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CLINICAL RESEARCH
Atrial fibrillation

Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion

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Aims Atrial fibrillation (AF) has been associated with cognitive impairment. Additionally, brain volume may be reduced in individuals with AF. Potential causes may include cerebral micro-embolism or reduced stroke volume due to the beat-to-beat variation in AF. The aims of this study were to measure cerebral blood flow and estimate whole brain perfusion in elderly individuals with and without AF.

Methods and results Blood flow in the cervical arteries was measured with phase contrast MRI and brain perfusion estimated in a large cohort from the AGES-Reykjavik Study. Individuals were divided into three groups at the time of the MRI: persistent AF, paroxysmal AF, and no history of AF. Of 2291 participants (mean age 79.5 years), 117 had persistent AF and 78 had paroxysmal AF but were in sinus rhythm at the time of imaging AF. Those with persistent AF had lower cholesterol and used more anti-hypertensive medication and warfarin. The three groups were similar with regard to other cardiovascular risk factors. Those in the persistent AF group had significantly lower total cerebral blood flow on average, 472.1 mL/min, both when compared with the paroxysmal AF group, 512.3 mL/min ($P < 0.05$) and the no AF group, 541.0 mL/min ($P < 0.001$). Brain perfusion was lowest in the persistent AF group, 46.4 mL/100 g/min compared with the paroxysmal AF group, 50.9 mL/100 g/min in ($P < 0.05$) and those with no AF, 52.8 mL/100 g/min ($P < 0.001$).

Conclusion Persistent AF decreases blood flow to the brain as well as perfusion of brain tissue compared with sinus rhythm.

Keywords Atrial fibrillation • Cognitive impairment • Dementia • Brain volume • Cerebral blood flow • Brain perfusion

Introduction

Atrial fibrillation (AF) is an important risk factor for stroke and has been implicated in up to a third of cases of ischaemic stroke.[1] More recently, AF has been linked to cognitive impairment and dementia.[1,2,3] We have previously demonstrated that AF was associated with a decreased brain volume in addition to decline in cognitive function, independent of cerebral infarcts.[4] Thus, AF appears to affect the brain in more ways than by causing cerebral emboli that lead to stroke.

The association of AF and decreased brain volume in our previous study was stronger with increased arrhythmia burden and also with longer time from first diagnosis of AF.[4] Other studies have shown AF to be associated with specific alterations in brain morphology rather than total brain volume but those studies had rather small cohorts

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What's new?

- Individuals with persistent atrial fibrillation (AF), which has previously been associated with cognitive impairment and smaller brain volume, had decreased total cerebral blood flow and estimated whole brain perfusion when compared with those in sinus rhythm.
- Those with paroxysmal AF but in sinus rhythm at the time of brain imaging had a slight but not significant lowering of cerebral blood flow and estimated brain perfusion than those with no history of the arrhythmia.
- These results suggest that lower cerebral blood flow and lower estimated whole brain perfusion may, at least in part, help explain previous findings of smaller brain volumes and cognitive decline in elderly individuals with AF.

and complete brain imaging studies had not been done on all participants.[5–7] Possible mechanisms connecting AF and decreased brain volume might include multiple micro-emboli causing small cerebral infarcts, decreased cerebral blood flow due to beat-to-beat variation in stroke volume, neurohumoral factors, or even changes in autoregulation of blood flow to the brain.

The aim of this study was to evaluate and compare measured total cerebral blood flow in the cervical arteries (mL/min) at the level of the skull base and estimated brain perfusion (mL/100 g brain tissue/min) measured with magnetic resonance imaging (MRI) in individuals with and without AF at the time of imaging. The data are from the large population-based Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-RS).

Methods

The AGES-RS, initiated in 2002, is a multidisciplinary study that was designed to investigate the genetic and environmental factors contributing to clinical and subclinical disease and disability in old age, providing detailed phenotypes related to the cardiovascular, neurocognitive, and musculoskeletal systems, and to body composition and metabolic regulation. The study is a continuation of the Reykjavik Study, a total population study of men and women born in 1907–1935, who were residents of the greater Reykjavik area in 1967. The Reykjavik Study was a longitudinal study performed from 1967 to 1994 to collect mid-life data on cardiovascular traits. The AGES-Reykjavik study cohort is a random recruitment of survivors from the previous Reykjavik Study, including 5764 subjects aged 67–93 years. The current study includes cross-sectional analysis of 3316 subjects aged 71–95 years of the cohort from the second visit of the AGES-RS, a follow-up examination of all surviving participants who agreed to participate, conducted in 2007–2011.

