



Longitudinal changes in cardiac function in the very elderly: the Jerusalem longitudinal cohort study

David Leibowitz^{1,2,#}, Irit Stessman-Lande², Hend Sliman², Jeremy M Jacobs^{1,3}, Jochanan Stessman^{1,3}, Dan Gilon²

¹Jerusalem Institute of Aging Research, Hadassah-Hebrew University Medical Center, Mount-Scopus, Jerusalem, Israel

²Coronary Care Unit, Hadassah-Hebrew University Medical Center, Mount-Scopus, Jerusalem, Israel

³Department of Geriatrics and Rehabilitation, Hadassah-Hebrew University Medical Center, Mount-Scopus, Jerusalem, Israel

Abstract

Background People over the age of 85 are a rapidly growing age group with a high incidence of congestive heart failure (CHF), in particular heart failure with preserved ejection fraction (HFpEF). The diagnosis of CHF is challenging and longitudinal data assessing cardiac structure and function are necessary to distinguish physiologic from pathologic cardiac aging. The objective of the study was to determine longitudinal changes in cardiac structure and function from ages 85 to 94 years using home echocardiography. **Methods** Subjects were recruited from the Jerusalem Longitudinal Cohort Study. Sixty three members of the initial cohort (32F, 31M) who underwent home echocardiography at age 85 were the subjects of the current study and underwent repeat home 2-D and Doppler echocardiographic assessment at age 94. **Results** There were no significant longitudinal changes in left ventricular mass index (LVMI), however LV end-diastolic volume significantly decreased from 113.4 ± 30 to 103.6 ± 35.5 mL ($P < 0.02$). Ejection fraction (EF) remained stable, however longitudinal systolic function significantly decreased with age from 7.9 ± 1.8 to 6.6 ± 1.4 cm/s² ($P < 0.0001$). Diastolic function as assessed by increased E: e' (11.2 ± 3.4 to 16 ± 7.5 , $P < 0.0001$) and increased left atrial volume index (34.1 ± 11.3 to 42.4 ± 13.7 mL/m², $P < 0.0001$) was reduced with aging. **Conclusions** This study demonstrated preserved EF with decreased longitudinal systolic function and diastolic function without significant change in LV mass. Changes in LV function in the very elderly may be independent of changes in LV geometry.

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1 Background

People over the age of 85 (the “oldest old”) are the world’s most rapidly growing age group.^[1] The aging of the population poses an increasing challenge for physicians treating congestive heart failure given the high frequency of congestive heart failure (CHF) in this population.^[2] Most patients with CHF are elderly with both incidence and prevalence of this disease increasing with age. Despite the rapid growth of this population and its high incidence of CHF, in particular heart failure with preserved ejection fraction (HFpEF), longitudinal data assessing cardiac structure and function in the very elderly are limited. Prospective longitudinal data are vital in this age group to

examine changes in cardiac structure and function in a community-based population and design diagnostic and therapeutic strategies to reduce cardiovascular morbidity. While age-related changes in cardiac structure and function including increased left ventricular (LV) mass, preserved systolic function and decreased diastolic function have been described, these studies that have included a broad range of ages with average ages of the samples generally remaining below 80 years of age.^[3–9] In addition, it remains unclear whether changes in LV systolic and diastolic function are secondary to changes in LV geometry or other causes.

Existing studies of cardiac function in the oldest old have been performed in the hospital or clinic setting, possibly contributing to a biased study population in this elderly age group as subjects find it harder to leave their homes.^[10] The introduction of portable echocardiography machines has made it possible to study patients in the home and therefore a more representative population of the oldest old. We have previously assessed cardiac function in a an age-homogenous, community-dwelling population at 85 years of age.^[11] The

#Correspondence to: David Leibowitz, MD, Coronary Care Unit, Hadassah-Hebrew University Medical Center, Mount-Scopus, Jerusalem 91240, Israel. E-mail: oleibo@hadassah.org.il

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aim of this study was to reassess cardiac structure and function and determine longitudinal changes in this unique population at age 94 years using home echocardiography.

2 Methods

Subjects were recruited from the Jerusalem Longitudinal Cohort Study that was initiated in 1990 and has followed an age homogenous cohort of West Jerusalem residents born between June 1920 and May 1921. The methodology has been described elsewhere in detail.^[12,13] The present study examines data from the third and fifth phases of data collection, which took place during 2005/2006 and 2015/2016. Subjects were interviewed and examined in their homes on two separate occasions, each session requiring the completion of a structured interview that lasted about an hour and a half. The institutional ethics committee of the Hadassah Hebrew University Medical Center approved the study design, and written informed consent was obtained from all participants.

