Myocardial contraction fraction predicts mortality in the oldest old

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\textbf{Article info}

Keywords:
- Elderly
- Echocardiography
- Ventricular function

\textbf{Abstract}

Background: People over the age of 85 are the world’s most rapidly growing age group. Ejection fraction (EF) may be limited prognostically in this population and myocardial contraction fraction (MCF) may be more accurate. The objective of this longitudinal study was to assess the prognosis of MCF in an age-homogenous, community-dwelling population of subjects.

Methods: Subjects were recruited from the Jerusalem Longitudinal Cohort Study. Echocardiography was performed with a portable echocardiograph at the subjects’ place of residence. Standard echocardiographic assessment of cardiac structure and function including MCF was performed. Values of EF and MCF above and below the median for males and females were defined as normal and abnormal in categorical analysis. 5-year mortality was assessed via a centralized government database.

Results: 418 subjects (199 males, 219 females) were enrolled in the study of whom 113 (27%) died at the time of 5-year follow-up. Subjects who died had significantly lower MCF (32 ± 14 \% vs 36 ± 12 \%; p < 0.004) and EF (51.6 ± 11.6 \% vs 56.3 ± 9.4 \%; p < 0.0001) than survivors. The association between MCF and mortality remained significant on clinical multivariate analysis as both a categorical and continuous variable while EF was only significant as a continuous variable. When both EF and MCF were added to the model only MCF as a categorical variable remained significant.

Conclusions: MCF assessed by home echocardiography provides additional prognostic information to EF and may be a superior predictor of 5-year mortality in a community-dwelling population of the oldest old.

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 is an increasing challenge for cardiovascular care given the relatively high frequency of cardiac death in this population [2]. Previous studies that have utilized echocardiography in elderly patients to examine prognosis included a broad range of ages with relatively few patients over the age of 80 [3–5]. In addition, existing studies of echocardiography in the “oldest old” have been performed in the hospital or clinic setting, contributing to a biased study population in this elderly age group as subjects may have difficulty in leaving their homes [6].

Left ventricular ejection fraction (EF) is the most commonly used echocardiographic measurement of LV systolic function. EF is a volumetric assessment which is dependent on loading conditions and which may not accurately assess systolic function in the setting of left ventricular hypertrophy and heart failure with preserved ejection fraction, findings common in the elderly population [7–9]. Myocardial contraction fraction (MCF) is defined as the ratio of LV stroke volume (SV) to myocardial volume and may more accurately assess LV systolic function than EF particularly in the setting of LVH and/or HFPEF [10–12]. The aim of this longitudinal study was to examine the association between MCF and 5-year mortality in an age-homogenous, community-dwelling population of 85–6 year olds.

2. Methods

2.1. Participants

Subjects were recruited from the Jerusalem Longitudinal Cohort Study that was initiated in 1990 and has followed an age homogenous representative cohort of West Jerusalem residents born between June

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https://doi.org/10.1016/j.ijcha.2022.101158
Received 21 July 2022; Received in revised form 14 November 2022; Accepted 23 November 2022

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2. Sampling

Subjects identified from the electoral register were randomly chosen from the total sample of people born 1920–21 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 to other subjects of the study group in comparison to the total same age stratum of the Jerusalem population. Echocardiography was performed in randomly selected subjects in a convenience sample by neighborhood, evenly distributed between new recruits and subjects participating from previous phases. No significant differences in medical diagnoses were noted between the members of the cohort who underwent echocardiography compared to those who did not. (Supplementary Table 1) Participants who underwent echocardiography were slightly more physically active with better functional status. Survival status at 5 year follow-up was assessed via the centralized Ministry of Interior database. Follow-up was available for all study subjects.

3. Measures

3.1. Cardiovascular

Diagnosis of ischemic heart disease (IHD) was based on a history of hospitalization for myocardial infarction (MI), or an acute coronary syndrome, coronary catheterization with evidence of a significant coronary artery disease, or previous coronary artery bypass grafting surgery. Hypertension was assessed by the examining study physician and defined as treatment with antihypertensive medications or subjects’ self-reporting. Blood pressure was measured with the participant in a sitting position three times with a use of a validated electronic sphygmomanometer (Omron 705IT; Omron Corporation, Kyoto, Japan) and the results were averaged. 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 (CHF) and the presence of renal disease 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 (<25) and high (>25). A cognitive assessment was performed according to a standardized Mini Mental State Examination with cognitive impairment defined as <24/30. Physically active was defined as at least 4 h a week self reported physical activity.

