Relation of Left Ventricular Ejection Fraction to Cognitive Aging (from the Framingham Heart Study)

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Heart failure is a risk factor for Alzheimer's disease and cerebrovascular disease. In the absence of heart failure, it was hypothesized that left ventricular ejection fraction (LVEF), an indicator of cardiac dysfunction, would be associated with preclinical brain magnetic resonance imaging (MRI) and neuropsychological markers of ischemia and Alzheimer disease in the community. Brain MRI, cardiac MRI, neuropsychological, and laboratory data were collected from 1,114 Framingham Heart Study Offspring Cohort participants free from clinical stroke or dementia (aged 40 to 89 years, mean age 67 ± 9 years, 54% women). Neuropsychological and neuroimaging markers of brain aging were related to cardiac MRI–assessed LVEF. In multivariable-adjusted linear regressions, LVEF was not associated with any brain aging variable (p values >0.15). However, LVEF quintile analyses yielded several U-shaped associations. Compared to the referent (quintile 2 to 4), the lowest quintile (quintile 1) LVEF was associated with lower mean cognitive performance, including Visual Reproduction Delayed Recall ($\beta = -0.27$, $p < 0.001$) and Hooper Visual Organization Test ($\beta = -0.27$, $p < 0.001$). Compared to the referent, the highest quintile (quintile 5) LVEF values also were associated with lower mean cognitive performance, including Logical Memory Delayed Recall ($\beta = -0.18$, $p = 0.03$), Visual Reproduction Delayed Recall ($\beta = -0.17$, $p = 0.03$), Trail Making Test Part B − Part A ($\beta = -0.22$, $p = 0.02$), and Hooper Visual Organization Test ($\beta = -0.20$, $p = 0.02$). Findings were similar when analyses were repeated excluding prevalent cardiovascular disease. In conclusion, although these observational cross-sectional data cannot establish causality, they suggest a nonlinear association between LVEF and measures of accelerated cognitive aging. **(Am J Cardiol 2011;108:1346–1351)**

In patients with severe cardiomyopathies, left ventricular ejection fraction (LVEF) is related to abnormal brain aging, including cognitive impairment,[1] structural neuroanatomic abnormalities,[2] and increased risk for Alzheimer's disease (AD).[3] Cognitive impairment diminishes[4] and cerebral blood flow increases by >50% after heart transplantation,[5] purportedly because of improvement in cardiac function. Therefore, a reduced LVEF may influence cerebral perfusion homeostasis and contribute to clinical brain injury. In the absence of end-stage heart disease, less is known about how LVEF affects or accelerates abnormal brain aging. The aim of this cross-sectional investigation was to better understand relations between LVEF and abnormal brain aging by extending previous work to a large, epidemiologic cohort, assessing LVEF using sensitive cardiac magnetic resonance imaging (MRI), and simultaneously considering shared vascular risks for brain and myocardial injury. On the basis of previous work, we hypothesized that a lower LVEF would be associated with cognitive and neuroimaging markers of preclinical AD[6,7] (learning and memory, brain volume, temporal horn volume, and hippocampal volume) and cerebrovascular changes[8,9] (executive functioning and white matter hyperintensities [WMH]) in a community-based cohort of adults free of clinical dementia or stroke.

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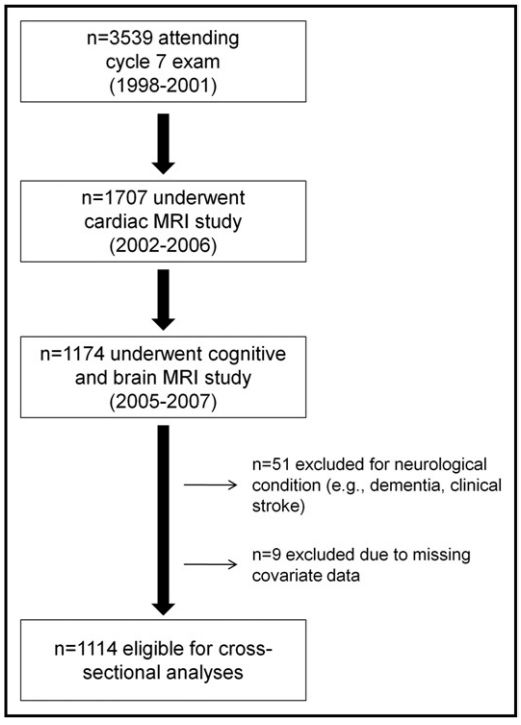

Figure 1. Participant enrollment and exclusion details.

