Lower Left Ventricular Ejection Fraction Relates to Cerebrospinal Fluid Biomarker Evidence of Neurodegeneration in Older Adults

Hailey A. Kresge,[a] Dandan Liu, PhD,[b] Deepak K. Gupta, MD,[c] Elizabeth E. Moore,[a] Katie E. Osborn, PsyD,[a] Lealani Mae Y. Acosta, MD,[a] Susan P. Bell, MBBS,[a,c,d] Kimberly R. Pechman, PhD,[a] Katherine A. Gifford, PsyD,[a] Lisa A. Mendes, MD,[c] Thomas J. Wang, MD,[c] Kaj Blennow, MD, PhD,[e,f] Henrik Zetterberg, MD, PhD,[e,f,g,h] Timothy J. Hohman, PhD,[a,i] Angela L. Jefferson, PhD,[a,c]

[a]*Vanderbilt Memory & Alzheimer's Center, Department of Neurology, Vanderbilt University Medical Center, Nashville, USA*

[b]*Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA*

[c]*Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA*

[d]*Center for Quality Aging, Division of General Internal Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA*

[e]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden*

[f]*Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden*

[g]*Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK*

[h]*UK Dementia Research Institute at UCL, London, UK*

[i]*Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA*

Corresponding Author:

Angela L. Jefferson, PhD
Vanderbilt Memory & Alzheimer's Center
1207 17th Avenue South, Suite 204
Nashville, TN 37212
Phone: 615-322-8676
Fax: 615-343-1302
Email: angela.jefferson@vumc.org

Abstract

BACKGROUND:

Subclinical cardiac dysfunction is associated with decreased cerebral blood flow, placing the aging brain at risk for Alzheimer's disease (AD) pathology and neurodegeneration.

OBJECTIVE:

This study investigates the association between subclinical cardiac dysfunction, measured by left ventricular ejection fraction (LVEF), and cerebrospinal fluid (CSF) biomarkers of AD and neurodegeneration.

METHODS:

Vanderbilt Memory & Aging Project participants free of dementia, stroke, and heart failure (n=152, 72±6 years, 68% male) underwent echocardiogram to quantify LVEF and lumbar puncture to measure CSF levels of amyloid-β42 (Aβ42), phosphorylated tau (p-tau), and total tau (t-tau). Linear regressions related LVEF to CSF biomarkers, adjusting for age, sex, race/ethnicity, education, Framingham Stroke Risk Profile, cognitive diagnosis, and apolipoprotein E ε4 status. Secondary models tested an LVEF x cognitive diagnosis interaction and then stratified by diagnosis (normal cognitive (NC), mild cognitive impairment (MCI)).

RESULTS:

Higher LVEF related to decreased CSF Aβ42 levels (β=-6.50, p=0.04) reflecting greater

cerebral amyloid accumulation, but this counterintuitive result was attenuated after excluding participants with cardiovascular disease and atrial fibrillation (p=0.07). We observed an interaction between LVEF and cognitive diagnosis on CSF t-tau (p=0.004) and p-tau levels (p=0.002), whereas lower LVEF was associated with increased CSF t-tau (β=-9.74, p=0.01) and p-tau in the NC (β=-1.41, p=0.003) but not MCI participants (p-values>0.13).

CONCLUSIONS:
Among cognitively normal older adults, subclinically lower LVEF relates to greater molecular evidence of tau phosphorylation and neurodegeneration. Modest age-related changes in cardiovascular function may have implications for pathophysiological changes in the brain later in life.

Keywords: ejection fraction; CSF biomarkers; tau; vascular risk factors; Alzheimer's disease; mild cognitive impairment; neurodegeneration

Clinical Perspective:

- Our study results are among the first to suggest that subclinical reductions in left ventricular ejection fraction relate to *in vivo* molecular evidence of tau phosphorylation and neurodegeneration among older adults without memory loss. These results suggest these associations precipitate the onset of cognitive impairment.

- Given our participants had no history of clinical heart failure, results suggest subclinical changes in cardiovascular function may place the aging brain at risk for neurodegeneration. Thus, early identification and intervention of at risk individuals may offer preventative strategies to minimize downstream changes in adverse brain aging and subsequent dementia.

1. Introduction

Heart failure is associated with cognitive impairment[1,2] and an increased risk of clinical dementia.[3] Emerging evidence suggests even subclinical changes in cardiac function relate to worse cognitive performance[4,5] and increased incidence of clinical dementia, including Alzheimer's disease (AD).[6] The exact etiology underlying these associations is poorly understood. Reduced cardiac function is associated with lower cerebral blood flow (CBF) in both animals[7,8] and humans[9] with recent findings suggesting this association exists in humans free of clinical heart failure where age-related cardiac changes are more subtle.[10] It is plausible these subtle CBF reductions result in oligemia, which deprives neurons of essential ions and nutrients and promotes pathological protein homeostasis.[11] Lower CBF may also reduce blood flow shear stress necessary for maintaining vascular endothelial cell health and survival,[12] resulting in blood brain barrier (BBB) breakdown. In older adults, decades of exposure to these subtle cardiac and corresponding CBF reductions may accelerate the development of abnormal age-related neuropathology, including accumulation of AD pathology or neurodegeneration.

Prior animal research has linked reductions in CBF to AD pathology, such that manipulation of CBF in transgenic AD mouse models results in increased levels of beta-amyloid$_{42}$ (Aβ_{42})[13,14] (the protein that aggregates to form plaques) and phosphorylated tau (p-tau)[15,16] (the main component of neurofibrillary tangles). Even mild CBF reductions to create oligemic hypoperfusion in transgenic AD mouse models similarly yield increased Aβ_{42} and p-tau levels in brain tissue.[17] Independent of AD pathology, CBF reductions may also contribute to non-specific neurodegeneration, and thus increased levels of total tau (t-tau), a marker of neurodegeneration. While evidence in

clinical samples suggests CBF correlates with p-tau and t-tau levels, to our knowledge limited research has studied *subclinical cardiac dysfunction* in relation to biomarkers of amyloidosis, tangle pathology, or neurodegeneration.