3.2. Echocardiography

Subjects had standard 2-D and Doppler echocardiography at their place of residence with a portable echocardiograph (Vivid I, GE Healthcare, Haifa, Israel). All subjects underwent 2-D and Doppler echocardiography with m-mode measurements of the interventricular septum, posterior wall, and left ventricular (LV) end-systolic and end-diastolic diameters according to the recommendations of the European Association of Echocardiography/American Society of Echocardiography [15]. Measurements were performed offline by an experienced echocardiographer (DL) for three consecutive cardiac cycles and averaged. Subject height and weight at the time of the study were recorded based on hospital discharge diagnosis and according to examining physician diagnosis at the time of examination at home. Body mass index was calculated and dichotomized to low (<25) and high (>25). A cognitive assessment was performed according to a standardized Mini Mental State Examination with cognitive impairment defined as <24/30. Physically active was defined as at least 4 h a week self reported physical activity.

| Table 1 | Clinical characteristics of the study population. |
|---------|-----------------------------------------------|
| Criterion | Total | |
| Gender | | |
| Female | 52.4 % (219) |
| | | |
| Education | | |
| < 12 years | 49.6 % (206) |
| Low | 33.2 % (130) |
| High | 24 % (94) |
| Physically active | Yes | 68.2 % (281) |
| Yes | 29.1 % (118) |
| Dementia | Yes | 16.6 % (66) |
| Hypertension | Yes | 69.6 % (291) |
| Blood pressure (mmHg) | Systolic | 146.3 ± 20.6 |
| Diastolic | 73.9 ± 10.5 |
| Ischemic heart disease | Yes | 37.6 % (157) |
| Diabetes mellitus | Yes | 22 % (92) |
| Chronic renal disease | Yes | 9.6 % (40) |

Fig. 1. Participant flow chart.
male had technically acceptable echocardiograms which enabled
performed using R 3.4.3.

4. Results

Echocardiographic parameters in the study population.

|          | Total Mean (SD) | Median (IQR) | Did not Die Mean (SD) | Median (IQR) | Died Mean (SD) | Median (IQR) | P-value |
|----------|----------------|--------------|-----------------------|--------------|---------------|--------------|---------|
| EF (%)   | 55 (10.2)      | 56.2 (50.7-61.7) | 56.30                 | 56.99        | 51.64         | 54.11        | 0.0001  |
| MCF (%)  | 0.35 (0.2)     | 0.3 (0.27-0.42) | 0.36                  | 0.35         | 0.32          | 0.29         | 0.0040  |
| E/e'     | 12.2 (4.8)     | 11.3 (9.2-14.1) | 11.74                 | 11.13        | 13.42         | 12.57        | 0.0160  |
| LV S wave (cm/s) | 7.7 (2.1) | 7.7 (6.2-9) | (4.32)               | (8.90,13.33) | (5.82)        | (9.67,15.97) | 0.3600  |
| LVESVI (ml/m2) | 31.7 (14.5) | 28.7 (22.1-37.3) | 29.92                | 28.17        | 36.59         | 32.47        | 0.0009  |
| LVMII (g/m2) | 121.7 (35.3) | 117.4 (97-139.8) | (12.33)              | (21.75,35.54) | (18.39)       | (23.09,45.23) | 0.0004  |
| LVEDVI (ml/m2) | 68.7 (18.5) | 66.8 (56.3-79.2) | 67.29                | 66.40        | 72.69         | 70.80        | 0.0310  |
| LAVI (ml/m2) | 38.4 (14.6) | 35.9 (29.1-45) | (16.46)              | (56.32,76.40) | (22.84)       | (57.38,86.25) | 0.0002  |

EF = ejection fraction.  
MCF = myocardial contraction fraction.  
LVESVI = left ventricular end-systolic volume index.  
LVEDVI = left ventricular end-diastolic volume index.  
LVMII = left ventricular mass index.

and below the median for males and females were defined as normal and abnormal in categorical analysis.

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) transmitial flow velocities and the ratio of early to late velocities (E/A). 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 [18].

3.3. Data analysis

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-tests and Chi-square test for proportions. Cumulative survival was assessed by Kaplan-Meier analysis and log rank test for statistical significance. Adjusted and unadjusted Cox proportional hazard models were performed for the variables of MCF and EF analyzed by tertiles. Adjusted clinical variables were selected based on p < 0.15 in the univariate analysis. Sensitivity analysis was performed analyzing the groups by median values as well as excluding participants with EF < 40 % (n = 36). Receiver operating curves were generated using both EF and MCF as variables for predicting mortality. All p values were 2-tailed and p < 0.05 was considered significant. The data storage and analysis was performed using R 3.4.3.