Methods

The Framingham Offspring Study design and selection criteria have been described elsewhere.[10] From 1971 to 1975, 5,124 participants were recruited and have been examined every 4 to 8 years since. Details on the derivation of the current sample are provided in Figure 1. The protocol was approved by the local institutional review board. Participants provided written informed consent before assessments.

Participants completed the following cognitive protocol, which was selected a priori to represent different cognitive systems: (1) delayed memory: Logical Memory Delayed Recall and Visual Reproduction Delayed Recall; (2) language: Boston Naming Test–30 Item; (3) executive functioning: a difference score of Trail Making Test Part B − Part A; (4) verbal reasoning: Similarities; and (5) visuoperceptual abilities: Hooper Visual Organization Test.

For brain imaging acquisition, images were obtained using a Siemens 1-T magnetic resonance machine (Siemens Medical Systems, Erlangen, Germany) using a T2-weighted double spin-echo coronal imaging sequence. Digital information was postprocessed by a central laboratory blinded to demographic and clinical information. A custom-written, semiautomatic segmentation protocol was used to quantify total cranial,[11] total brain,[12] frontal lobar,[13] temporal horn,[13] and hippocampal[14] volumes and WMH segmentation.[12] Interrater reliabilities for these methods have been published elsewhere.[11,13,15,16] For this study, intra- and interrater reliabilities were consistently >0.90. Hippocampal data were available for a subset of participants (n = 423). For cardiac MRI acquisition, images were obtained with participants in the supine position using a Philips 1.5-T MR system (Philips Medical Systems, Andover, Massachusetts) with a 5-element (3 anterior, 2 posterior) surface coil. Images were acquired at end-tidal breath hold and analyzed by a single, experienced, blinded reviewer using a commercial workstation (EasyVision 4.0; Philips Medical Systems). End-systolic phase was determined as the minimal cross-sectional area of a midventricular slice. The time delay from the QRS complex (phase) was analyzed for each contiguous slice, and endocardial borders were segmented. End-diastolic volume and end-systolic volume were computed by summation of disks (i.e., modified Simpson's rule) to derive the LVEF ([end-diastolic volume − end-systolic volume]/end-diastolic volume). Intra- and interobserver coefficients of variation for these methods have been published elsewhere.[17] For this study, interrater reliabilities were consistently >0.92.[18]

Table 1
Clinical and imaging characteristics (n = 1,114)

Variable	Value
Age at brain MRI (years)	67 ± 9
Women	602 (54%)
Systolic blood pressure (mm Hg)	124 ± 17
Cigarette smokers	102 (9%)
Diabetes mellitus	93 (8%)
Atrial fibrillation	20 (2%)
Hypertension treatment	293 (26%)
Prevalent CVD	77 (7%)
Time to brain MRI (years)	6.9 ± 0.9
Time from cardiac MRI to brain MRI (years)	2.5 ± 1.1
LVEF (%)	67.3 ± 6.7
Quintile 1	225 (<62.0%)
Quintile 2	217 (62.0%–65.9%)
Quintile 3	226 (65.9%–68.8%)
Quintile 4	226 (68.8%–73.2%)
Quintile 5	220 (≥73.2%)

Data are expressed as mean ± SD or as percentages.

Total brain, frontal lobe, temporal horn, and hippocampal volumes and WMH were expressed as percentages of total cranial volume. WMH, Trail Making Test Part B − Part A, and Hooper Visual Organization Test were natural log–transformed to normalize distributions. As previously described,[18] neuropsychological scores were adjusted for age and education, separately by sex, to enable comparison across measures. Resulting values were standardized, separately by gender, to a mean of 0 and a standard deviation of 1 (i.e., values were transformed to represent standard deviation units from the mean).