This study aims to elucidate underlying pathological processes that may account for previously reported associations linking subtle reductions in cardiac function to cognitive impairment[4,5] and clinical dementia.[6] To achieve this aim, we relate a common and clinical gold standard measure of cardiac function, left ventricular ejection fraction (LVEF), to *in vivo* molecular biomarkers of AD and neurodegeneration. These biomarkers, quantified in cerebrospinal fluid (CSF), include cerebral amyloidosis ($A\beta_{42}$), tau phosphorylation which relates to neurofibrillary tangle pathology (p-tau), and neurodegeneration (t-tau).[18] Based on prior research,[19,20] we hypothesize that lower (worse) LVEF will relate to lower CSF $A\beta_{42}$ (reflecting more amyloid being sequestered in the brain), higher CSF p-tau (reflecting more tangle formation), and higher CSF t-tau concentrations (reflecting greater non-specific neurodegeneration).

2. Methods

2.1. Study Cohort

The Vanderbilt Memory & Aging Project is a longitudinal study investigating vascular health and brain aging, enriched for mild cognitive impairment (MCI).[21] Inclusion required participants be age ≥60 years, speak English, have adequate auditory and visual acuity, and have a reliable study partner. At eligibility, participants underwent record review, medical history, clinical interview (including functional assessment and Clinical Dementia Rating[22] with a reliable informant), and neuropsychological assessment. Participants were excluded for a cognitive diagnosis other than normal cognition (NC), early MCI,[23] or MCI based on the National Institute on Aging/Alzheimer's Association Workgroup clinical criteria;[24] MRI contraindication; history of major psychiatric illness, neurological disease (e.g., stroke), head injury with loss of consciousness >5 minutes, heart failure, and systemic or terminal illness that would affect follow-up participation. At enrollment participants completed an evaluation, including (but not limited to) fasting blood draw, clinical interview with medication review, physical examination, neuropsychological assessment, echocardiogram, cardiac magnetic resonance imaging, and optional lumbar puncture for CSF acquisition. Participants were excluded from the current study for missing echocardiogram, covariate, or CSF data (see **Figure 1** for inclusion and exclusion details).

2.2. Standard Protocol Approvals, Registrations, & Participant Consent

The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. Written informed consent was obtained prior to data collection. Due to

participant consent restrictions in data sharing, a subset of data is available to others for purposes of reproducing the results or replicating procedures. These data, analytical methods, and study materials can be obtained by contacting the corresponding author.

2.3. Echocardiogram

Standard 2D, M-mode, and Doppler transthoracic echocardiography was completed by a single research sonographer at the Vanderbilt University Medical Center Clinical Research Center on a Phillips IE33 cardiac ultrasound machine (Phillips Medical, Andover, MD). One of two board certified cardiologists (DKG, LAM) blinded to clinical information confirmed the quantitative measures of cardiac structure and function using commercially available software (HeartLab, AGFA Healthcare, Greenville, SC).

Image acquisition and quantification was completed according to American Society of Echocardiography guidelines. Left ventricular ejection fraction was calculated by the biplane Simpson's method from the apical 4 and 2 chamber views as (end diastolic volume – end systolic volume)/end diastolic volume * 100. Final measurements were from a single cardiac cycle for participants in normal sinus rhythm or an average of 3 cardiac cycles for participants in atrial fibrillation.

2.4. Lumbar Puncture & Biochemical Analyses

CSF was collected with polypropylene syringes using a Sprotte 25-gauge spinal needle in an intervertebral lumbar space. Samples were aliquoted in polypropylene tubes, stored at -80°C, and analyzed in batch using commercially available enzyme-linked immunosorbent assays (ELISA; Fujirebio, Ghent, Belgium) to determine $A\beta_{42}$

(INNOTEST® β-AMYLOID$_{(1-42)}$), p-tau (INNOTEST® PHOSPHO-TAU$_{(181P)}$), and t-tau levels (INNOTEST® hTAU). Intra-assay coefficients of variation were <10%. Board certified laboratory technicians processed data blinded to clinical information.

2.5. Analytical Plan

Analytical covariates were defined as follows: systolic blood pressure was the mean of two measurements. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, hemoglobin A1C≥6.5%, or oral hypoglycemic or insulin medication usage. Medication review determined anti-hypertensive medication use. Left ventricular hypertrophy (LVH) was defined on echocardiogram (LV mass index >115 g/m^2 in men, >95 g/m^2 in women). Self-report atrial fibrillation was corroborated by any one of the following sources: echocardiogram, cardiac magnetic resonance, documented prior procedure/ablation for atrial fibrillation, or medication usage for atrial fibrillation. Current cigarette smoking (yes/no within the year prior to baseline) was ascertained by self-report. Self-report prevalent cardiovascular disease (CVD) with supporting medical record evidence included coronary heart disease, angina, or myocardial infarction (note, heart failure was a parent study exclusion). Framingham Stroke Risk Profile (FSRP) score was calculated by applying points by sex for age, systolic blood pressure, anti-hypertensive medication usage, diabetes mellitus, current cigarette smoking, LVH, CVD, and atrial fibrillation. Apolipoprotein E (*APOE*) genotyping was performed on whole blood samples. *APOE-ε4* carrier (*APOE-ε4*) status was defined as positive (ε2/ε4, ε3/ε4, ε4/ε4) or negative (ε2/ε2, ε2/ε3, ε3/ε3).

