Figure 1B] (2 year survival estimates 43 vs. 76%). Most of the patients with a restrictive pattern were ≥ 80 years old (5/7) and had an LVEF ≤ 30% (5/7), whereas only one had acute Q-wave myocardial infarction at the index hospitalization. Two patients had undergone previous coronary artery bypass surgery. Coronary angiography was performed in two of the seven restrictive patients; both had triple-vessel disease and neither underwent revascularization.

A restrictive LV filling pattern remained a significant predictor of survival following adjustment for EF (P = 0.043). In a multivariate analysis that included also medical treatment at discharge (aspirin, beta-lockers, statins, diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) and hemoglobin on admission, the independent predictors of poor survival were restrictive filling pattern, heart failure on admission, and older age [Table 2].

Table 2. Independent predictors of mortality

	Hazard ratio	95% confidence interval
Restrictive filing pattern	4.6	1.6–13.5
Congestive heart failure on admission	2.9	1.5–5.8
Age*	1.06	1.0–1.13

* Hazard ratio per 1 year of age

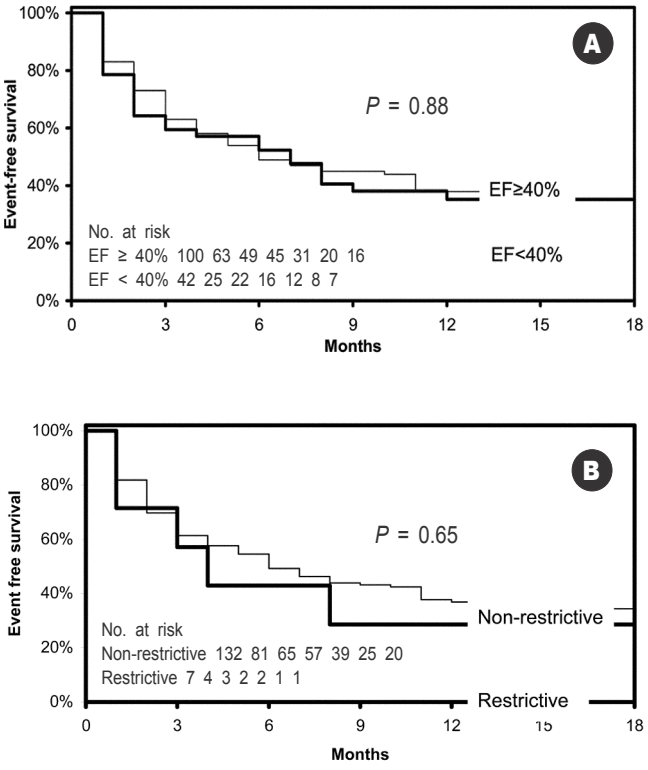

Figure 2. Survival free of repeat hospitalization in acute coronary syndrome and LVEF < or ≥ 40% **[A]**. Survival free of repeat hospitalization by presence or absence of restrictive filling pattern **[B]**.

Repeat hospitalization

Survival free of repeat hospitalization was low (33% at 18 months) [Figure 2]. Neither EF nor restrictive filling pattern predicted survival free of repeat hospitalization. Discharge diagnoses were available for 75/87 patients (86%) with repeat hospitalization during follow-up. The reason for repeat hospitalization was cardiac in 58 patients (77%) and non-cardiac in 17 (23%). Recurrent angina was the cause for readmission in 48/75 (64%) and heart failure in 19/75 (25%).

Coronary angiography and revascularization

Coronary angiography was performed during the index hospitalization in 60/142 patients (42%) and revascularization in 38 (27%); 21 had percutaneous coronary intervention and 17 coronary artery bypass surgery. Death or repeat hospitalization occurred in 39/60 patients (65%) who had coronary angiography (and revascularization if suitable) and 57/82 (70%) who were treated medically (P = NS). Patients were more likely to be referred for coronary angiography if they had EF < 40%, 23/42 (55%), compared to patients with EF ≥ 40%, 37/100 (37%) (P = 0.05). Revascularization was performed in 14/42 (33%) with EF < 40% and 24/100 (24%) with EF ≥ 40% (P = NS), and in none of the patients with a restrictive filling pattern.

Discussion

The study showed that in a cohort of consecutive elderly patients hospitalized with ACS, a restrictive filling pattern on echo, as well as a reduced LVEF, were significant and powerful predictors of mortality, as in the young. A restrictive filling pattern, although not a frequent finding, was the strongest independent predictor after adjustment for age, EF, and presence of clinical heart failure on admission. Tsang et al. [11] found that in an elderly population ≥ 65 years without a previous cardiovascular event, systolic and diastolic LV function, left atrial volume index and echocardiographic LV mass were independent predictors of first age-related cardiovascular events.