We used regression to assess linear relations between the LVEF and each brain aging variable. Next, we compared brain aging variables among participants classified by LVEF quintile and noted U-shaped associations. We therefore compared the lower (quintile 1) and upper (quintile 5) quintiles to the referent (quintiles 2 to 4) for each brain aging variable. On the basis of previous work,[18] we adjusted for covariates defined at the seventh examination cycle, including age, sex, systolic blood pressure, smoking status, diabetes mellitus (i.e., history of fasting blood glucose ≥126 mg/dl or use of oral hypoglycemic or insulin), hypertension treatment, atrial fibrillation, and prevalent cardiovascular disease (CVD), including coronary heart disease, heart failure, and intermittent claudication.[19] Secondary analyses were performed (1) excluding prevalent CVD (n = 77); (2) using the categorical LVEF variable (i.e., quintile 1, quintile 5, and referent quintiles 2 to 4) assessing effect modification by sex, age (<60 vs ≥60 years),

Table 2
Left ventricular ejection fraction and brain aging data

Variable	Total Sample (n = 1,114)	Quintile 1 (n=225)	Quintiles 2 to 4 (n = 669)	Quintile 5 (n = 220)
Brain MRI data (% of total cranial volume)				
WMH*	−2.38 ± 1.13	−2.42 ± 1.17	−2.45 ± 1.10	−2.15 ± 1.15
Total brain volume†	79.02 ± 3.81	79.35 ± 3.66	79.14 ± 3.82	78.32 ± 3.87
Frontal lobar volume†	36.07 ± 3.37	36.23 ± 3.40	36.25 ± 3.30	35.35 ± 3.49
Temporal horn volume*,†	−3.08 ± 0.88	−3.10 ± 0.84	−3.10 ± 0.92	−3.00 ± 0.80
Hippocampal volume†	0.37 ± 0.06 (n = 423)	0.37 ± 0.06 (n = 88)	0.37 ± 0.06 (n = 245)	0.37 ± 0.06 (n = 90)
	Total sample (n = 1,114)	Quintile 1 (n = 222)	Quintiles 2 to 4 (n = 665)	Quintile 5 (n = 217)
Neuropsychological data				
Logical Memory Delayed Recall, total	12 (0, 22)	12 (0, 22)	12 (0, 22)	11 (0, 19)
Visual Reproduction Delayed Recall, total	9 (0, 14)	8 (0, 14)	9 (0, 14)	8 (1, 14)
Boston Naming Test–30 Item, total	28 (12, 30)	28 (15, 30)	28 (16, 30)	28 (12, 30)
Trail Making Test Part B − Part A, minutes	0.77 (0.08, 9.62)	0.77 (0.15, 9.30)	0.74 (0.08, 9.62)	0.84 (0.10, 9.55)
Hooper Visual Organization Test, total	25.5 (11.5, 30.0)	25.25 (14.5, 30.0)	26 (12.5, 30.0)	25 (11.5, 30.0)
Similarities, total	18 (2, 26)	17 (6, 25)	18 (2, 26)	17 (5, 25)

Data are expressed as mean ± SD or as median (minimum, maximum). For WMH and temporal horn volume, negative values indicate worse pathology.
* Natural log transformed.
† Expressed as a percentage of total cranial volume.

Table 3
Left ventricular ejection fraction, brain magnetic resonance imaging, and neuropsychological regression data