Subjects identified from the electoral register were randomly chosen from the total sample of people born in 1920–1921 and living in Jerusalem in 2005. As reported previously, we performed an examination of death certificates and hospital admission records three years following the initiation of the study compared the study group to other subjects of the sample frame in Jerusalem who either refused or were not invited to enroll in the cohort study.^[12,13] Subjects of the study group, those who declined to participate and those baseline cohort members not enrolled had near identical mortality and disease specific hospital morbidity, thus demonstrating the representative nature of the initial study group in comparison to the total same age stratum of the Jerusalem population. Echocardiography was initially performed in 450 randomly selected subjects at ages 85 and repeated in surviving subjects at age 94. Exams at both time points were performed by the same sonographer and interpreted by the same physician (DL).

Diagnosis of ischemic heart disease was based on a history of hospitalization for myocardial infarction, or an acute coronary syndrome, coronary catheterization with evidence of significant coronary artery disease, a history typical for angina pectoris on exertion previous coronary revascularization. Hypertension was defined as treatment with antihypertensive medications or blood pressure higher than 140 mmHg systolic or 90 mmHg diastolic on exam. Hyperlipidemia was defined as use of cholesterol-lowering medications. Diabetes mellitus was a composite of hypoglycemic medications, personal history or a medical record diagnosis. Congestive heart failure and chronic renal failure

was based on hospital discharge diagnosis and according to examining research physician diagnosis at the time of examination at home. Body mass index was calculated and dichotomized to low ($\leq 25 \text{ kg/m}^2$) and high ($> 25 \text{ kg/m}^2$).

All subjects had standard 2-D and Doppler echocardiography at their place of residence with a portable echocardiograph (Vivid I, GE Healthcare, Haifa, Israel) and underwent 2-D and Doppler echocardiography with measurements of the interventricular septum, posterior wall, and LV end-systolic and end-diastolic diameters according to the recommendations of the European Association of Echocardiography/American Society of Echocardiography.^[14] Measurements were performed for three consecutive cardiac cycles and averaged. Subject height and weight at the time of the study were recorded and body surface area calculated. LV mass was calculated according to a necropsy validated formula of LV mass (g) = $0.8 \times (1.04 \times (\text{septal thickness} + \text{LV internal diameter} + \text{posterior wall thickness})^3 - (\text{LV internal diameter})^3 + 0.6)$ and indexed to body surface area.^[15] Given the high prevalence of basal septal hypertrophy in this population, septal thickness measurements were taken below the level of the basal septum. Upper septal hypertrophy was defined as upper septal thickness of $\geq 14 \text{ mm}$ with a ≥ 1.3 ratio between upper and mid septal thickness.^[16] Measurement of tricuspid regurgitation velocity was performed in standard fashion and converted to right ventricular to right atrial pressure gradient using the modified Bernoulli equation. Mitral annular calcification (MAC) was defined as an intense echodensity located at the junction of the atrioventricular groove and the posterior mitral leaflet with severe MAC defined as a maximal thickness of $> 4 \text{ mm}$.^[17] The maximal velocity across the aortic valve was measured with continuous Doppler from apical views. Aortic stenosis was defined as reduced systolic opening on 2D imaging with a velocity of at least 2.5 m/s across the valve.^[18]

Ejection fraction (EF) was calculated by averaging measurements of end-diastolic and end-systolic volumes from the apical 4-chamber and 2-chamber views using the Simpson's biplane method for three consecutive beats.^[14] In patients with atrial fibrillation, measurements were averaged for five consecutive beats. Normal systolic function was defined as ejection fraction $> 52\%$ in men and $> 54\%$ in women. In addition, peak systolic mitral annular function (s wave) was measured as an additional index of systolic function.

Diastolic parameters were measured from the apical 4-chamber view using pulsed-wave Doppler at the level of the mitral leaflet tips and tissue Doppler imaging of the septal and lateral myocardial walls and included early (E)

and late (A) transmitral flow velocities, the ratio of early to late velocities (E/A), deceleration time of E velocity and isovolumic relaxation time. Early (e') and late (a') diastolic mitral annular tissue velocities at both the septum and lateral walls were obtained and the ratio of E/e' using the average of septal and lateral tissue velocities obtained was calculated as an index of diastolic function.^[19] Normal E/e' was defined as ≤ 14 .^[19] Patients with atrial fibrillation were excluded from analyses of a wave velocities. Left atrium (LA) volumes were assessed by the biplane Simpson's method from apical views.

