Atrial Fibrillation Is Associated With Lower Cognitive Performance in the Framingham Offspring Men

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The purpose of this study was to investigate the association of atrial fibrillation (AFIB) with multiple measures of cognitive performance in a large community-based sample extensively characterized for vascular risk factors. Our primary analysis included 1011 Framingham Offspring Study (Framingham, Mass) men, mean age = 61.0 (37-89) years, free of clinical stroke and dementia. Using multivariable linear regression models, we related the presence (n = 59) versus absence (n = 952) of AFIB in men to a global measure of performance and multiple measures of specific cognitive abilities assessed an average of 8 months after the AFIB surveillance period. Adjusting for age, education, multiple cardiovascular risk factors, and cardiovascular disease, men with AFIB exhibited significantly lower mean levels of cognitive performance compared with men in normal sinus rhythm. Men with AFIB exhibited lower performance on global cognitive ability and cognitive abilities including Similarities (abstract reasoning), Visual Reproductions-Immediate Recall, Visual Reproductions-Delayed Recall, Visual Organization, Logical Memory-Delayed Recall, and Trail Making A (scanning and tracking) and Trail Making B (scanning, tracking, and executive functioning). Further studies leading to a better understanding of the mechanisms underlying the relation between AFIB and cognitive performance are important. **Key Words:** Atrial fibrillation—cognition—cognitive performance—male—cardiovascular diseases—cardiovascular epidemiology.

Atrial fibrillation (AFIB) is the most common sustained cardiac arrhythmia encountered in clinical practice[1,2] and remains a major risk factor for stroke.[3] AFIB has been associated with reduced cardiac output, resultant cerebral hypoperfusion,[4] systemic arterial embolism,[5-7] periventricular white matter lesions,[8] and all-cause mortality.[9]

Consequently, it is not surprising to find that AFIB is associated with lower cognitive performance. Indeed, AFIB

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is related to prestroke dementia even after adjustment for cerebral atrophy, age, and past transient ischemic attack.[10] As compared with matched referents in normal sinus rhythm, older adults with AFIB but no clinical history of stroke exhibited poorer cognitive performance on several neuropsychologic tests.[11,12] Sabatini et al,[13] adjusting for age, sex, education, activities of daily living, severity-of-disease (APACHE II) scores, and depressed mood, reported that patients in acute care with AFIB over 70 years of age performed at a lower level on the Mini-Mental Status Examination (MMSE) in comparison with a reference group in normal sinus rhythm. After exclusion of patients with history of transient ischemic attack, stroke, or both, persons with chronic AFIB have exhibited a 3-fold risk of cognitive deficit compared with persons in normal sinus rhythm even after statistically adjusting for age, education, depressed mood, hypertension, and diabetes.[14]

Community-based studies also have reported an association between AFIB and lowered cognitive performance. The Uppsala, Sweden Study investigators reported that in elderly men without prior stroke, AFIB was associated with lower cognitive composite scores (MMSE and Trail Making Tests) after accounting for age, education, occupation, 24-hour diastolic blood pressure, diabetes, and ejection fraction.[15] In the Rotterdam Study, stroke-free women with AFIB had a higher prevalence of dementia and cognitive impairment (MMSE < 26).[16] These associations were attenuated modestly by adjustment for myocardial infarction, blood pressure, peripheral atherosclerosis, diabetes mellitus, education level, and various medications.

The Uppsala and Rotterdam investigations[15,16] point to the importance of examining relations between AFIB and cognitive ability in community-based samples, but these studies used the MMSE test alone[16] or both the MMSE and the Trail Making Tests.[15] In the current study we used a large community-based sample, the Framingham Offspring Study, to examine the association between AFIB and multiple cognitive abilities. For our analysis, we made use of an existing data set containing information on prevalent AFIB and neuropsychologic test performance. Less than 2% of the sample of women (n = 17) were diagnosed with AFIB and, thus, we confined our primary analyses to men because the prevalence of AFIB was higher (n = 59, 6%) and an interpretable set of analyses was possible.