Data collection included a questionnaire, clinical examination, cognitive testing, and imaging of the brain, musculoskeletal system, body composition, vasculature, and the heart. The study design and initial assessments of the cohort have been described previously in more detail.[8] The AGES-Reykjavik study has been approved by the Icelandic National Bioethics Committee, which acts as the Institutional Review Board for the Icelandic Heart Association, and by the Institutional Review Board for the Intramural Research Program of the National Institute on Aging, National Institute of Health, Bethesda, MD as well as The Icelandic Data Protection Authority (VSN-063). Informed written consent was obtained from all participants.

Definition and categorization of AF status

Participants in this current study were divided into three groups according to presence or absence of AF at the time of a brain MRI examination and a previous history of the arrhythmia: (i) those with AF according to a 12-lead electrocardiogram (EKG), (ii) those in sinus rhythm but with a previous history of AF (as determined from hospital records or medical history), and (iii) those in sinus rhythm and with no previous history of the arrhythmia. To make the presentation of the data easier to understand, the group of individuals with AF at the time of the MRI exams were defined as persistent AF and the group with a previous history, but in sinus rhythm at the time of imaging, as paroxysmal AF. This was done with the understanding that the some of the former may have had paroxysmal AF but happened to have AF at the time of MRI.

Potential confounders

Age, sex, education level (primary/secondary/college or university), smoking status (ever smoker/former smoker/current smoker), and alcohol consumption (g/week) were assessed by questionnaire. Body mass index was calculated from measured height and weight. Hypertension was defined as self-reported doctor's diagnosis, use of hypertensive medication or measured systolic blood pressure ≥140 mmHg systolic or diastolic blood pressure ≥90 mmHg. Myocardial infarction was defined as self-reported history of myocardial infarction or evidence on EKG of possible or probable myocardial infarction and coronary heart disease was defined as prevalent disease using hospital data pertaining to diagnosis of myocardial infarction, hospital operations including percutaneous transluminal coronary angioplasty and coronary artery bypass surgery. The diagnosis of heart failure was based on hospital discharge diagnosis codes from all hospitals in Reykjavik. Hypercholesterolaemia was defined as total cholesterol level >6.6 mmol/L. Diabetes mellitus type 2 was defined as a self-reported doctor's diagnosis, use of diabetes medication or fasting blood glucose >7 mmol/L. At the time of data collection, warfarin was the only anticoagulant used for stroke prevention in Iceland. Depressive symptoms were classified as a score of 5 or higher on the 15-item Geriatric Depression Scale and cognitive impairment was classified as 23 points or lower on the mini-mental state examination (MMSE) and 17 or lower on digit symbol substitution test (DSST). Stroke was determined using hospital data and coronary artery calcium was calculated using the Agatston method from computed tomography examination of the coronary arteries performed on a Siemens Somatom Sensation 4 multidetector CT scanner (Siemens Healthcare, Erlangen, Germany) with prospective ECG triggering. Participants with dementia and diagnosis of heart failure were excluded.

MRI acquisition and image processing

All participants without contraindications underwent brain MRI on a 1.5-T Signa Twinspeed system (General Electric Medical Systems, Waukesha, WI, USA) including a phase-contrast scan for flow measurements and anatomical imaging of the whole brain for measurement of brain volume and estimation of brain perfusion. The AGES-Reykjavik brain MRI image acquisition protocol has previously been described in detail.[9] In brief, the protocol included a T1-weighted three-dimensional spoiled gradient echo sequence, a proton density/T2-weighted fast-spin echo sequence, a T2-weighted gradient echo-type echo planar imaging sequence, and a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence. All images were acquired to give full brain coverage in the oblique-axial plane. Brain tissue volumes including cerebrospinal fluid (CSF), grey matter (GM), white matter (WM), and white matter hyperintensities (WMH) were computed with a validated automatic image post-processing pipeline.[9]

Total brain volume (TBV) was computed in millilitres (mL) as the sum of GM volume, WM volume, and WMH volume. The intracranial volume was computed as the sum of TBV and CSF volume. Brain volumes in this study were normalized to intracranial volume and presented as percentages of intracranial volume (TBV/ICV * 100).