Descriptive statistics were performed and as the cardiac parameter data was normally distributed, results are described as means and standard deviations. Percentages were calculated as appropriate. For continuous variables differences between means were calculated using *t*-test and correlations coefficients and *P* values were performed as appropriate. Categorical variables were examined using McNemars tests. Linear regression multivariate models were performed to analyze the effect of different medical diagnoses at the age of 85 on changes in measurements of cardiac structure and function between the ages of 85 and 94. Reproducibility of measurements of ejection fraction was evaluated in a randomly selected subset of 20 subjects using a Bland-Altman plot. Mean difference was 3.2% with 95% limits of agreement of (-3/7-1/0.1). All *P* values were 2-tailed and *P* < 0.05 was considered significant. The data storage and analysis was performed using SAS version 9.1e (SAS Institute, Inc., Cary, NC).

3 Results

Of the 450 subjects in the initial cohort at age 85-86, 298 were deceased at the time of follow-up at age 94. An additional 89 subjects could not be included for logistical reasons (refused, lost to follow-up, unable to give consent, etc). Therefore, the study population included 63 patients (32 F, 31 M) who underwent home echocardiography at ages 85 and 94. Clinical characteristics of the study cohort at ages 85 and 94 are depicted in Table 1. Absolute echocardiographic measurements at both time points as well as the degree of change are shown in Table 2. There were no significant longitudinal changes in septal or posterior wall thickness or in left ventricular mass index (LVMI), however LV end-diastolic volume significantly decreased. Systolic function as assessed by ejection fraction remained stable, however longitudinal systolic function as reflected by tissue Doppler s wave significantly decreased with age. Diastolic function as assessed by E: e' significantly decreased with age as well. A significant longitudinal increase in LAVI

consistent with decreased diastolic function was noted. As expected there was a high incidence of MAC with 27 (43%) of subjects having mild and an additional 21 (33%) of subjects having severe MAC. Eight (13%) subjects had significant aortic stenosis and 14 (22%) had upper septal hypertrophy.

When the echocardiographic data was examined categorically (Table 3), there was no difference between the groups in subjects having abnormal left ventricle ejection

Table 1. Clinical characteristics of the study cohort at ages 85 and 94 years.

	Age: 85 yrs	Age: 94 yrs
Male	31 (49.2%)	31 (49.2%)
Education > 12 yrs	48 (76.2%)	48 (76.2%)
Married	33 (52.4%)	20 (31.8%)
BMI < 25 kg/m ²	20 (33.3%)	32 (56.1%)
25 ≤ BMI < 30 kg/m ²	32 (53.3%)	17 (29.8%)
BMI ≥ 30 kg/m ²	8 (13.3%)	8 (14.0%)
ADL dependency	4 (6.4%)	29 (47.5%)
ADL difficulty	54 (85.7%)	54 (88.5%)
Smokes or smoked	22 (34.9%)	21 (34.4%)
MM < 25	1 (2.4%)	25 (46.3%)
Diabetes	10 (15.9%)	16 (25.4%)
HTN	40 (63.5%)	52 (82.5%)
IHD	22 (34.9%)	24 (38.1%)
CHF	2 (3.2%)	17 (27.0%)
CRF	3 (4.8%)	5 (7.9%)

Data are presented as *n* (%). ADL: activities of daily living; BMI: body mass index; CHF: congestive heart failure; CRF: chronic renal failure; HTN: hypertension; IHD: ischemic heart disease; MM: mini-mental.

Table 2. Echocardiography of the study cohort at ages 85 and 94 years.

	Age: 85 yrs	Age: 94 yrs	Change	<i>P</i> -value
LVMI, g/m ²	105.3 ± 24.9	110 ± 25.1	4.4 ± 29.3	0.32
EF	56.0% ± 8.5%	56.2% ± 8.9%	0.4% ± 9.0%	0.70
S wave, cm/s	7.9 ± 1.8	6.6 ± 1.4	-1.2 ± 1.8	< 0.0001
E: e'	11.2 ± 3.4	16 ± 7.5	4.5 ± 6.4	< 0.0001
LVESV, mL	50.5 ± 19.5	47.3 ± 24.9	-3.4 ± -3.5	0.20
LVEDV, mL	113.4 ± 30.0	103.6 ± 35.5	-9.3 ± 29.8	0.02
IVS, cm	0 ± 0.2	1.1 ± 0.2	0 ± 0.2	0.10
PW, cm	0 ± 0.2	1.0 ± 0.1	0 ± 0.2	0.07
LAVI, mL/m ²	34.1 ± 11.3	42.4 ± 13.7	7.4 ± 10.8	< 0.0001

Data are presented as mean ± SD. EF: ejection fraction; IVS: interventricular septum; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVMI: left ventricular mass index; PW: posterior wall; LAVI: left ventricular volume index.