For hypothesis testing, linear regression models with ordinary least square

estimates related LVEF to CSF biomarkers (one biomarker per model). All models were adjusted for age, sex, race/ethnicity, education, FSRP (excluding points assigned for age), cognitive diagnosis (NC, early MCI, MCI), and *APOE-ε4* status. To determine if effects were influenced by biological sex (as AD pathology is more common in women than men),[25] secondary models tested an *LVEF x sex* interaction and then stratified by sex. To determine if effects were driven by participants with cognitive impairment, secondary models restricting the sample to participants with NC or MCI tested an *LVEF x diagnosis* interaction and then stratified by diagnosis (NC, MCI). These models excluded early MCI participants due to the small sample size. Sensitivity analyses were performed for all models by excluding participants with atrial fibrillation and prevalent CVD. Significance was set *a priori* at $p<0.05$. Analyses were conducted using R 3.4.3 (www.r-project.org).

3. Results

3.1. Participant Characteristics

Participants included 152 adults age 60-90 years (72±6 years), 68% were men, and 93% self-identified as non-Hispanic White. LVEF ranged 51% to 82%. $A\beta_{42}$ levels ranged 289 pg/mL to 1195 pg/mL. T-tau levels ranged 77 pg/mL to 1542 pg/mL. P-tau levels ranged 13 pg/mL to 157 pg/mL. See **Table 1** for total sample characteristics and by cognitive diagnosis.

3.2. LVEF & CSF Biomarkers

LVEF related to $A\beta_{42}$ levels (β=-6.50, p=0.04), but the result was counterintuitive suggesting better LVEF corresponded to lower $A\beta_{42}$ levels reflecting greater cerebral amyloid aggregation. LVEF was unrelated to t-tau (p=0.79) or p-tau (p=0.47). In sensitivity analyses excluding participants with prevalent CVD or atrial fibrillation, the association between LVEF and $A\beta_{42}$ was attenuated (p=0.07) and non-significant models persisted with t-tau (p=0.85) or p-tau (p=0.53).

3.3. LVEF x Sex & CSF Biomarkers

The *LVEF x sex* interaction term related to $A\beta_{42}$ levels (p=0.04), whereby better LVEF counterintuitively related to lower $A\beta_{42}$ levels in female (β=-12.13, p=0.02) but not male participants (β=-1.49, p=0.72). The *LVEF x sex* interaction term did not relate to t-tau (p=0.67) or p-tau (p=0.55) levels.

To better understand the counterintuitive finding between LVEF and $A\beta_{42}$ levels in female participants, we performed several post-hoc analyses. First, we repeated the

stratified model in females without adjustments and results were similar (p=0.02). Next, we explored potential LVEF interactions with covariates on Aβ42 levels just in the female participants. All LVEF and covariate interaction terms were unrelated to Aβ42, including *LVEF x age* (p=0.59), *LVEF x education* (p=0.38), *LVEF x race/ethnicity* (p=0.18), *LVEF x APOE-ε4* (p=0.46), *LVEF x diagnosis* (p=0.38), and *LVEF x FSRP* (p=0.96). When examining interactions between LVEF and the individual FSRP components, comparisons were again null (p-values≥0.13).

3.4. LVEF x Cognitive Diagnosis & CSF Biomarkers

The *LVEF x cognitive diagnosis* interaction term related to Aβ42 levels, though this association did not meet ***a priori*** significance (p=0.06). In stratified models, better LVEF was again counterintuitively associated with lower Aβ42 levels among MCI (β=-10.80, p=0.01) but not NC participants (p=0.95). The *LVEF x cognitive diagnosis* interaction term related to t-tau (p=0.004) and p-tau (p=0.002), such that lower LVEF was associated with higher t-tau (β=-9.74, p=0.01) and p-tau levels in the NC (β=-1.41, p=0.003) but not MCI participants (p-values>0.13).

To better understand the counterintuitive finding between LVEF and Aβ42 levels in MCI participants, several post-hoc analyses were performed. First, we repeated the stratified model in MCI without adjustments and results were similar (p=0.01). Next, we explored potential LVEF interactions with covariates on CSF Aβ42 levels among MCI participants. Most LVEF and covariate interaction terms were unrelated to Aβ42 levels, including *LVEF x age* (p=0.56), *LVEF x sex* (p=0.64), *LVEF x education* (p=0.96), *LVEF x race/ethnicity* (p=0.50), *LVEF x APOE-ε4* (p=0.46), and *LVEF x FSRP* (p=0.62). When

examining interactions between LVEF and the individual components of the FSRP, a majority of comparisons were again null, including *LVEF x systolic blood pressure* (p=0.61), *LVEF x anti-hypertensive medication usage* (p=0.97), and *LVEF x LVH* (p=0.58). The exception was an association between *LVEF x diabetes* and $A\beta_{42}$ levels (p=0.02). When results were stratified, LVEF was related to $A\beta_{42}$ levels in non-diabetic MCI participants (p=0.003).

4. Discussion

The aim of this study was to elucidate underlying pathways that may provide biological insights into previously reported associations linking subtle cardiac function reductions to worse cognitive outcomes among aging adults.[4,5] [6] In main effect models, LVEF was unrelated to *in vivo* molecular biomarkers of AD and neurodegeneration. However, a diagnostic interaction between LVEF and CSF biomarkers emerged in which lower LVEF related to greater molecular evidence of neurodegeneration (t-tau) and neurofibrillary tangle pathology (p-tau) in participants with normal cognition. These associations were present despite statistically adjusting for vascular risk factors and excluding participants with prevalent CVD and atrial fibrillation, suggesting results cannot be explained by shared risk factors or comorbid disease.

Previous work, including our own, has reported subclinical reductions in cardiac function relate to worse cognition in aging adults,[4,5] including incident clinical dementia.[6] These associations are presumably due to decreased blood flow delivery to the brain, an observation supported by a recent report that subclinical reductions in cardiac output relate to modestly decreased CBF in aging adults.[10] Our current findings build on these prior observations by suggesting subtle cardiac dysfunction relates to *in vivo* molecular biomarker evidence of phosphorylation of tau and neurodegeneration. Thus, if age-related cardiac changes impact blood flow delivery to the brain (even subtly), decreased CBF may induce the earliest biochemical changes underlying neurofibrillary tangle formation and contribute to neuronal death prior to the onset of memory loss or other cognitive symptoms.