Total cerebral blood flow (mL/min) was measured using phase-contrast MRI at the level of the skull base for flow measurement in all the cervical arteries, both the internal carotid arteries and the basilar artery. Estimated brain perfusion in the entire brain expressed in mL/100 g brain tissue/min was defined as the average blood flow volume divided by the whole brain volume assuming an average brain density of 1.05 g/mL. More details on the acquisition and analysis of phase-contrast images, the calculation of flow and perfusion, as well as on estimating brain perfusion has previously been described in detail.[10] The operators of the MRI system and the MR image analysts were blinded to all clinical information on the study participants, including the AF status of each participant.

Statistical analyses

Characteristics between groups were compared using generalized linear models (GLM) with age and sex adjustment. The assumption of a normal distribution of the two continuous blood flow measures was verified by inspecting qq-plots of residuals from the regression models.

Analysis of total cerebral blood flow difference between groups was performed using GLM with age and sex adjustment, as well as adjustment for brain volume, and for warfarin use and use of anti-hypertensive medication. Analysis of brain perfusion was done similarly with adjustments for warfarin use and use of anti-hypertensive medication, but adjustment for brain volume was not necessary since the outcome was already standardized by total brain volume.

All analyses were performed using SAS System/STAT software version 9.2 (SAS Institute Inc., Cary, NC, USA). Data are presented as mean (standard deviation) for continuous variables and as % for categorical variables. A *P*-value <0.05 was considered statistically significant.

Analytical sample

Survivors of the AGES-Reykjavik Study were invited for a follow-up visit. A total of 5245 individuals from the original cohort were alive at the start of recruitment. Reasons for not participating were death before examination ($n = 520$), refusal ($n = 1198$) or loss to follow-up ($n = 211$). A total of 3316 individuals gave informed consent to match the study data to hospital and private physicians' records. Of these, 648 lacked brain MRI data, 376 individuals refused MRI imaging mainly due to claustrophobia or physical inability to undergo the investigation and 272 were excluded because of other contraindications (mainly pacemaker). Individuals with dementia ($n = 180$) and prevalent heart failure ($n = 104$) were excluded. Of the 2384 remaining subjects, 4 did not possess EKG-data and 89 did not have cerebral blood flow measurements, resulting in a final study sample of 2291 individuals.

Results

Of the 2291 individuals, 117 had persistent AF and 78 had a prior history of the arrhythmia but were in sinus rhythm at the time of the brain MRI (paroxysmal AF). The mean age of the cohort was 79.5 years, ranging from 71 to 95 years (*Table 1*). Compared with those without AF and those with paroxysmal AF, participants with persistent AF were older and more often men. They had lower measured blood pressure, lower cholesterol and used more anti-hypertensive medication and warfarin but less aspirin. As might be expected, stroke was significantly more common in the persistent AF group and in the paroxysmal AF group when compared with those with no history of the arrhythmia. Those with persistent AF were not significantly different to the other two groups with regards to body mass index; type 2 diabetes, self-reported hypertension, coronary artery calcium, and history of myocardial infarction or coronary artery disease. Likewise, the persistent AF group did not differ significantly from the other two with regard to alcohol consumption, smoking status, or educational status and they scored similar on cognitive and depressive measures.

Individuals with persistent AF had the smallest relative brain volumes (69.3%) when compared with the paroxysmal AF group (70.3%) and to those with no history of AF (71.7%) (*Table 1*).

Participants in the persistent AF group had significantly lower total cerebral blood flow on average, 472.1 mL/min, both when compared with the paroxysmal AF group, 512.3 mL/min ($P < 0.05$) and the no AF group, 541.0 mL/min ($P < 0.001$) (*Table 2*, *Figure 1A*). The total cerebral blood flow in the paroxysmal AF group was lower than in the no AF group ($P < 0.05$). Adjusting for relative brain volume (*Table 2*) and then warfarin use as well as use of anti-hypertensive medication did not alter the difference between those in the persistent AF group vs. the no AF group but after adjustment there was no longer a significant difference in total cerebral blood flow between the paroxysmal AF group and those without any previous history of the arrhythmia (*Table 2* and *Figure 1B*).

On average, estimated whole brain perfusion was significantly lowest in the persistent AF group, 46.4 mL/100 g/min when compared with the paroxysmal AF group, 50.9 mL/100 g/min in ($P < 0.05$) and those with no AF, 52.8 mL/100 g/min ($P < 0.001$) (*Table 2* and *Figure 2A*). After correcting for warfarin use and use of anti-hypertensive medication the results remained unchanged, with brain perfusion still significantly lowest in the persistent AF group (*Table 2* and *Figure 2B*). Estimated whole brain perfusion in those with paroxysmal AF was not significantly lower than in the group with no history of the arrhythmia, neither before nor after adjustment.