Variable	LVEF (n = 1,114)		LVEF Quintiles (n = 1,114)				
			Quintile 1 (Bottom/Low)		Quintiles 2–4 (Middle)	Quintile 5 (Top/High)	
	β ± SE	p Value	β ± SE	p Value		β ± SE	p Value
Brain MRI data							
WMH	0.000 ± 0.03	0.999	0.13 ± 0.08	0.079	Referent	0.04 ± 0.08	0.584
Total brain volume	0.003 ± 0.02	0.903	0.13 ± 0.23	0.564	Referent	0.13 ± 0.23	0.593
Frontal lobar volume	−0.03 ± 0.03	0.186	0.13 ± 0.21	0.551	Referent	−0.21 ± 0.21	0.319
Temporal horn volume	0.02 ± 0.02	0.349	−0.04 ± 0.06	0.542	Referent	−0.03 ± 0.06	0.577
Hippocampal volume (n = 423)	0.06 ± 0.05	0.208	−0.002 ± 0.01	0.808	Referent	0.01 ± 0.01	0.430
Neuropsychological data							
Logical Memory Delayed Recall	−0.01 ± 0.03	0.821	−0.12 ± 0.08	0.159	Referent	−0.18 ± 0.08	0.031*
Visual Reproduction Delayed Recall	0.05 ± 0.03	0.131	−0.27 ± 0.08	<0.001*	Referent	−0.17 ± 0.08	0.029*
Boston Naming Test–30 Item	−0.01 ± 0.03	0.780	−0.05 ± 0.08	0.521	Referent	−0.05 ± 0.08	0.519
Trail Making Test Part B − Part A	−0.01 ± 0.04	0.750	−0.13 ± 0.09	0.174	Referent	−0.22 ± 0.09	0.022*
Similarities	0.000 ± 0.03	0.997	−0.12 ± 0.08	0.114	Referent	−0.11 ± 0.08	0.178
Hooper Visual Organization Test	−0.006 ± 0.03	0.856	−0.27 ± 0.08	<0.001*	Referent	−0.20 ± 0.08	0.015*

Models adjusted for age, sex, systolic blood pressure, smoking status, diabetes mellitus, hypertension treatment, atrial fibrillation, and prevalent CVD. LVEF quintiles were <62% for quintile 1 (n = 225), 62% to 65.9% for quintile 2 (n = 217), 65.95 to 68.8% for quintile 3 (n = 226), 68.8% to 73.19% for quintile 4 (n = 226), and >73.19% for quintile 5 (n = 220).
* Statistically significant (p <0.05).

and APOE-ε4 status[20] (ε4− vs ε4+) and stratifying analyses by subgroups as indicated. Significance was set at p <0.05 for all models. Data were analyzed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

Results

Clinical characteristics are listed in Table 1. Cardiac MRI, brain MRI, and neuropsychological descriptive variables are listed in Table 2. As a continuous variable, the LVEF was unrelated to any brain MRI or neuropsychological variable (Table 3). Findings were not altered when participants with CVD were excluded (Table 4).

When LVEF quintiles were compared to assess associations with brain aging variables, participants in quintile 1 did not differ from the referent group (quintiles 2 to 4) for any of the brain MRI variables (Table 3). However, participants in quintile 1 differed from the referent group for Visual Reproduction Delayed Recall (p <0.001) and Hooper Visual Organization Test (p <0.001) (Table 3), such that lower LVEF values were associated with poorer mean cognitive performance. When participants with prevalent CVD were excluded, findings were similar (Table 4). Compared to the referent, participants in quintile 5 performed more poorly on Logical Memory Delayed Recall

Table 4
Left ventricular ejection fraction, brain magnetic resonance imaging, and neuropsychological regression data excluding cardiovascular disease

Variable	LVEF (n = 1,037)		LVEF Quintiles (n = 1,037)				
			Quintile 1 (Lowest)		Quintiles 2–4 (Middle)	Quintile 5 (Highest)	
	β ± SE	p Value	β ± SE	p Value		β ± SE	p Value
Brain MRI data							
WMH	0.01 ± 0.03	0.768	0.10 ± 0.08	0.193	Referent	0.02 ± 0.08	0.805
Total brain volume	0.01 ± 0.03	0.808	0.13 ± 0.24	0.594	Referent	0.20 ± 0.24	0.410
Frontal lobar volume	−0.04 ± 0.03	0.164	0.14 ± 0.22	0.514	Referent	−0.22 ± 0.22	0.333
Temporal horn volume	0.01 ± 0.03	0.690	−0.01 ± 0.06	0.930	Referent	−0.03 ± 0.06	0.574
Hippocampal volume (n = 391)	0.07 ± 0.05	0.151	−0.002 ± 0.01	0.841	Referent	0.01 ± 0.01	0.425
Neuropsychological data							
Logical Memory Delayed Recall	−0.02 ± 0.03	0.495	−0.11 ± 0.09	0.213	Referent	−0.20 ± 0.09	0.020*
Visual Reproduction Delayed Recall	0.05 ± 0.03	0.129	−0.24 ± 0.08	0.003*	Referent	−0.14 ± 0.08	0.073
Boston Naming Test–30 Item	−0.03 ± 0.03	0.377	−0.003 ± 0.08	0.973	Referent	−0.06 ± 0.09	0.465
Trail Making Test Part B − Part A	−0.01 ± 0.04	0.806	−0.12 ± 0.10	0.202	Referent	−0.24 ± 0.10	0.017*
Similarities	0.03 ± 0.03	0.425	−0.15 ± 0.08	0.069	Referent	−0.10 ± 0.08	0.203
Hooper Visual Organization Test	0.01 ± 0.03	0.886	−0.27 ± 0.08	0.001*	Referent	−0.15 ± 0.08	0.078