Table 3. Echocardiographic findings analyzed categorically.

	Age: 85 yrs	Age: 94 yrs	P-value
EF	> 0.52 (M)	26 (62.7%)	0.3268
	> 0.54 (W)	21 (72.9%)	
	< 0.52 (M)	22 (37.3%)	
	< 0.54 (W)	38 (27.1%)	
E:e'	< 14	27 (75.6%)	0.0033
	≥ 14	14 (24.4%)	

Data are presented as *n* (%). EF: ejection fraction.

fraction (LVEF), however there was a significant increase in the number of subjects with abnormal diastolic function at age 94.

When the study population was divided by gender, similar trends of preserved LVEF, decreased longitudinal function, decreased diastolic function with an increase in E/e' as well as LAVI without significant changes in LV mass were seen in both males and females (Table 4).

Multivariate models examining correlations between the clinical variables of gender, hypertension, diabetes, ischemic heart disease, congestive heart failure and changes in cardiac structure and function were performed (Table 5).

Table 4. Echocardiography of the study cohort divided by gender.

	Age: 85 yrs	Age: 94 yrs	Change	P-value
Females				
LVM, g/m ²	107.3 ± 27.4	110.2 ± 19.3	6.8 ± 29.3	0.27
EF	56.4% ± 8.0%	57.9% ± 8.6%	1.6% ± 9.4%	0.35
S wave, cm/s	7.3 ± 1.5	6.5 ± 1.5	-0.7 ± 1.8	0.06
E: e'	11.7 ± 3.4	15.8 ± 6.8	3.7 ± 3.5	< 0.01
LVESV, mL	44.7 ± 14.1	39.6 ± 19.7	-5.1 ± -16.3	0.09
LVEDV, mL	102.4 ± 24.3	90.7 ± 27.6	-11.3 ± 28.0	0.03
IVS, cm	1.2 ± 0.2	1.2 ± 0.2	0.8 ± 0.2	0.04
PW, cm	1.0 ± 0.2	1.0 ± 0.1	0 ± 0.2	0.29
LAVI, mL/m ²	34.9 ± 11.9	42.2 ± 13.8	7.4 ± 11.3	0.0026
Males				
LVM, g/m ²	103.0 ± 22.1	110.0 ± 29.6	2.3 ± 31.2	0.72
EF	55.7% ± 9.2%	54.6% ± 8.9%	-0.8% ± 8.5%	0.61
S wave, cm/s	8.5 ± 2.0	6.7 ± 1.3	-1.7 ± 1.6	< 0.0001
E: e'	10.8 ± 3.3	16.2 ± 8.1	5.2 ± 6.8	< 0.001
LV-ESV, mL	56.8 ± 22.8	55.0 ± 27.3	-1.5 ± -23.4	0.72
LV EDV, mL	125.6 ± 31.4	116.5 ± 38.2	-7.2 ± 32.0	0.23
IVS, cm	1.1 ± 0.2	1.1 ± 0.2	0 ± 0.2	0.80
PW, cm	0.1 ± 0.2	1.0 ± 0.1	0.1 ± 0.2	0.15
LAVI, mL/m ²	33.2 ± 10.8	42.6 ± 13.9	7.5 ± 10.5	0.003

EF: ejection fraction; IVS: interventricular septum; LAVI: left ventricular volume index; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVM: left ventricular mass index; PW: posterior wall.

Table 5. Multivariate analysis of baseline clinical findings at age 85 on changes in cardiac structure and function at age 94 years.

Dependent Variable	Variable	Parameter	Standard	Pr > t
LVM	Sex	-2.948	8.902	0.742
	DM	-14.590	12.638	0.255
	HTN	1.187	9.145	0.897
	IHD	4.434	10.036	0.661
EF	sex	-2.625	2.604	0.318
	DM	-1.900	3.533	0.593
	HTN	-2.075	2.683	0.443
	IHD	-0.257	2.755	0.926
S wave	Sex	-1.022	0.516	0.053
	DM	-0.417	0.694	0.551
	HTN	-0.121	0.539	0.823
	IHD	-0.145	0.558	0.797
E: e'	Sex	0.106	2.234	0.963
	DM	3.424	3.279	0.304
	HTN	-2.524	2.256	0.271
	IHD	0.547	2.309	0.814

DM: diabetes mellitus; EF: ejection fraction; HTN: hypertension; IHD: ischemic heart disease; LVM: left ventricular mass index.