The battery of tests used with the Framingham Offspring sample allowed us to relate AFIB to deficits in multiple cognitive abilities. Further, because of the extensive characterization of these study participants for cardiovascular disease and cardiovascular disease risk factors, we were able to adjust associations between AFIB and cognitive performance for multiple potential confounders. Because of the stroke and dementia review conducted for the Framingham Offspring[17,18] we were able to exclude persons with a history of clinical stroke and dementia. The focus on the relation between AFIB and lowered levels of performance within a generally normal range of performance is important given the fact that, for some individuals, lower performance levels in midlife can progress to more serious forms of cognitive deficit.[19] Whereas a number of previous studies focused on older adults, we extended the age range downward so as to include middle-aged and elderly adults (range: 37-89 years).

We hypothesized that men with AFIB would exhibit lower levels of cognitive performance than persons free from AFIB, adjusting for age, education, cardiovascular risk factors, and prevalent cardiovascular disease.

Methods

Study Sample

The Framingham Offspring Study participants, recruited in 1971, were biological children or related by marriage to a biological child of members of the original Framingham Heart Study cohort. Participants were examined 7 times during a 30-year period to identify risk factors for cardiovascular and cerebrovascular disease. All 1506 male Offspring Study members who participated in the seventh examination were eligible for the current investigation. Women were not excluded from the sample by design, but rather because there were too few with AFIB for analyses to be performed for women separately.

Of the 1506 eligible men, we excluded 495 participants for the following reasons: declined to participate in the neuropsychologic examination (n = 457); diagnosed dementia (n = 2); and prior clinical stroke (n = 36). After exclusions, 1011 men remained eligible. Of those eligible, 59 had been given a diagnosis of AFIB. Details of stroke surveillance and diagnostic methods have been published previously.[18-20] Stroke was defined as a focal neurologic deficit of acute onset persisting more than 24 hours. Offspring participants were systematically queried on each of the 7 periodic examinations regarding the occurrence of symptoms of stroke and all interim medical visits involved a stroke review. Offspring suggested to have stroke were given a neurologic examination after hospital admission and at 3, 6, and 12 months after discharge from the hospital using computed tomography or magnetic resonance imaging. Scan films were reviewed and hospital surveillance data were collected to identify all in-hospital strokes. The screening and examination procedures for dementia have been described previously.[20] The final diagnosis of dementia was determined by a neurology-neuropsychology review panel, using well-established clinical criteria.[21,22]

Table 1. *Description of the cognitive tests administered to the participants of the Framingham Offspring Study (1971-2005) and the means and SD of the raw scores for men*

Neuropsychologic test	Latent cognitive ability tested	Mean	SD
Wechsler adult intelligence scale			
Similarities	Abstract reasoning	16.8	3.8
Wechsler memory scale			
Paired associates learning	New learning and memory	13.0	3.3
Logical memory-immediate recall	Immediate recall of verbal passages	10.9	3.5
Logical memory-delayed recall	Delayed recall of verbal passages	9.9	3.6
Logical memory-delayed recognition	Delayed recognition of verbal passages	9.3	1.4
Visual reproductions-immediate recall	Immediate recall of visual/spatial stimuli	9.0	3.3
Visual reproductions-delayed recall	Delayed recall of visual/spatial stimuli	8.2	3.5
Visual reproductions-delayed recognition	Delayed recognition of visual/spatial stimuli	3.0	1.1
Hooper visual organization test	Visual organization with some demands on executive function	24.7	3.5
Halstead-Reitan Battery			
Trail making A	Attention, concentration, visual scanning, and speed of tracking	34.2	16.9
Trail making B	Attention, concentration, visual scanning, and speed of tracking; demands on executive function	85.4	46.6

Raw scores and SDs may be used to derive the raw score least square means given in *z* scores in Table 3.
Detailed test descriptions may be found in Au et al[26] and Lezak.[27]

The Framingham Study was reviewed by our institutional review board and all participants signed written informed consent.

Design

Presence of AFIB was related to neuropsychologic test performance, which was assessed at an average of 8 months (SD = 7 months) after the seventh examination. AFIB was diagnosed if AFIB or atrial flutter was present on an electrocardiogram (ECG) (or Holter) obtained from the hospital (69%), an outside physician (14%), at the Framingham Study examination (11%), or by review of the participants history (6%) at any point at, or before, examination 7 (i.e., the participant had a history of paroxysmal or chronic AFIB).[23] The ECG interpretation was confirmed by one of two Framingham cardiologists.