Models adjusted for age, sex, systolic blood pressure, smoking status, diabetes mellitus, hypertension treatment, and atrial fibrillation.
* Statistically significant (p <0.05).

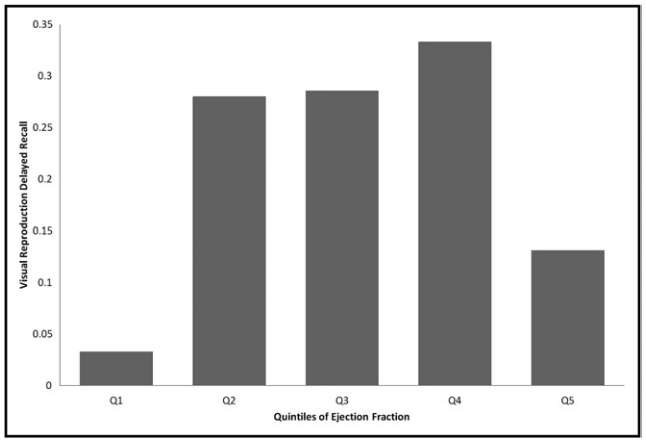

Figure 2. Mean Visual Reproduction Delayed Recall performance adjusted for age, sex, systolic blood pressure, cigarette smoking status, diabetes mellitus, hypertension treatment, atrial fibrillation, and prevalent CVD is depicted by quintile (Q) of the LVEF. The referent (quintiles 2 to 4) is significantly different from quintile 1 (p <0.001) and quintile 5 (p = 0.03).

(p = 0.03), Visual Reproduction Delayed Recall (p = 0.03), Trail Making Test Part B − Part A (p = 0.02), and the Hooper Visual Organization Test (p = 0.02) (Table 3). The nonlinear association between LVEF quintiles and Visual Reproduction Delayed Recall is illustrated in Figure 2. When analyses were repeated excluding participants with prevalent CVD, findings were similar (Table 4).

To determine if a clinically low LVEF accounted for the association between quintile 1 and cognition, participants in quintile 1 were dichotomized into groups with LVEF <55% (n = 41) and LVEF ≥55% (n = 184). Compared to the referent (quintiles 2 to 4), the lowest (<55%) LVEF subgroup had worse Visual Reproduction Delayed Recall (β = −0.42, p = 0.01) but not Hooper Visual Organization Test (β = −0.16, p = 0.34) performance. However, the low normal (≥55%) LVEF subgroup had worse Visual Reproduction Delayed Recall (β = −0.24, p = 0.004) and Hooper Visual Organization Test (β = −0.29, p <0.001) performance compared to the referent group. In post hoc analyses, the quintile 1 subgroups did not significantly differ for Hooper Visual Organization Test (p = 0.49) or Visual Reproduction Delayed Recall (p = 0.30) performance. Findings were similar when excluding patients with prevalent CVD.

To better understand the observed U-shaped association (and the relation between quintile 5 LVEF and worse cognitive performances), the multivariate-adjusted 3-category models were repeated, excluding participants with prevalent CVD and adding heart rate, C-reactive protein, body mass index, cardiac index,[18] and height-indexed left ventricular mass as covariates, which resulted in strengthened statistical significance of the primary findings (see Supplemental Table 1). The frequencies of mitral and aortic regurgitation were not disproportionately higher or lower in the highest LVEF quintile.

There was an interaction between sex and the categorical LVEF variable (quintile 1, quintiles 2 to 4, and quintile 5) in their association with Boston Naming Test–30 Item (p = 0.03), but there was no effect in stratified analyses (all p values >0.09). No interactions were observed between LVEF category and age or APOE-ε4 status in relation to the brain aging variables.