There are multiple pathways by which subclinical cardiac dysfunction and subsequent reductions in CBF may affect phosphorylation of tau and neurodegeneration. Tau is normally modified via the attachment of a monosaccharide to prevent phosphorylation.[26] This modification, however, has been shown to be down-regulated when CBF is reduced, resulting in phosphorylation of tau.[27] Research in transgenic AD mouse models has also shown that CBF reductions inhibit enzymes that function to dephosphorylate tau.[28,29] Alternatively, slight CBF reductions can result in BBB breakdown due to a loss of shear stress required to maintain vascular endothelial cells.[12] Such breakdown creates vulnerability in which toxic blood-derived proteins (e.g., thrombin, plasminogen, fibrinogen) can enter the brain,[30] resulting in neuronal toxicity and death.[31,32] This vulnerability can be exacerbated in older adults who have been shown to have increased age-related BBB breakdown in the hippocampus,[33] which anatomically corresponds to where neurofibrillary tangles first evolve in AD.[34] Therefore, subclinical reductions in LVEF may affect CBF delivery, creating or exacerbating a vulnerable environment for BBB breakdown, and inducing phosphorylation of tau, neuronal toxicity, and neuronal death.

Alternatively, while a direct pathway between age-related subclinical cardiovascular dysfunction and molecular biomarkers of tau phosphorylation and neurodegeneration is plausible, the pathway may be centrally rather than systemically driven. That is, abnormal tangle formation begins decades prior to onset of cognitive symptoms,[35] and this evolving neuropathology and subsequent neurodegeneration may drive disruptions of autonomic control circuits responsible for hemodynamic control.[36] Similarly, we cannot rule out the possibility of a shared upstream mechanism or

epiphenomenon explaining our results. Animal and additional human studies are needed to better understand mechanisms underlying this association as well as direction of effect.

It is noteworthy that associations between lower LVEF and higher CSF t-tau and p-tau levels were observed in NC but not MCI participants. The lack of association in MCI participants may be due to these participants having higher levels of neuropathological burden from concomitant disease processes (e.g., amyloidosis, cerebral small vessel disease, Lewy bodies, TAR DNA-binding protein 43) that drive their cognitive symptom manifestation. That is, other competing factors likely explain more variance in p-tau and t-tau levels among MCI participants, reducing the relative contribution of subclinical cardiac changes on these biomarker outcomes. The observation that subclinical cardiac changes relate to molecular biomarkers of neurofibrillary tangle pathology and neurodegeneration prior to onset of cognitive symptoms suggests vascular changes may initiate or contribute to early tangle pathology or cell death rather than accelerate it. Indeed, a comprehensive data driven model in older adults recently showed that vascular dysfunction precipitates AD pathology and downstream events, including $A\beta_{42}$ deposition, neurodegeneration, and cognitive impairment.[37]

We observed counterintuitive findings whereby better LVEF related to decreased CSF $A\beta_{42}$ concentrations (reflecting greater amyloid accumulation) particularly among MCI participants and among our female participants. These results were present in adjusted and unadjusted models suggesting overfitting cannot explain the unexpected results. In post-hoc analyses, we failed to identify an interaction between LVEF and

most covariates (e.g., age, education, race/ethnicity, FSRP, and *APOE*-ε4) on CSF $A\beta_{42}$ levels within the MCI or female participant subgroups. Among MCI participants, we did identify an interaction between LVEF and diabetes on CSF $A\beta_{42}$ levels. Stratified models aligned with the initial counterintuitive finding, such that higher LVEF was associated with lower CSF $A\beta_{42}$ levels (greater cerebral amyloid aggregation) in non-diabetic MCI participants. It is plausible that in the presence of $A\beta_{42}$ overaccumulation, cardiac function increases in a compensatory manner to support cerebral $A\beta_{42}$ clearance; however, that explanation is purely speculative. Alternatively, and more likely, this counterintuitive finding may be due to participant selection bias (e.g., recruitment into a memory-focused study in which participants were excluded for clinical heart failure) or due to a more complex, multivariable (e.g., 3-way) interaction or confound not captured by our methods.

Our study has several strengths, including using a well-validated and reliable measure of cardiac function reflecting the clinical gold standard, a core laboratory for processing both cardiac and CSF measurements where technicians were blinded to participant information, comprehensive ascertainment of potential confounders, and stringent quality control procedures. However, several limitations must be considered. Given the cross-sectional nature of our results we cannot draw any conclusions regarding causality. Additionally, participants were well-educated, predominantly White, and have less cardiovascular burden compared to the general population. Generalizability to other races, ethnicities, ages, or adults with poorer health is unknown. In a cohort with increased vascular risk or disease, we might expect stronger associations between cardiovascular dysfunction and *in vivo* molecular biomarkers of

neuropathology than observed here. Replication is needed, especially to better understand the counterintuitive finding with amyloidosis and to rule out the possibility of a false positive finding.

In summary, subclinical cardiac changes, captured by lower LVEF, relate to *in vivo* molecular biomarker evidence of neurofibrillary tangle pathology and neurodegeneration among cognitively normal older adults without clinical heart failure. Modest age-related changes in cardiovascular function may have implications for abnormal biochemical changes in the brain in late life, presumably through subtle reductions in blood flow delivery to the brain. Future research is needed to determine the exact mechanism and direction of effect underlying these associations.

5. Acknowledgements

The authors would like to thank the dedicated Vanderbilt Memory & Aging Project participants, their loved ones, and our devoted staff and trainees who contributed to recruitment, screening, and enrollment of the cohort. We also thank our skilled laboratory technicians at the Clinical Neurochemistry Laboratory in Mölndal, Sweden.