Covariates

Age and education at the time of neuropsychologic testing (examination 7) were determined by self-report. Clinical covariate data were based on data obtained between examinations 1 to 7 unless otherwise specified. At each examination, the following covariate data were obtained. Systolic blood pressures were recorded as the average of the Framingham clinic physician's two measurements with the participant in a sitting position. Current smoking (cigarettes/day within year before examination) and alcohol consumption (oz/wk) were classified by self-report. Body mass index (BMI) was measured as weight (kg)/height (m)^2. Methods for total cholesterol (mm/dL) determinations have been described previously.[24] Depressed mood was defined as a score greater than 16 on the Center for Epidemiological Studies Depression Scale (CESD) at examination 7.[25] Diabetes was considered present if, at examination 7, the participant had a fasting blood sugar of at least 126 mg/dL, had a diagnosis of diabetes mellitus before examination 7, or used a hypoglycemic agent or insulin. Cardiovascular disease included the presence of one or more of the following diagnoses before and including examination 7: coronary heart disease (myocardial infarction, angina pectoris, coronary insufficiency), intermittent claudication, and heart failure. Left ventricular (LV) hypertrophy was defined as present if the ECG revealed voltage criteria for hypertrophy accompanied by a strain pattern at examination 7. Coronary artery bypass graft (CABG) surgery was defined as CABG at any time before and including examination 7. Treatment with antihypertensive drugs, anticoagulant drugs, digitalis, and beta-blocking drugs was determined at examination 7.

Neuropsychologic Battery

The Framingham Offspring neuropsychologic test battery has been described in detail previously.[26] The psychometric tests used in the current study are briefly described in Table 1. These tests are predictive of future stroke and dementia in previous Framingham investigations.[17,19] A detailed description of each test may be found in a text by Lezak.[27] Table 1 summarizes the abilities measured by each test, and gives the raw score mean and SD obtained for the final sample of men reported in the current study.

Statistical Analyses

To be able to compare the results of each of these tests on the same scale of measurement, raw test scores were transformed to z (standardized) scores. This linear transformation does not change the distribution of scores but allows all scores to be expressed in SD units. Inspection of the distributions of the cognitive test scores indicated that the Trails A and B time scores were positively skewed, so they were natural log transformed before z score transformation. The z scores for each of the cognitive tests were summed and divided by the number of tests to obtain a Global Composite score. The Global Composite score was designated as the primary cognitive variable for analyses so as to protect against error related to multiple testing. The decision rule was as follows: if the Global Composite score did not reach statistical significance in relation to AFIB we did not pursue the tests of associations between AFIB and the individual test scores. A 2-sided P value ($P < .05$) was considered statistically significant.

General linear models were used to accommodate class variables and continuously distributed variables in the same multivariable regression model. The exposure AFIB (yes/no) was a class variable, but the covariate models consisted of mixed class and continuously distributed variables. Adjustment for covariates was done in two steps: (1) basic model (age + education); and (2) multivariable model: basic model + systolic blood pressure (average mm Hg), diabetes mellitus (yes/no), LV hypertrophy (yes/no), cardiovascular disease (yes/no), depressed mood (yes/no), total cholesterol (average mg/dL), antihypertensive treatment (yes/no), cigarettes/day (average), alcohol use (average mL/wk), and BMI (average kg/m^2).

History of CABG surgery and drugs commonly used in the treatment of AFIB, anticoagulants, digitalis, and beta-blockers were used as additional covariates in a secondary set of analyses dealing with potential confounds other than cardiovascular risk factors and events. In additional secondary analyses we adjusted for pre-folate fortification plasma homocysteine concentrations at examination 5 (μmol/L) and apolipoprotein ϵ4 genotype (ϵ2/ϵ4, ϵ3/ϵ4, ϵ4/ϵ4 present v no ϵ4 allele present). These variables were not included as covariates in the primary multivariable analyses (reported above) because of the loss of data for 166 men (including 9 persons with AFIB).

Results

To evaluate potential sample bias, men who participated in this study were compared with those men who were excluded because of lack of neuropsychologic test data. The pattern of results was the same for men in the AFIB and non-AFIB groups. In general, men who were included in our study exhibited lower ($P < .05$) mean systolic blood pressure (126 v 128 mm Hg), lower prevalence of hypertension (33% v 41%), and drank less alcohol (101 v 118 mL/wk) but did not differ from participants with respect to other health characteristics (Table 2) or age, although those who agreed to testing had modestly higher levels of education (14.7 v 14.5 years, $P < .05$).