Discussion

Our epidemiologic findings suggest a U-shaped association, rather than a linear relation, between LVEF and markers of abnormal brain aging. Participants in the lowest and highest LVEF quintiles had cross-sectional evidence of abnormal cognitive changes compared to the middle referent group. The observation that a lower LVEF is associated with abnormal brain changes extends previous research examining patients with severe cardiomyopathies, which reported that a reduced LVEF was associated with memory,[4,21] reasoning,[22] and sequencing impairments.[22] In the

absence of clinical heart failure and prevalent CVD, our findings suggest that lower LVEFs are also related to abnormal brain aging. It is noteworthy that the lowest quintile of LVEF (which had significant associations with visuospatial memory and object recognition) included mostly participants with clinically normal values (i.e., 55% to 62%). The observation that even low normal values of systolic function can be associated with cross-sectional markers of abnormal brain aging is consistent with our recent work reporting that low normal values of cardiac index are associated with smaller brain volumes.[18]

The mechanism underlying associations between a lower LVEF at rest and abnormal brain aging is unknown. Despite auto-regulatory mechanisms, cerebral blood flow values are low in heart transplantation candidates but return to normal after heart transplantation.[23] Disruption of cerebral perfusion may contribute to clinical or subclinical brain injury by propagating or exacerbating cerebrovascular disease, including alterations in microvessel structure, expression of vascular cell receptors, microvessel permeability changes, and vascular remodeling.[24,25] Chronic cerebral hypoperfusion in animals leads to the development[8,9] and progression[8] of white matter changes. Another pathologic mechanism could be AD, as rats develop AD-related neuropathology, including diffuse β-amyloid peptide and amyloid precursor protein expression in the hippocampus, entorhinal cortex, and neocortex, after the acute cessation of blood flow.[26] Chronic cerebral hypoperfusion places the brain at risk for amyloid deposition, resulting in neuronal death in transgenic AD mice.[27] More research is needed to understand the mechanism accounting for the associations reported here.

An unexpected observation from the present study was that participants in the highest (top) LVEF quintile also had poorer cognitive performance in verbal and visuospatial memory, executive functioning, and visuoperceptual abilities compared to the referent. These findings persisted despite adjusting for multiple covariates, excluding participants with prevalent CVD, and post hoc consideration of additional possible confounders (e.g., enhanced inflammatory process, greater body mass index, lower cardiac index, or left ventricular hypertrophy). The mechanism underlying this observation is unknown. Whereas healthy LVEFs may be good for brain health, very high LVEFs may correspond to subtle cognitive impairment. Alternatively, our observation may reflect an epiphenomenon or another pathologic process that was not analytically considered in our models, such as anemia or thyroid disease.[28] The observed U-shaped association between the LVEF and cognitive aging requires further study, including the clinical significance of cognitive impairment, such as early functional loss.[29]

Our study had several strengths, including the large community-based cohort free of clinical dementia and stroke, comprehensive ascertainment of possible confounders, innovative cardiac imaging, rigorous quality control procedures, and core reading laboratory for processing measurements, blinded to the participants' cognitive status. However, there were methodologic limitations. The cohort was predominantly white, of European descent, and middle aged to elderly, so the generalizability to other races, ethnicities, and age groups is unknown. The ambulatory nature of the cohort, the exclusion of participants with clinical stroke or dementia, and the inclusion of subjects willing to undergo MRI yielded a healthier sample, reducing the likelihood of detecting relations that may be present in patients with more co-morbidities. The smaller data set available for analyses relating LVEF to hippocampal volume may have been insufficiently powered. Analyses were cross sectional and observational; hence, we are unable to establish a causal connection between cardiac function and brain measures. The potential for false-positive findings given the multiple statistical tests is also a concern. By accounting for multiple potential confounders, we may have "overadjusted" our models, as LVEF may predispose to cognitive impairment through intermediate mechanisms, such as hypertension or diabetes. Finally, the cardiac MRI data were acquired on average 2.5 years before the brain MRI and neuropsychological data.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2011.06.056.

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