4. Results

A total of 526 participants underwent echocardiography and were included in the study. 418 subjects of whom 219 were female and 199 male had technically acceptable echocardiograms which enabled accurate calculations of both EF and MCF. (Fig. 1) A total of 113 subjects (27 %) died at 5 year follow-up. Demographic and clinical characteristics of the study population as a whole is depicted in Table 1. Survivors were significantly more physically active and had significantly less dementia, ischemic heart disease, diabetes, chronic kidney disease and congestive heart failure.

Echocardiographic measurements of the study population are presented in Table 2. Subjects who died had significantly lower MCF (32 ± 14 % vs 36 ± 12 %; p < 0.004) ad EF (51.6 ± 11.6 % vs 56.3 ± 9.4 %; p < 0.0001) than survivors. In addition, non survivors had significantly lower indices of LV volumes, LA volumes and LV mass index (LVMII) than survivors.

When parameters were dichotomized, a significantly higher percentage of non-survivors had MCF below the median for the population (63.7 vs 36.3 %; p 0.0008). A significantly higher percentage of non-survivors had EF below the median as well (60.2 % vs 39.8.5 %; p < 0.0004) than survivors. In addition, non survivors had significantly lower indices of LV volumes, LA volumes and LV mass index (LVMII) than survivors.

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Kaplan-Meier curves by tertiles are presented in Fig. 2. For males, tertiles of MCF were < 29 %, 29–40 % and > 40 % and of EF were < 51 %, 51–58 % and > 58 %. For females, tertiles of MCF were < 29 %, 29–38 % and > 38 % and of EF were < 54 %, 54–61 % and > 61 % Both EF and MCF were predictive of mortality. Receiver operating curves are presented in Fig. 3. The area under the curve for MCF was 0.63 while for EF it was 0.61, this difference did not reach statistical significance. When ROC analysis was repeated including only subjects with preserved EF, the results remained not statistically significant.

Table 3 depicts the multivariate adjusted Cox proportional hazard models for both MCF and EF examined as tertiles. The lowest tertile of MCF was significantly associated with increased mortality. EF by tertiles was no longer significantly associated with mortality.

Table 4 depicts the multivariate adjusted Cox proportional hazard models for both MCF and EF examined independently as continuous as
Fig. 2. Kaplan-Meier analysis of mortality of EF and MCF by tertiles demonstrating significantly reduced survival in the lowest tertile of both EF and MCF.
Multivariate model for mortality (Cox proportional hazard) according to tertiles.

| Variable                          | Categorical          | HR    | (95% CI)     | P-value |
|-----------------------------------|----------------------|-------|--------------|---------|
| **MCF**                           |                      |       |              |         |
| MCF- lowest tertile               | 2.34                 | (1.4, 3.92) | 0.0012 |
| MCF- middle tertile               | 1.68                 | (0.96, 2.94) | 0.0708 |
| Sex                               | 1.35                 | (0.89, 2.06) | 0.1555 |
| Education < 12 years              | 1.03                 | (0.87, 1.21) | 0.4525 |
| **Categorical**                   |                      |       |              |         |
| Reduced ADL                       | 3.55                 | (2.04, 5.5) | <0.0001 |
| Ischemic heart disease            | 1.05                 | (1.07, 1.80) | 0.0234 |
| Diabetes                          | 1.03                 | (0.77, 1.01) | 0.3704 |
| Chronic renal disease             | 1.03                 | (1.08, 1.35) | 0.0258 |
| Physical activity                 | 0.72                 | (0.44, 1.18) | 0.1914 |
| **EF**                            |                      |       |              |         |
| EF- lowest tertile                | 1.46                 | (0.85, 2.51) | 0.1745 |
| EF- middle tertile                | 1.38                 | (0.81, 2.37) | 0.2394 |
| Sex                               | 1.34                 | (0.89, 2.04) | 0.1632 |
| Education < 12 years              | 0.77                 | (0.5, 1.19) | 0.2354 |
| Dementia                          | 1.11                 | (0.65, 1.87) | 0.7091 |
| Reduced ADL                       | 3.4                  | (2.07, 5.56) | <0.0001 |
| Ischemic heart disease            | 1.54                 | (1.01, 2.33) | 0.0427 |
| Diabetes                          | 1.17                 | (0.72, 1.9) | 0.5346 |
| Chronic renal disease             | 1.99                 | (1.11, 3.58) | 0.0213 |
| Physical activity                 | 0.8                  | (0.49, 1.31) | 0.3729 |

In conclusion, our results show that echocardiography in a subset of the total cohort, however this was a random subgroup and there were no significant differences in demographics such as gender, diabetes, hypertension and ischemic heart disease between the subjects who underwent echocardiography and those who did not so that the chance of selection bias is minimal. In addition, we do not have information regarding causes of mortality of incidence of cardiovascular events. There was a 13 % incidence of mitral annular calcification in this elderly cohort which may have affected tissue Doppler annular measurements. Strain measurements were not available at the time the study was performed.