Discussion

In this cross sectional study of a large cohort of elderly individuals from the general population, persistent AF was associated with decreased total cerebral blood flow and estimated whole brain perfusion assessed by phase contrast MRI of the brain. Individuals with paroxysmal AF, but nevertheless in sinus rhythm at the time of imaging, had similar cerebral blood flow and brain perfusion as those with no history of the arrhythmia. The presence of the arrhythmia at the time of measurement of cerebral blood flow and brain perfusion thus appears to be of key importance.

We have previously shown an association between brain volume and AF in an elderly cohort.[4] A linear trend was found between longer duration of AF and greater reduction in total brain volume suggesting a cumulative effect with increasing burden of the arrhythmia. Brain atrophy both of the grey and white matter has indeed been associated with a decline in cognitive function.[11]

There are a number of possible explanations for the observed association between reduced brain volume and AF. Those include cerebral micro-infarcts caused by small emboli from the heart,

Table 1 Characteristics

	Persistent AF ($n = 117$)	Paroxysmal AF ($n = 78$)	No AF ($n = 2096$)	All groups *P*-value	Persistent AF vs. no AF[a] *P*-value	Persistent AF vs. paroxysmal AF and no AF[a] *P*-value
Age (years)	81.2 (5.1)	79.6 (4.3)	79.4 (4.5)	$P < 0.001$	$P < 0.001$	$P < 0.001$
Sex, % men	63.3	52.6	38.8	$P < 0.001$	$P < 0.001$	$P < 0.001$
Education, % primary education	12.0	20.5	20.1	$P = 0.16$	$P = 0.07$	$P = 0.06$
Ever smoker, former or current	49.6	57.1	47.4	$P = 0.40$	$P = 1.00$	$P = 0.45$
Alcohol consumption (g/week)[b]	6.4 (1.6–26.4)	3.2 (1.6–16.1)	3.2 (0–16.1)	$P = 0.91$	$P = 0.71$	$P = 0.71$
Height, cm	171.6 (9.9)	169.4 (9.8)	167.0 (9.1)	$P < 0.01$	$P < 0.01$	$P < 0.001$
Body mass index (kg/m^2)	27.0 (3.9)	27.3 (4.3)	26.8 (4.3)	$P = 0.18$	$P = 0.17$	$P = 0.19$
Hypertension	94.0	94.9	88.7	$P = 0.06$	$P = 0.09$	$P = 0.11$
Systolic blood pressure (mmHg)	141.3 (22.8)	142.7 (22.6)	145.3 (20.7)	$P < 0.05$	$P < 0.01$	$P < 0.01$
Myocardial infarction	13.7	16.7	12.3	$P = 0.63$	$P = 0.60$	$P = 0.57$
Coronary heart disease	28.2	42.3	24.2	$P < 0.01$	$P = 0.75$	$P = 0.63$
Cholesterol	4.9 (1.1)	4.7 (1.1)	5.3 (1.1)	$P < 0.001$	$P < 0.01$	$P < 0.05$
Diabetes mellitus type 2	15.4	15.4	11.7	$P = 0.58$	$P = 0.44$	$P = 0.47$
Anti-hypertensive medication use	84.6	91.0	69.5	$P < 0.001$	$P < 0.001$	$P < 0.01$
Warfarin use	67.5	33.3	2.2	$P < 0.001$	$P < 0.001$	$P < 0.001$
Aspirin use	31.6	51.3	42.2	$P < 0.01$	$P < 0.01$	$P < 0.001$
GDS scale	2.4 (1.9)	2.6 (1.9)	2.1 (2.0)	$P < 0.05$	$P = 0.24$	$P = 0.28$
MMSE score	26.2 (2.4)	26.3 (3.7)	26.6 (2.6)	$P = 0.85$	$P = 0.67$	$P = 0.66$
DSST score	27.4 (9.6)	29.4 (9.4)	30.6 (10.1)	$P = 0.30$	$P = 0.17$	$P = 0.18$
Stroke	16.2	19.2	6.4	$P < 0.001$	$P < 0.001$	$P < 0.01$
Coronary artery calcium[b]	671 (197–2027)	630 (126–1974)	404 (78–1173)	$P = 0.57$	$P = 0.48$	$P = 0.51$
Total brain volume (BV) (mL)	1073.2 (103.1)	1061.3 (109.6)	1066.1 (98.3)	$P = 0.09$	$P = 0.25$	$P = 0.28$
Intracranial volume (ICV) (mL)	1550.7 (157.6)	1510.9 (151.6)	1490.2 (146.7)	$P = 0.35$	$P = 0.18$	$P = 0.18$
Relative BV (%) (TBV/ICV×100)	69.3 (3.6)	70.3 (4.0)	71.7 (3.8)	$P < 0.001$	$P < 0.001$	$P < 0.001$