Table 2 summarizes the demographic and health characteristics (covariates) by AFIB history. The AFIB group was older; exhibited higher mean systolic blood pressure and BMI; and included more persons with diabetes, cardiovascular disease, LV hypertrophy, and CABG surgery. The proportions of persons treated with antihypertensive drugs, anticoagulant drugs, digitalis, beta-blocking drugs, or a combination of these were also significantly higher in the AFIB group. Mean duration of AFIB was 5.9 years (SD = 4.9).

Table 3 displays means and SE for the non-AFIB and the AFIB groups with age and education adjustment and with adjustment for the multivariable covariate model. With adjustment for age and education, AFIB was significantly associated with lower cognitive performance for the Global Composite, Similarities (abstract reasoning), Visual Reproductions-Immediate Recall, Visual Reproductions-Delayed Recall, Hooper Visual Organization, Logical Memory-Delayed Recall, Logical Memory-Delayed Recognition, and Trail Making A and Trail Making B. Most importantly, with adjustment for the multivariable covariate set, AFIB was related to the Global Composite score and the same cognitive measures with the following exceptions. With multivariable adjustment, AFIB was no longer significantly associated with Logical Memory-Delayed Recognition.

The magnitude of the association of AFIB with cognitive performance may be appreciated by examining the mean z scores for AFIB and non-AFIB groups for the men adjusted for the multivariable covariate set shown in Table 3. Using the test of abstract reasoning, Similarities,[28] as an example, the difference in performance between the non-AFIB and the AFIB cohorts was approximately 0.5 SD. Compared with their counterparts without AFIB, the Global Composite score in participants with AFIB was approximately 0.25 SD lower. To provide a perspective in terms of risk of poor performance, we calculated the odds ratio associated with achieving a Global Composite score below the lower 25th percentile of the total distribution of the Global Composite scores for the total sample (excluding stroke and dementia) with

Table 2. *Demographic characteristics and covariables of the Framingham Offspring Study (1971/2005) participants in the atrial fibrillation and cognition study of men*

Variable	No atrial fibrillation (n = 952)			Atrial fibrillation (n = 59)		
	Mean	SD	Percent	Mean	SD	Percent
Age, y§	60.5	9.4		68.1	7.0	
Education, y	14.8	2.5		14.2	2.9	
Systolic blood pressure, mm Hg*‖	126	12		130	14	
Diastolic blood pressure, mm Hg‖	79	7		78	6	
Alcohol, mL/wk‖	115	112		124	136	
Cigarettes/day‖	6	9		5	7	
Total cholesterol‖	201	29		202	27	
BMI†‖	27.5	3.6		28.9	3.6	
Depressed mood (CESD > 16)			4.7			8.5
Diagnosis of diabetes†			11.3			23.7
History of cardiovascular disease§			12.0			57.6
ECG left ventricular hypertrophy‡			2.9			11.3
Coronary artery bypass graft surgery§			4.0			34.0
Treatment with antihypertensive drugs§			32.8			62.7
Treatment with anticoagulant drugs§			1.3			39.0
Treatment with digitalis§			0.7			32.6
Treatment with beta-blockers§			17.0			55.1

BMI, Body mass index; *CESD*, Center for Epidemiological Studies Depression Scale; *ECG*, electrocardiogram.
*$P < .05$; †$P < .01$; ‡$P < .001$; §$P < .0001$.
‖Mean value based on average of determinations during examinations 1/7. A definition of each variable is contained in the section on covariates under methods.

adjustment for age, education, and the other covariates in the multivariable model. The odds ratio associated with performance at or below the 25th percentile in the presence of AFIB was 4.01, P less than .0005 (95% confidence limits = 1.84, 8.74).

Secondary Analyses

Heart failure has been identified as a potentially important confounder of the association between AFIB and cognitive performance.[29] Therefore, although it was a component of our aggregate cardiovascular disease variable, we substituted heart failure for cardiovascular disease and repeated the analyses with the multivariable models previously reported. The pattern of significant findings was unaltered by this substitution.

Of the men free from AFIB, 4% had undergone CABG surgery some time before or including examination 7 as compared with 34% with AFIB. When CABG surgery (yes/no) was added to the multivariable model, it was not significantly related to the Global Composite score (P = .34) or to any of the cognitive outcome measures (P range = .09-.95), and its presence in the model did not change the pattern of significant relations between AFIB and cognitive performance. Thus, for example, z score means for the Global Composite were 0.02 and −0.25, respectively (P < .001) for the non-AFIB and AFIB groups.