6. Funding Sources

This research was supported by Alzheimer's Association IIRG-08-88733 (ALJ), R01-AG034962 (ALJ), R01-AG056534 (ALJ), R01-NS100980 (ALJ), K24-AG046373 (ALJ), Paul B. Beeson Career Development Award in Aging K23-AG045966 (KAG), Paul B. Beeson Career Development Award in Aging K23-AG048347 (SPB), K01-AG049164 (TJH), K12-HL109019 (DKG), T32-GM007347 (EMM), F32-AG058395 (KEO), UL1-TR000445 (Vanderbilt Clinical Translational Science Award), S10-OD023680 (Vanderbilt's High-Performance Computer Cluster for Biomedical Research), and the Vanderbilt Memory & Alzheimer's Center.

7. Disclosures

HZ has served at scientific advisory boards for Roche Diagnostics, Samumed, Wave and CogRx, has given open lectures arranged by Alzecure, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg (all outside the submitted work).

8. References

1. Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: A clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry*. 1997;63:509-512
2. Jefferson AL, Himali JJ, Au R, Seshadri S, DeCarli C, O'Donnell CJ, Wolf PA, Manning WJ, Beiser AS, Benjamin EJ. Relation of left ventricular fraction to cognitive aging (from the framingham heart study). *The American journal of cardiology*. 2011;108:1346-1351
3. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and alzheimer disease: A population-based cohort study. *Archives of Internal Medicine*. 2006;166:1003-1008
4. Kresge HA, Khan OA, Wegener MA, Liu D, Terry JG, Nair S, Cambronero FE, Gifford KA, Osborn KE, Hohman TJ, Pechman KR, Bell SP, Wang TJ, Carr JJ, Jefferson AL. Subclinical compromise in cardiac strain relates to lower cognitive performances in older adults. *Journal of the American Heart Association*. 2018;7:e007562
5. Sabayan B, van Buchem MA, Sigurdsson S, Zhang Q, Harris TB, Gudnason V, Arai AE, Launer LJ. Cardiac hemodynamics are linked with structural and functional features of brain aging: The age, gene/environment susceptibility (ages)-reykjavik study. *Journal of the American Heart Association*. 2015;4:e001294
6. Jefferson AL, Beiser AS, Himali JJ, Seshadri S, O'Donnell CJ, Manning WJ, Wolf PA, Au R, Benjamin EJ. Low cardiac index is associated with incident dementia

and alzheimer disease: The framingham heart study. *Circulation*. 2015;131:1333-13339

7. Wanless RB, Anand IS, Gurden J, Harris P, Poole-Wilson PA. Regional blood flow and hemodynamics in the rabbit with adriamycin cardiomyopathy: Effects of isosorbide dinitrate, dobutamine and captopril. *The Journal of pharmacology and experimental therapeutics*. 1987;243:1101-1106
8. Tranmer BI, Keller TS, Kindt GW, Archer D. Loss of cerebral regulation during cardiac output variations in focal cerebral ischemia. *Journal of neurosurgery*. 1992;77:253-259
9. Massaro AR, Dutra AP, Almeida DR, Diniz RV, Malheiros SM. Transcranial doppler assessment of cerebral blood flow: Effect of cardiac transplantation. *Neurology*. 2006;66:124-126
10. Jefferson AL, Liu D, Gupta DK, Pechman KR, Watchmaker JM, Gordon EA, Rane S, Bell SP, Mendes LA, Davis LT, Gifford KA, Hohman TJ, Wang TJ, Donahue MJ. Lower cardiac index levels relate to lower cerebral blood flow in older adults. *Neurology*. 2017;89:2327-2334
11. Mies G, Ishimaru S, Xie Y, Seo K, Hossmann KA. Ischemic thresholds of cerebral protein synthesis and energy state following middle cerebral artery occlusion in rat. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 1991;11:753-761
12. Cucullo L, Hossain M, Puvenna V, Marchi N, Janigro D. The role of shear stress in blood-brain barrier endothelial physiology. *BMC neuroscience*. 2011;12:40

13. Makinen S, van Groen T, Clarke J, Thornell A, Corbett D, Hiltunen M, Soininen H, Jolkkonen J. Coaccumulation of calcium and beta-amyloid in the thalamus after transient middle cerebral artery occlusion in rats. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2008;28:263-268

14. van Groen T, Puurunen K, Maki HM, Sivenius J, Jolkkonen J. Transformation of diffuse beta-amyloid precursor protein and beta-amyloid deposits to plaques in the thalamus after transient occlusion of the middle cerebral artery in rats. *Stroke*. 2005;36:1551-1556

15. Wen Y, Yang S, Liu R, Simpkins JW. Transient cerebral ischemia induces site-specific hyperphosphorylation of tau protein. *Brain research*. 2004;1022:30-38

16. Wen Y, Yang SH, Liu R, Perez EJ, Brun-Zinkernagel AM, Koulen P, Simpkins JW. Cdk5 is involved in nft-like tauopathy induced by transient cerebral ischemia in female rats. *Biochimica et biophysica acta*. 2007;1772:473-483

17. Koike MA, Green KN, Blurton-Jones M, Laferla FM. Oligemic hypoperfusion differentially affects tau and amyloid-{beta}. *Am J Pathol*. 2010;177:300-310

18. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in alzheimer's disease. *Nat Rev Neurol*. 2010;6:131-144

19. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergstrom M, Savitcheva I, Huang GF, Estrada S, Ausen B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Langstrom B. Imaging brain amyloid in alzheimer's disease with pittsburgh compound-b. *Ann Neurol*. 2004;55:306-319

20. Yoon S, Zuccarello M, Rapoport RM. Pco(2) and ph regulation of cerebral blood flow. *Front Physiol*. 2012;3:365

21. Jefferson AL, Gifford KA, Acosta LM, Bell SP, Donahue MJ, Taylor Davis L, Gottlieb J, Gupta DK, Hohman TJ, Lane EM, Libon DJ, Mendes LA, Niswender K, Pechman KR, Rane S, Ruberg FL, Ru Su Y, Zetterberg H, Liu D. The vanderbilt memory & aging project: Study design and baseline cohort overview. *J Alzheimers Dis*. 2016;52:539-559