Data are shown as mean (standard deviation) for continuous variables and as % for categorical variables.
Persistent AF, those with atrial fibrillation (AF) at the time of imaging; paroxysmal AF, those in sinus rhythm at imaging but with a previous history of AF; no AF, those in sinus rhythm and no history of the arrhythmia. GDS, geriatric depression scale; MMSE, mini mental-state examination; DSST, digit symbol substitution test; BV, brain volume; ICV, intracranial volume.
[a]Age and sex adjusted.
[b]Median and quartiles.

Table 2 Total cerebral blood flow and average estimated brain perfusion

	Persistent AF	Paroxysmal AF	No AF	*P*-value*
Total cerebral blood flow (mL/min)	472.1	512.3	541.0	<0.001
Total cerebral blood flow (mL/min)[a]	482.9	520.7	542.2	<0.001
Total cerebral blood flow (mL/min)[b]	487.3	520.0	535.5	<0.001
Brain perfusion (mL/100 g/min)	46.4	50.9	52.8	<0.001
Brain perfusion (mL/100 g/min)[c]	46.7	50.7	50.7	<0.001

Persistent AF, those with atrial fibrillation (AF) at the time of imaging; paroxysmal AF, those in sinus rhythm at imaging but with a previous history of AF; no AF, those in sinus rhythm and no history of the arrhythmia.
[a]Adjusted for brain volume.
[b]Adjusted for brain volume, use of anti-hypertensive medication and warfarin use.
[c]Adjusted for use of anti-hypertensive medication and warfarin use. mL/min: flow in cervical arteries in millilitres per minute; mL/100 g/min: brain perfusion in millilitres per 100 grams of brain tissue per minute.
*Difference between persistent AF and no AF.