Drugs used in the treatment of AFIB may confound the relation between AFIB and cognitive performance. Consequently, we added treatment with digitalis (yes/no), beta-blocking agents (yes/no), and anticoagulation drugs to the multivariable model (Table 3). Neither digitalis (P = .88) nor beta-blocking agents (P = .94) were related to the Global Composite score or any of the other measures (P range = .11-.97) and including them in the model did not alter the relations between AFIB and cognitive performance reported in Table 3. The results were the same with antihypertensive treatment (yes/no) included or excluded from the analysis above.

Anticoagulation treatment was associated with poorer performance on the Global Composite score (P < .05) and on the Visual Reproductions-Immediate Recall (P < .05), Visual Reproductions-Delayed Recall (P < .01), and Trail Making B (P < .01) tests. In the context of this model, relations between AFIB and cognitive performance were modestly attenuated, but all relations between AFIB and the cognitive measures that were significant in the absence of the adjustment for anticoagulant drugs (Table 3) remained significant with a single exception. Men with AFIB no longer differed significantly from men without AFIB on the Hooper Visual Organization Test (P = .13).

Table 3. *Age-, education-, and multivariable-adjusted means and SE by atrial fibrillation status for Framingham Offspring Study (1971/2005) men*

	Age- and education-adjusted			Multivariable-adjusted		
Cognitive test	*z* Mean	SE	*P* <	*z* Mean	SE	*P* <
Global composite						
No atrial fibrillation	0.0118	0.0280	.0001	0.0175	0.0172	.0003
Atrial fibrillation	−0.3100	0.0702		−0.2667	0.0759	
Similarities						
No atrial fibrillation	0.0293	0.0281	.0001	0.0371	0.0285	.0001
Atrial fibrillation	−0.4672	0.1146		−0.4749	0.1253	
Paired associates learning						
No atrial fibrillation	0.0047	0.0303	.40	0.0145	0.0307	.56
Atrial fibrillation	0.1032	0.1244		−0.0670	0.1360	
Visual reproductions-immediate recall						
No atrial fibrillation	0.0306	0.0289	.0001	0.0338	0.0293	.0005
Atrial fibrillation	−0.4760	0.1179		−0.4340	0.1289	
Visual reproductions-delayed recall						
No atrial fibrillation	0.0279	0.0292	.0002	0.0281	0.0295	.002
Atrial fibrillation	−0.4274	0.1187		−0.3924	0.1297	
Visual reproductions-delayed recognition						
No atrial fibrillation	0.0084	0.0309	.33	0.0039	0.0312	.81
Atrial fibrillation	−0.1185	0.1256		−0.0308	0.1371	
Hooper visual organization						
No atrial fibrillation	0.0227	0.0294	.002	0.0241	0.0294	.04
Atrial fibrillation	−0.3697	0.1207		−0.2488	0.1306	
Logical memory-immediate recall						
No atrial fibrillation	0.0086	0.0301	.24	0.0136	0.0303	.26
Atrial fibrillation	−0.1393	0.1226		−0.1408	0.1333	
Logical memory-delayed recall						
No atrial fibrillation	0.0161	0.0303	.03	−0.0199	0.0305	.04
Atrial fibrillation	−0.2752	0.1233		−0.2683	0.1339	
Logical memory-delayed recognition						
No atrial fibrillation	0.0160	0.0316	.04	0.0162	0.0313	.36
Atrial fibrillation	−0.2563	0.1286		−0.1152	0.1377	
Trail making A						
No atrial fibrillation	0.0194	0.0297	.008	0.0264	0.0299	.008
Atrial fibrillation	−0.3164	0.1218		−0.3373	0.1326	
Trail making B						
No atrial fibrillation	0.0293	0.0280	.0001	0.0385	0.0283	.0004
Atrial fibrillation	−0.4663	0.1137		−0.4169	0.1241	

Multivariable-adjusted model includes the following covariates: age, education, systolic blood pressure, cigarettes/day, alcohol (oz/wk), body mass index, total cholesterol, depressed mood, electrocardiographic left ventricular hypertrophy, diabetes, cardiovascular disease, and treatment with antihypertensive drugs.