22. Morris JC. The clinical dementia rating (cdr): Current version and scoring rules. *Neurology*. 1993;43:2412-2414

23. Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, Walter S, Trojanowski JQ, Shaw LM, Beckett LA, Jack CR, Jr., Jagust W, Toga AW, Saykin AJ, Morris JC, Green RC, Weiner MW, Alzheimer's Disease Neuroimaging I. Clinical core of the alzheimer's disease neuroimaging initiative: Progress and plans. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* 2010;6:239-246

24. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to alzheimer's disease: Recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2011;7:270-279

25. Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of alzheimer disease pathology. *Arch Gen Psychiatry*. 2005;62:685-691

26. Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong CX. O-glcnacylation regulates phosphorylation of tau: A mechanism involved in alzheimer's disease. *Proc Natl Acad Sci U S A*. 2004;101:10804-10809

27. Zhao Y, Gu JH, Dai CL, Liu Q, Iqbal K, Liu F, Gong CX. Chronic cerebral hypoperfusion causes decrease of o-glcnacylation, hyperphosphorylation of tau and behavioral deficits in mice. *Front Aging Neurosci*. 2014;6:10

28. Song B, Ao Q, Wang Z, Liu W, Niu Y, Shen Q, Zuo H, Zhang X, Gong Y. Phosphorylation of tau protein over time in rats subjected to transient brain ischemia. *Neural regeneration research*. 2013;8:3173-3182

29. Koh PO. Focal cerebral ischemia reduces protein phosphatase 2a subunit b expression in brain tissue and ht22 cells. *Laboratory animal research*. 2011;27:73-76

30. Nelson AR, Sweeney MD, Sagare AP, Zlokovic BV. Neurovascular dysfunction and neurodegeneration in dementia and alzheimer's disease. *Biochimica et biophysica acta*. 2016;1862:887-900

31. Mhatre M, Nguyen A, Kashani S, Pham T, Adesina A, Grammas P. Thrombin, a mediator of neurotoxicity and memory impairment. *Neurobiol Aging*. 2004;25:783-793

32. Chen ZL, Strickland S. Neuronal death in the hippocampus is promoted by plasmin-catalyzed degradation of laminin. *Cell*. 1997;91:917-925

33. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, Toga AW, Jacobs RE, Liu CY, Amezcua L, Harrington MG, Chui HC, Law M, Zlokovic BV. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85:296-302

34. Braak H, Braak E. Neuropathological stageing of alzheimer-related changes. *Acta Neuropathol*. 1991;82:239-259

35. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in alzheimer disease: Age categories from 1 to 100 years. *J Neuropathol Exp Neurol*. 2011;70:960-969

36. Cencetti S, Lagi A, Cipriani M, Fattorini L, Bandinelli G, Bernardi L. Autonomic control of the cerebral circulation during normal and impaired peripheral circulatory control. *Heart*. 1999;82:365-372

37. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Perez JM, Evans AC. Early role of vascular dysregulation on late-onset alzheimer's disease based on multifactorial data-driven analysis. *Nature communications*. 2016;7:11934

38. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between csf biomarkers and incipient alzheimer's disease in patients with mild cognitive impairment: A follow-up study. *Lancet Neurol*. 2006;5:228-234

39. Baldacci F, Toschi N, Lista S, Zetterberg H, Blennow K, Kilimann I, Teipel S, Cavedo E, Dos Santos AM, Epelbaum S, Lamari F, Dubois B, Floris R, Garaci F, Bonuccelli U, Hampel H. Two-level diagnostic classification using cerebrospinal fluid ykl-40 in alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2017

9. Tables

Table 1. Participant Characteristics

	Total n=152	NC n=80	eMCI n=15	MCI n=57	p-value
Demographic & Health Characteristics					
Age, years	72±6	72±7	73±6	73±6	0.74
Sex, % male	68	71	80	60	0.20
Race, % Non-Hispanic White	93	94	93	91	0.85
Education, years	16±3	17±2	16±3	15±3	**<0.001****
Montreal Cognitive Assessment, total	26±3	27±2	26±2	24±3	**<0.001**$^{\|\|,\#,**}$
APOE-ε4, % carrier	33	29	13	44	**0.04**
Cardiovascular Characteristics					
Framingham Stroke Risk Profile,* total	11.70±3.61	11.09±3.60	12.67±2.69	12.33±3.72	0.06
Systolic blood pressure, mmHg	142±16	139±15	148±15	145±18	**0.05**$^{\|\|}$
Anti-hypertensive medication usage, %	45	45	40	47	0.87
Diabetes, %	16	11	27	21	0.17
Cigarette smoking, % current	1	0	7	2	0.11
Prevalent CVD, %	3	4	0	2	0.62
Atrial fibrillation, %	3	5	0	2	0.43
Left ventricular hypertrophy, %	3	0	7	5	0.10
Left ventricular ejection fraction, %	65±5	64±5	66±5	65±6	0.64
CSF Biomarkers					
$A\beta_{42}$, pg/mL	719±246	770±227	817±282	621±232	**<0.001**$^{\|\|,\#}$
Amyloid positive,† %	29	19	20	46	**0.002****
P-tau, pg/mL	61±26	55.8±22.1	63.4±17.2	67.6±31.0	**0.04**$^{\#}$
P-tau positive,‡ %	21	16	13	30	0.12
T-tau, pg/mL	426±228	371±176	429±125	502±288	**0.009**$^{\#}$
T-tau positive,§ %	42	29	60	56	**0.002**$^{\|\|,**}$

Note. Values denoted as mean±standard deviation or frequency. *=a modified score was included in statistical models, which excluded points assigned to age (Total=5.96±2.59; NC=5.51±2.56; eMCI=6.73±2.15; MCI=6.39±2.65). †amyloid positive=$A\beta_{42}$≤530 pg/mL.[38] ‡p-tau positive=p-tau≥80 pg/mL.[39] §t-tau positive=t-tau≥400 pg/mL.[39] P-values are presented for the main-effect comparisons across diagnostic groups; statistically significant between group-differences denoted with the following distinctions: ||NC vs. eMCI, #eMCI vs. MCI, **NC vs MCI; $A\beta_{42}$=β-amyloid$_{42}$. *APOE=Apolipoprotein E*. CVD=cardiovascular disease. CSF=cerebrospinal fluid. eMCI=early mild cognitive impairment. MCI=mild cognitive impairment. NC=normal cognition. p-tau=phosphorylated tau. t-tau=total tau.