In conclusion, our results show that echocardiographically determined MCF provides additional prognostic information to EF and may be a superior predictor of 5-year mortality in a community-dwelling population of the oldest old.
population of the oldest old.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101158.

Table 4

Multivariate model for mortality (Cox proportional hazard).

| Continuous | Categorical |
|------------|-------------|
| MCF (%)    | HR (95 %CI) | P-value | HR (95 %CI) | P-value |
| 0.08       | (0.01, 0.46) | 0.0046  | 0.58       | (0.38, 0.87) | 0.009  |
| Gender     | 1.38       | (0.91, 2.09) | 0.1299   | 1.36       | (0.9, 2.06) | 0.15  |
| High Education | 0.74       | (0.48, 1.15) | 0.1774   | 0.72       | (0.47, 1.1) | 0.126 |
| Dementia   | 1.04       | (0.61, 1.75) | 0.8951   | 1.02       | (0.61, 1.72) | 0.9336 |
| Problem in ADL | 3.45       | (2.12, 5.62) | <0.0001  | 3.44       | (2.11, 5.61) | <0.0001 |
| Ischemic HD | 1.57       | (1.05, 2.35) | 0.0294   | 1.62       | (1.08, 2.42) | 0.0185 |
| Diabetes   | 1.17       | (0.73, 1.89) | 0.5093   | 1.16       | (0.72, 1.88) | 0.5388 |
| Kidney Disease | 1.93       | (1.08, 3.43) | 0.0258   | 1.91       | (1.07, 3.42) | 0.0292 |
| Physically Active | 0.77       | (0.47, 1.25) | 0.2887   | 0.78       | (0.48, 1.28) | 0.3271 |

| EF (%)     | HR (95 %CI) | P-value | HR (95 %CI) | P-value |
| 0.97       | (0.95, 0.99) | 0.0028  | 0.75       | (0.49, 1.1) | 0.1751 |
| Gender     | 1.2        | (0.79, 1.83) | 0.3928   | 1.34       | (0.89, 2.03) | 0.1664 |
| High Education | 0.77       | (0.5, 1.19) | 0.2418   | 0.76       | (0.49, 1.18) | 0.2202 |
| Dementia   | 1.18       | (0.7, 2.02) | 0.5328   | 1.09       | (0.64, 1.84) | 0.7529 |
| Problem in ADL | 3.19       | (1.96, 5.2) | <0.0001  | 3.48       | (2.14, 5.66) | <0.0001 |
| Ischemic HD | 1.34       | (0.87, 2.06) | 0.19     | 1.55       | (1.02, 2.34) | 0.039  |
| Diabetes   | 1.11       | (0.69, 1.8)  | 0.6723   | 1.14       | (0.7, 1.86)  | 0.5905 |
| Kidney Disease | 2.12       | (1.18, 3.81) | 0.012    | 1.93       | (1.08, 3.46) | 0.0277 |
| Physically Active | 0.27       | (0.47, 1.25) | 0.2987   | 0.81       | (0.5, 1.33)  | 0.4074 |

III. Multivariate analysis including both EF and MCF as tertiles

| Continuous | Categorical |
|------------|-------------|
| EF- low tertile | 1.22       | (0.75, 1.99) | 0.4279 |
| EF- middle tertile | 1.01        | (0.56, 1.84) | 0.9701 |
| MCF- low tertile | 2.43       | (1.37, 4.28) | 0.0022 |
| MCF- middle tertile | 1.66         | (0.94, 2.93) | 0.0815 |
| Gender- Male | 1.36        | (0.89, 2.06) | 0.1526 |
| Education-< 12 years | 0.74        | (0.48, 1.14) | 0.169 |
| Dementia | 1.00        | (0.59, 1.70) | 0.9994 |
| Reduced ADL | 3.34         | (2.02, 5.52) | <0.0001 |
| Ischemic Heart Disease | 1.61       | (1.06, 2.45) | 0.0264 |
| Diabetes | 1.26        | (0.78, 2.03) | 0.3519 |
| Chronic Renal Disease | 1.96       | (1.09, 3.51) | 0.0238 |
| Physical activity | 0.72        | (0.44, 1.18) | 0.1954 |

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