In an additional secondary analysis we adjusted for pre-folate fortification plasma homocysteine concentrations at examination 5 (μmol/L) and apolipoprotein ϵ4 genotype. Again, the same pattern of findings was observed as was reported for the multivariable model (Table 3) except that AFIB was not associated with the Hooper Visual Organization Test ($P = .12$).

Women were excluded from the primary analyses because of the low number who experienced AFIB (n = 17) as compared with those free of AFIB (n = 1114). A power analysis making use of data for the men confirmed the fact that there was insufficient power to perform the analyses for women. The difference in the Global Composite scores between men with prevalent AFIB and men free of AFIB were 0.42 SD after adjustment for age and education and 0.38 SD after multivariable adjustment. These translated to effect sizes on the order of 0.5 SD difference between comparison groups in men. This study had power of 53% to detect an effect size of the same magnitude in women. A difference between women with AFIB and free of AFIB of 0.67 SD in the Global Composite score is required to ensure 80% power in the women.

An analysis was done to determine if adding the women to the sample of men would alter the pattern of findings observed for men. Results were the same as those obtained for men.

Discussion

Compared with their counterparts in normal sinus rhythm, men with a history of AFIB performed more poorly on a composite of cognitive abilities and on a range of cognitive performance measures. In our study, as in the two previous large community-based studies,[15,16] AFIB was associated with a measure of overall cognitive ability. Ott et al[16] used the MMSE and Kilander et al[15] used the MMSE and the Trails A and B tests in a composite score. In our study, global ability was indexed by a composite score derived by averaging performance over the standardized scores for the 11 individual test scores in our battery. More importantly, because we used 11 cognitive tests, we were able to examine associations between AFIB and performance for a range of cognitive abilities.

For the basic model (age and education adjustment) and for the multivariable covariate models used (Table 3), AFIB in men was associated with lower mean levels of performance on the following neuropsychologic tests: Similarities; Visual Reproductions-Immediate Recall; Visual Reproductions-Delayed Recall; Hooper Visual Organization Test; Logical Memory-Delayed Recall; Trail Making A; and Trail Making B.

History of CABG surgery between examinations 1 and 7 was unrelated to cognitive performance and did not affect findings with the multivariable model (Table 3). Antihypertensive drugs, beta-blockers specifically, and digitalis were unrelated to any of the cognitive measures, but anticoagulant drug treatment (yes/no) was related to lower cognitive performance for several cognitive test scores. However, when anticoagulant drug treatment was added to the multivariable model, only 1 of the 8 previously significant associations between AFIB and cognitive performance (AFIB with the Hooper Visual Organization Test) was rendered nonsignificant. A conclusion that anticoagulant drug treatment causes performance decrement is clearly not warranted. Anticoagulant drugs may be a proxy for comorbidities in AFIB. Of the persons with AFIB, 55% were being treated with anticoagulant drugs; guidelines recommend treating individuals in AFIB with anticoagulants if they are older or have comorbidities associated with an increased likelihood of stroke.

The pattern of poorer cognitive performance in this investigation is consistent with the vascular cognitive impairment construct as defined by Bowler and Hachinski.[30] We see, in the pattern of magnitude of regression coefficients (Table 3) and the pattern of tests related significantly to AFIB, 3 elements of AFIB-related deficit characteristic of vascular cognitive impairment so defined: (1) AFIB was associated with multiple domains of cognitive performance; (2) AFIB was related to deficits in visual memory (Visual Spatial-Immediate and Delayed Recall) and verbal memory (Logical Memory-Delayed Recall), but not exclusive of other deficits; (3) AFIB was related to speed of performance (Trails A and B) and executive functioning (Trails B). Verbal memory was impaired but less impaired than visual spatial memory and verbal memory loss did not predominate. The magnitude of relations was larger for visual-spatial memory, speeded performance, and executive function.

To our knowledge, one other study has used multiple measures of cognitive performance in a community-based sample including participants with AFIB. Using volunteers from a general practice, over age 60 years, Park et al[31] compared patients with AFIB (n = 174) with control subjects in normal sinus rhythm (n = 188). With statistical adjustment for age, the AFIB group performed more poorly on a timed telephone task but there were no differences between those with and without AFIB on variants of this task and other measures of cognition. Coronary heart disease, diabetes, hypertension, cholesterol, general health status, heart failure, duration of AFIB, and education were unrelated to neuropsychologic test performance and, thus, were not used as statistical controls. Our study differs in several respects from the study of Park et al.[31] Foremost among these differences is that we did not use a case-control study with patient volunteers and did not restrict our study to older adults. We used a community-based sample with a large non-AFIB referent group and our patients ranged in age from 37 to 89 years at neuropsychologic testing.