Table 2. Left Ventricular Ejection Fraction and CSF Biomarkers

	Primary Models			Sensitivity Models Excluding CVD and Atrial Fibrillation		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Main Effects						
$A\beta_{42}$	-6.5	-12.7, -0.3	**0.04**	-6.0	-12.5, 0.4	0.07
P-Tau	-0.3	-1.1, 0.5	0.47	-0.2	-1.0, 0.5	0.53
T-Tau	-0.9	-7.6, 5.8	0.79	-0.7	-7.6, 6.2	0.85
LVEF x Sex Interaction						
$A\beta_{42}$	-13.0	-25.7, -0.3	**0.04**	-13.7	-26.8, -0.5	**0.04**
P-Tau	-0.5	-2.1, 1.1	0.55	-0.3	-1.9, 1.3	0.72
T-Tau	-3.0	-16.9, 11.0	0.67	-1.2	-15.5, 13.1	0.87
Males						
$A\beta_{42}$	-1.5	-9.6, 6.7	0.72	-1.0	-9.4, 7.5	0.82
P-Tau	-0.2	-1.0, 0.7	0.74	-0.2	-1.1, 0.7	0.68
T-Tau	-0.1	-7.2, 7.1	0.98	-0.6	-7.9, 6.8	0.88
Females						
$A\beta_{42}$	-12.1	-22.6, -1.7	**0.02**	-12.7	-23.8, -1.7	**0.03**
P-Tau	-0.6	-2.4, 1.1	0.48	-0.6	-2.4, 1.1	0.45
T-Tau	-2.7	-18.7, 13.4	0.74	-2.7	-19.1, 13.8	0.75
LVEF x Diagnostic Interaction						
$A\beta_{42}$	-12.1	-24.8, 0.6	0.06	-13.6	-26.8, -0.4	**0.04**
P-Tau	2.6	1.0, 4.2	**0.002**	2.3	0.7, 3.9	**0.006**
T-Tau	20.9	6.9, 35.0	**0.004**	19.2	4.6, 33.7	**0.01**
NC Sample						
$A\beta_{42}$	0.3	-9.1, 9.8	0.95	1.5	-8.5, 11.5	0.76
P-Tau	-1.4	-2.3, -0.5	**0.003**	-1.3	-2.2, -0.3	**0.008**
T-Tau	-9.7	-17.1, -2.4	**0.01**	-8.7	-16.3, -1.2	**0.02**
MCI Sample						
$A\beta_{42}$	-10.8	-19.4, -2.2	**0.01**	-10.9	-19.7, -2.1	**0.02**
P-Tau	1.1	-0.4, 2.6	0.13	1.0	-0.5, 2.6	0.19
T-Tau	10.2	-3.4, 23.8	0.14	9.7	-4.5, 23.9	0.18

Note. Analyses performed on n=152 participants. Models were adjusted for age, race/ethnicity, education, Framingham Stroke Risk Profile (FSRP) minus age, and cognitive diagnosis; $A\beta_{42}$=β-amyloid$_{42}$; CI=confidence interval; CSF=cerebrospinal fluid; CVD=cardiovascular disease; MCI=mild cognitive impairment; NC=normal cognition; p-tau=phosphorylated tau; t-tau=total tau.

10. Figures

Figure 1: Participant Inclusion and Exclusion Details

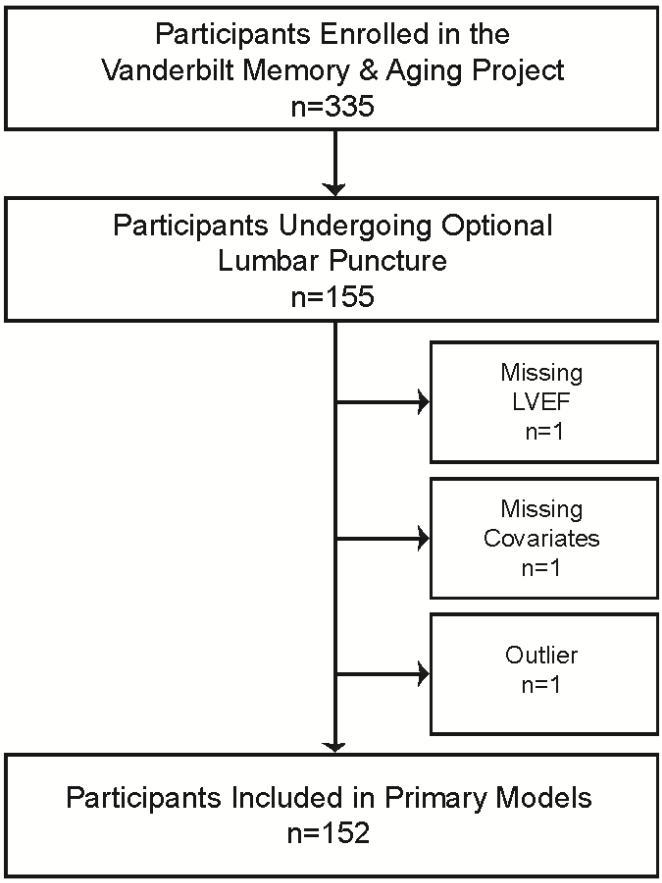
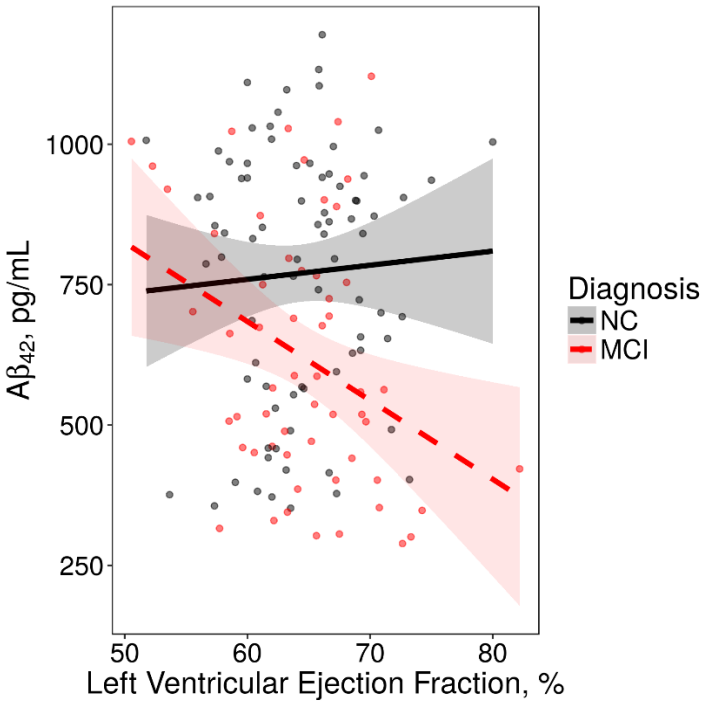