Except for a borderline association between gender and tissue Doppler s wave, no significant correlations were noted.

4 Discussion

This unique longitudinal assessment of cardiac structure and function in the very elderly performed at the subject's home demonstrated preserved EF with decreased longitudinal systolic function and decreased diastolic function without significant change in LV mass in this age cohort. Our findings suggest that changes in LV systolic and diastolic function in the very elderly may be independent of changes in LV geometry.

Very few previous studies have longitudinally studied cardiac structure and function in the very elderly. In a younger population (mean age 60 years) studied over a four year period, Borlaug, *et al.*^[20] demonstrated an increase in age-related systolic and diastolic stiffness using echocardiography. They noted preserved systolic function as well as worsening diastolic function with no change in LV mass, findings consistent with our study. The presence of hypertension did not affect these findings. The MESA study recently reported results of a 10 year longitudinal study using MRI in a population with a mean age of 63 years at baseline. In this study, LV mass increased over 10 years in the subgroup of subjects under 55 years of age with atte-

nuated, non-significant increases in older subjects, again consistent with our study in a significantly older population.^[7] Multiple cross-sectional studies have well documented decreases in longitudinal systolic function and diastolic dysfunction with aging.^[21] Ejection fraction remains preserved in this age group despite worsening longitudinal function probably due to increased torsion.^[21] Our longitudinal study extends these findings to a very elderly community population.

Our findings have important implications for the diagnosis of HFpEF in this age group. This entity is extremely common in the elderly but diagnostic criteria, particularly in the very elderly, remain controversial. Recent publications have in fact suggested adding age to the echocardiographic assessment of diastolic dysfunction.^[22,23] Mitter, *et al.*^[22] suggested in their algorithm adding age adjusted assessment of e' velocity, however the upper cutoff was above 65 years of age. The mean age in the derivation cohort in the work of Selmer, *et al.*^[23] was only 49 ± 14 years. Our findings suggest that different cutoffs for values such as e' and E: e' should be considered at more advanced ages. An inaccurate diagnosis of HFpEF in an elderly patient with for example dyspnea could overlook other potentially life-threatening diagnoses.

We have previously demonstrated that elevated LAVI and LVMI as well as decreased LV systolic function predict 5-year mortality in the cohort initially studied at 85 years of age. Elevated E: e' did not predict mortality in this cohort. It seems plausible that abnormalities of systolic function which are not part of the innate aging process are associated with mortality in this age group while diastolic abnormalities which are more common are not.^[24]

Our study as well as previous studies suggest that the increase in concentric remodeling and LV mass seen with aging is attenuated at the extremes of aging.^[24,25] On the other hand, other physiologic changes associated with aging in particular decreases in longitudinal systolic function and diastolic function continue to progress. The reasons for this discrepancy in the very elderly age group remain unclear. A previous study in rats demonstrated increased myocyte cellular hyperplasia with loss of total number of myocytes and increased areas of fibrosis with aging.^[26] It is possible that the LV eventually loses the ability to compensate for age-related changes such as vascular stiffness or hypertension by hyperplasia and concentric remodeling. Alternatively, it is possible that as with any long-term pressure overload, the LV, at advanced ages, transitions to a more dilated or congestive phenotype.^[27] In any event, our findings suggest that age-related changes in longitudinal and diastolic function are at least partially independent of changes in LV geometry.

The major strengths of our study are the use of an age-homogenous cohort and the use of home echocardiography to study a more representative sample of this age group and avoid bias. The major limitations of the study are the small number of subjects and the use of echocardiography in a subset of the total cohort. This was a random subgroup of the initial cohort and there were no significant differences in demographics between the subjects who initially underwent echocardiography at age 85 and those who did not. In addition, mainly due to the high mortality expected in the age group studied, repeat echocardiography was performed in a relatively small subset of the initial population studied. As in any longitudinal study in this age group, possible survivor bias should be taken into account. Given the high prevalence of morbidity and risk factors in this very elderly population, the echocardiographic findings are not strictly those of a truly "healthy" population, however, studying a community-based population in the home presumably provides a relatively representative sample.

In conclusion, our study demonstrated preserved EF with decreased longitudinal systolic function and decreased diastolic function without significant change in LV mass in this very elderly cohort. Our findings suggest that changes in LV systolic and diastolic function in the very elderly may be independent of changes in LV geometry. Further study is necessary to elucidate mechanisms underlying cardiac changes associated with aging.

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