Potential Mechanisms

A variety of mechanisms linking AFIB to performance deficits and dementia have been postulated, including vascular insufficiency, subclinical stroke, poorer cardiac output, and shared burden of cardiovascular risk factors.[11,12,16,32-40] White matter lesions are associated with AFIB[8,39] and to lower cognitive performance and dementia.[15,16,39]

AFIB is common among elderly individuals and is often associated with heart failure[41] and reduced cardiac output and consequent cerebral hypoperfusion.[4,5,38] Sabatini et al[13] note that hypoperfusion can also result from beat-to-beat variability in the length of the cardiac cycle. Lavy et al[42] reported that cerebral blood flow was lower in patients with chronic AFIB as opposed to referents in normal sinus rhythm. Interestingly, hypoperfusion and altered cerebral blood flow have long been suggested as possible mechanisms explaining mild cognitive deficits associated with sustained untreated hypertension.[43,44]

Clearly, it is important to separate the adverse influences of heart disease (in general) on cognition from that of AFIB. As Vingerhoets[32] points out in a review of this literature, AFIB is related to a wide spectrum of heart disease and, thus, it is not clear whether cardiogenic emboli in AFIB result from AFIB per se or from underlying cardiac disease. Indeed, an important question if relating AFIB to cognitive performance is whether AFIB is just a marker for cardiovascular disease in general. Among other potential confounds, we adjusted for age, education, blood pressure, smoking, diabetes mellitus, ECG LV hypertrophy, total cholesterol, depressed mood, BMI, and prevalent cardiovascular disease. Regardless of these adjustments, AFIB was associated with the Global Composite score and 8 measures of cognitive ability. Thus, it does not appear that cardiovascular disease in general provides a complete explanation of our results (or previous findings) demonstrating that lower cognitive performance was associated with AFIB. However, we cannot exclude the possibility that AFIB may serve as a proxy for duration or severity of the burden of cardiovascular disease and its risk factors.

Limitations

Participants of the Framingham Study are highly educated and mostly white and our study excluded women because of the small percentage of women in the sample who had been given the diagnosis of AFIB. Thus, our findings may not generalize to persons of lower educational levels, to other ethnic groups, and to women.

Sample bias toward modestly healthier participants may have occurred because those who agreed to the neuropsychologic examination drank slightly less alcohol and exhibited lower blood pressure values. Similarly, it is possible that persons with more complicated AFIB did not survive to participate at examination 7. If anything, selecting for a healthy cohort would serve to underestimate the association between AFIB and cognitive function.

Whereas the surveillance for presence of AFIB was based on longitudinal data, neuropsychologic assessment was based on a single assessment of cognitive performance after examination 7. As noted above, we cannot establish either a temporal or causal relation between AFIB and a decline in cognitive performance; the lower cognitive performance may have antedated the AFIB or may be related to the higher burden of cardiovascular disease and its risk factors present in individuals with AFIB. Longitudinal studies are clearly necessary.

The absence of routine Holter monitoring for every patient in our study is a limitation; as such we cannot comment on variation of cognitive performance by paroxysmal versus chronic AFIB. We adjusted for a number of potentially important confounds in this study. It is, thus, our hope that these data from the Framingham Offspring Study will cause more attention to focus on AFIB in relation to cognition. This would seem particularly important in view of data suggesting that AFIB may be one of a number of risk factors for conversion from mild cognitive deficit to dementia.[45]

Contributions and Implications

Our community-based study highlights the importance of the association between AFIB and multiple cognitive abilities in the absence of stroke and dementia. The risk of performance in the lower quartile of global ability was raised 4-fold by the presence of AFIB. Importantly, these associations between AFIB and cognitive performance persisted after adjustment for age, education, multiple cardiovascular disease risk factors, prevalent cardiovascular disease, and other potential confounds.

Clearly, more attention should focus on the lower cognitive functioning observed with AFIB. A number of hypotheses as to the mechanisms underlying the associations between AFIB and cognitive performance have been advanced in the literature. Future studies, particularly studies with longitudinal data on both AFIB and cognitive performance, should be directed to a better understanding of these mechanisms.

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