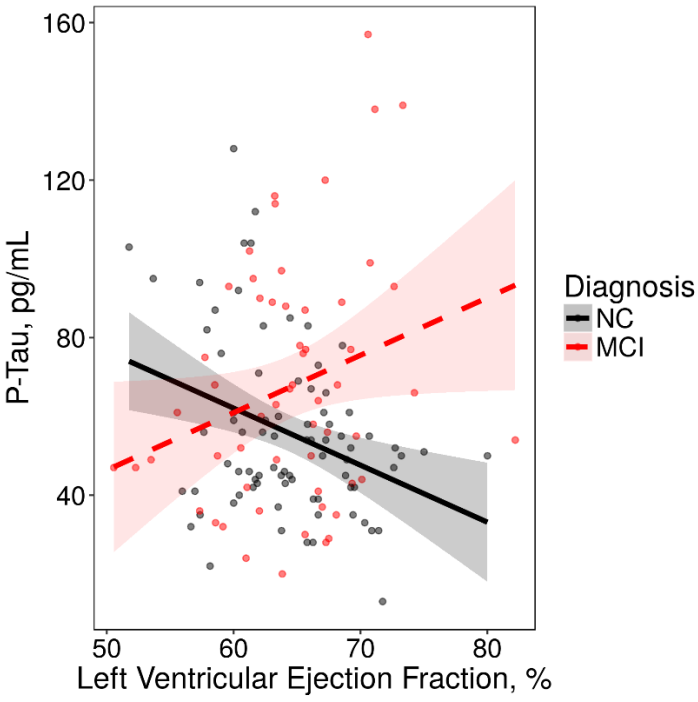
Figure 1 Legend: Missing data categories are mutually exclusive. Outlier was defined as 7 standard deviations outside the group mean. In secondary models, sensitivity analyses excluded 8 participants with cardiovascular disease or atrial fibrillation. LVEF=left ventricular ejection fraction.

Figure 2. Left Ventricular Ejection Fraction and CSF Biomarkers

Panel A. β-amyloid$_{42}$



Panel B. Phosphorylated Tau



Panel C. Total Tau

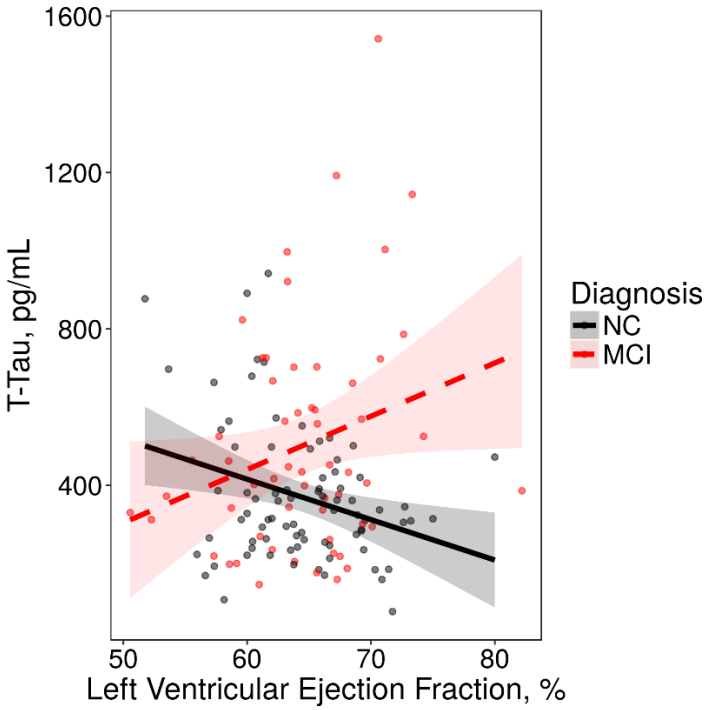


Figure 2 Legend: Solid and dashed lines reflect values of CSF biomarker outcomes (Y axis) corresponding to left ventricular ejection fraction (X axis) for a given participant profile (solid black line=normal cognition (NC), dashed red line=mild cognitive impairment (MCI)). Shading reflects 95% confidence interval. $A\beta_{42}$=beta-amyloid$_{42}$. CSF=cerebrospinal fluid. P-tau=phosphorylated tau. T-tau=total tau.