Echo assessment of diastolic function in the elderly

Cardiac aging is associated with myocyte hypertrophy, altered intracellular Ca^{2+} handling and interstitial matrix collagen deposition, leading to impaired LV relaxation and decreased LV compliance [12,13]. Mitral E/A ratio decreases with age and in the elderly is usually < 1 [14]. Elderly patients are therefore not expected to have normal diastolic function, and a mitral inflow pattern with 1 < E/A ratio < 2 would be expected to be pseudonormal (grade 2 diastolic dysfunction) rather than truly normal [10]. However, Arbab-Zadeh and colleagues [15] have shown that aging does not always lead to decreased LV compliance, which may be truly normal in healthy elderly athletes. In the present study, neither mitral E/A ratio nor early mitral deceleration time correlated with mortality. Newer techniques such as Doppler tissue imaging and color M-mode may better define diastolic function and LV filling pressure in elderly patients with preserved LV contraction and inconclusive echocardiograms (1 < E/A ratio < 2 but normal left atrial size, no LV hypertrophy and absence

of triphasic mitral inflow pattern), but these were not routinely recorded at the time the patients were included in this registry [16-18].

Other echocardiographic predictors

Left atrial size, a function of LV diastolic properties and LV filling pressure, has been shown to predict survival after acute myocardial infarction [19,20]. In our study left atrial diameter was increased but was similar in survivors and non-survivors [Table 2] and had no predictive value in elderly patients with ACS. Left atrial volume index rather than left atrial diameter might have been a better predictor of survival [20]. Left atrial size is a marker of chronic LV diastolic dysfunction, whereas a restrictive pattern of LV filling may better represent acute changes in left atrial pressure resulting from acute LV dysfunction in patients with ACS. It is possible that in our patient cohort, echocardiographic parameters more representative of the patients' acute ischemic status or subsequent decompensation were the dominant predictors of longer term survival. Other echocardiographic findings such as aortic stenosis and mitral regurgitation were not significant predictors of survival in this study, probably due to the limited size of the cohort.

Repeat hospitalization

Most repeat hospitalizations in this study were cardiac related and due particularly to recurrent episodes of angina pectoris. Neither systolic nor diastolic LV function predicted the combined event of death or repeat hospitalization, which was high in all subgroups. Only acute myocardial infarction on admission, prior functional capacity and diabetes mellitus were significant independent predictors of survival free of repeat hospitalization in the overall patient cohort [8]. Patients found to be at higher cardiac risk may do better with interventional therapy, but elderly patients are less likely to be treated according to current guidelines and to undergo revascularization; moreover, data from randomized trials comparing invasive and medical strategies for elderly patients with ACS are inconclusive [21-24]. Elderly patients with ACS should probably be considered for invasive procedures on an individual basis, and the present study shows that echocardiography may be a valuable tool in this regard.

Study limitations

Echocardiography was not performed routinely in all patients in the ACS registry. Patients referred for echocardiography were on average a year older and more likely to have recent acute myocardial infarction, heart failure and severe coronary artery disease. Although they appeared to be slightly sicker than other registry patients, mortality rates were similar. Patients with atrial fibrillation were excluded due to difficulty in analyzing diastolic function in this group. These patients probably have a worse outcome. Estimation of LVEF from multiple two-dimensional views is prone to viewer bias. Tissue Doppler imaging and color M-mode would better define diastolic function but were not used routinely at the time of the registry. Also, during the study period, troponin I or T measurements were not performed routinely in all patients. The use of troponin in the diagnosis and stratification of ACS would have altered the diagnosis of myocardial infarction [25].

Conclusions

Echocardiography is a valuable adjunctive tool for identifying high risk patients with ACS in the elderly age group, who may benefit from a more aggressive treatment and possible revascularization strategy.

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Correspondence: Dr. B.S. Lewis, Dept. of Cardiovascular Medicine, Lady Davis Carmel Medical Center, 7 Michal Street, Haifa 34362, Israel.
Phone: (972-4) 825-0288, Fax: (972-4) 834-3755
email: lewis@tx.technion.ac.il

Capsule

Reversal of Rett syndrome in mice

Rett syndrome is a rare genetic disease caused by a mutation in the X-linked gene *MECP2*, which causes mental retardation and autism-like symptoms in young girls. Guy et al. engineered mice with an inserted sequence in the *MECP2* gene that blocks its expression, and show that the mice exhibit many of the symptoms of Rett syndrome. Reactivation of *MECP2* in these mice before symptoms appear prevents disease. Reactivation in animals exhibiting Rett syndrome eliminated disease in both young adult males and mature females. Although such genetic manipulations are not possible in human patients, the apparent reversible nature of the disease suggests that therapy may be feasible.

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Eitan Israeli

Capsule

Axon regeneration

After an injury to its axon, a neuron must reorganize rapidly in order to establish a new growth cone at the tip of the transected segment. The growth cone can then search for and reestablish synaptic contacts, but the axon must supply the requisite materials to promote regrowth. By imaging cultured Aplysia neurons after axotomy, Erez and team followed the events by which axons establish new growth cones. Soon after an axon has been cut, the end of the portion still attached to the cell body partitions into two compartments. In the proximal region, vesicles can be observed en route to the plasma membrane from the Golgi complex; if the production of Golgi-derived vesicles is blocked, a new growth cone cannot be established. In the distal region, vesicles also accumulate, but these arise via the retrieval of membrane from the cell surface. What drives this traffic are the microtubules, which form the structural scaffold of the axon and rearrange to establish a region that segregates the two classes of vesicles. This process, which involves the reorientation of polarized microtubules, collects and concentrates the components needed to regenerate a motile growth cone.

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Eitan Israeli