Atrial Fibrillation is Independently Associated with Structural and Cognitive Markers of Neurodegeneration

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RATIONALE AND OBJECTIVE

- Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 1-2% of the population (1).
- AF is an established cardiac risk factor for stroke, independently increasing stroke risk by 5-fold (2).
- There is increasing observational evidence for an association between AF and the risk of dementia, independent of clinical stroke (3).
- However, previous studies have shown inconsistent relationships between AF and structural and cognitive markers of neurodegeneration (4,5).

The present study sought to examine associations between AF and MRI-derived markers of neurodegeneration, including global atrophy and white matter hyperintensity burden, and performance on domain-specific cognitive tests

METHODS

1. Alzheimer's Disease Neuroimaging Initiative (ADNI): Phase 1 [6]

- Multi-site longitudinal brain imaging study (2004–2010) in the US (53 sites) and Canada (5 sites)
- We ascertained a cohort of healthy elderly adults and patients with mild cognitive impairment (MCI) and Alzheimer's dementia (AD) with and without comorbid AF from Phase 1 of ADNI (N=505)

Table 1. Cohort Characteristics

	Overall (N=505)	Known AF (N=51)	No Known AF (N=454)
Age, mean	75.9±6.4	77.71±6.8	75.7±6.3
Male, N(%)	302 (59.8)	32 (6.3)	270 (53.5)
CHADS2 score, median	1.0	2.0	1.0
On anticoagulation, N(%)	23 (4.6)	8 (1.6)	15 (3.0)
Prior stroke, N (%)	24 (4.7)	0 (0)	24 (4.7)
Baseline MMSE, median	27.0	28.0	27.0

METHODS

2. Study Outcomes

- Primary Outcome:
- MRI-derived structural volumetrics
  a. global atrophy (brain parenchymal fraction,BPF)
  b. white matter hyperintensity (WMH) burden
- Secondary Outcomes:
- Performance on domain-specific cognitive tests
  a. standardized scores on tests of verbal learning, working memory, and executive function

3. Statistical Analyses

- Multivariate linear regression used to evaluate associations between AF and volumetric and cognitive outcomes.
- All models adjusted for age, gender, diagnostic classification, baseline MMSE score, apolipoprotein E (APOE4) status, and CHADS2 score, including adjustment for prior clinical stroke

RESULTS

Table 1. Associations between AF and MRI-derived volumetrics; multivariate linear regression, adjusted for age, gender, diagnostic classification, baseline MMSE score, APOE4 status, and CHADS2 score

	β	95%CI	p-value
Mean BPF	0.27	(0.10-0.45)	**0.04**
WMH Burden	0.99	(0.98-1.14)	0.59

Table 2. Associations between AF and cognitive function; multivariate linear regression, adjusted for age, gender, diagnostic classification, baseline MMSE score, APOE4 status, and CHADS2 score

	β	95%CI	p-value
Rey Verbal Learning	0.85	(0.83-0.92)	**0.02**
Trails Making B	1.16	(1.13-1.17)	**0.04**

DISCUSSION

- AF was significantly associated with reductions in mean BPF and impaired performance on tests of verbal learning, working memory, and executive function.
- These findings indicate that cardiac arrhythmias, including AF, have adverse effects on brain morphology and cognitive function, independent of stroke.
- Consistent with recent findings from the Framingham study (7), no relationship was observed between AF and WMH burden, suggesting mechanisms other than hypertensive arteriolosclerosis underlie this relationship.
- AF has been associated with several factors that may contribute to brain atrophy and cognitive impairment in the absence of overt stroke, including endothelial damage, low cardiac output, and the presence of microemboli or microinfarcts (8).

SIGNIFICANCE

- Cardiac arrhythmias, including AF, may be an important a risk factor for adverse effects on brain morphology and cognitive function independent of stroke.
- As oral anticoagulation reduces the risk of stroke or systemic embolism up to two-thirds in patients with AF (9), AF represents an important potential treatment target for the prevention of cognitive decline and progression to dementia.

FUTURE DIRECTIONS

- Future studies evaluating whether preclincial markers of AF are associated with brain atrophy and cognition are required.
- Clinical trials evaluating structural and cognitive endpoints are required to determine the efficacy of treatments for AF for the prevention of neurodegeneration and cognitive decline.

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REFERENCES

1. Go et al. JAMA. 2001;285:2370-5.
2. Wolf et al. *Stroke*. 1991;22:983-988
3. de Bruijn et al. JAMA Neurol. 2015;72:1288-94
4. Knecht et al. Eur Heart J. 2008;29:2125-32.
5. Stefansdottir et al. Stroke 2013;44:1020-25.
6. ADNI:www.loni.ucla.edu/ADNI
7. Piers et al. Heart Rhythm 2016;doi:2016.07.004
8. Kalantarian et al. Ann Intern Med. 2014;161:650-8
9. Connolly et al. 2011. NEJM; 364(9):806-817