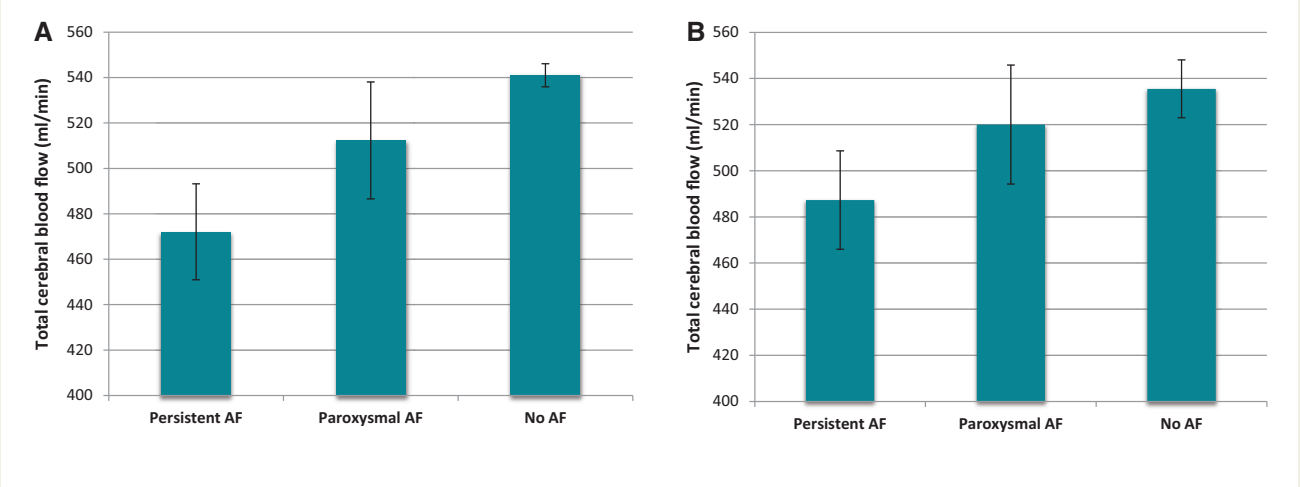

Figure 1 (*A*) Total cerebral blood flow in the cervical arteries in mL/min in the three groups. Persistent AF: those with atrial fibrillation (AF) at the time of imaging; paroxysmal AF: those in sinus rhythm at imaging but with a previous history of AF; no AF: those in sinus rhythm and with no history of the arrhythmia. Adjustments were made for age and sex. Persistent AF vs. paroxysmal AF: $P < 0.05$; persistent vs. no AF: $P < 0.001$; paroxysmal AF vs. no AF: $P < 0.05$. (*B*) Total cerebral blood flow in the cervical arteries in mL/min in the three groups. Persistent AF: those with atrial fibrillation (AF) at the time of imaging; paroxysmal AF: those in sinus rhythm at imaging but with a previous history of AF; no AF: those in sinus rhythm and with no history of the arrhythmia. Adjustments were made for age, sex, brain volume, use of anti-hypertensive medication, and warfarin use. Persistent AF vs. paroxysmal AF: $P = 0.05$; persistent vs. no AF: $P < 0.001$; paroxysmal AF vs. no AF: $P > 0.05$.

leading to ischaemia and brain injury and possibly even atrophy.[12] However, in our previous study on AF and brain volume, there was no significant difference in brain volumes between those who were taking warfarin anticoagulation or not.

Another explanation could be cerebral hypo-perfusion, perhaps related to beat-to-beat variation in stroke volume in AF. Decreased cerebral perfusion has been associated with a reduction in both grey and white matter although the effect may be greater on the grey matter due to higher metabolic demand.[4,13] There was a stronger association between AF and lower grey matter volume than white matter volume in our prior study, possibly lending support to the cerebral hypo-perfusion hypothesis. Other factors such as neurohumoral effects or even altered auto-regulation of blood flow may also be playing a role.

In order to explore possible causes we undertook a study to examine whether there was a difference in cerebral blood flow and brain perfusion in individuals with persistent AF and individuals in sinus rhythm. In this study individuals with AF at the time of imaging had lower total cerebral blood flow and estimated whole brain perfusion compared with those in sinus rhythm regardless of a previous history of the arrhythmia. The adverse haemodynamic effects of having AF while the brain was imaged thus appear to be the most important variable in this observed difference. No temporal information was available as to when individuals in sinus rhythm at the time of imaging, but with paroxysmal AF, had their most recent episode of arrhythmia.

Whilst cerebral flood flow in AF is not a particularly well-studied subject there is some clinical data to support the theory that brain hypo-perfusion flow may occur and blood flow be diminished in AF. In one study regional cerebral blood flow was decreased in 17 subjects with AF compared with 13 in sinus rhythm using SPECT brain imaging, suggesting that cerebral hypo-perfusion occurred with the arrhythmia[13] and another study showed cerebral blood flow measured with trans-cranial Doppler and by Xenon-133 inhalation technique to be lowered during AF and increased after cardioversion.[14–16] A small Danish study also showed improvement of cerebral blood flow after cardioversion for AF by injecting Xenon-133 intravenously and measuring the clearance of the isotope with a brain scintillation detector and it has also suggested that individuals with AF may have decreased cerebral blood flow that could be reversed.[17,18] More recently AF has been shown to adversely affect haemodynamic parameters, microcirculation, and cerebral oxygenation.[19,20]

In the current study individuals with persistent AF had the lowest relative brain volume and the lowest total cerebral blood flow and brain perfusion. However, after correction for brain volume, individuals with paroxysmal AF but in sinus rhythm at the time of imaging and those with no history of the arrhythmia still had higher cerebral blood flow than those with persistent AF, emphasizing that a relatively smaller brain did not explain lowered cerebral blood flow in individuals with the arrhythmia.

Individuals with persistent AF were similar to individuals with paroxysmal AF and those with no history of AF with regard to BMI, diabetes, cardiovascular risk factors, and coronary heart disease. They were however older, and age is the most important factor affecting the brain but whether the threshold for adequate cerebral flood flow and brain perfusion may be affected by age, atherosclerosis, or specific brain functions is not known. Likewise, older brains may be more susceptible to the effects of reduced blood flow and perfusion.

In all likelihood, the haemodynamic effects on the brain are complex and involve multiple mechanisms. These results do however

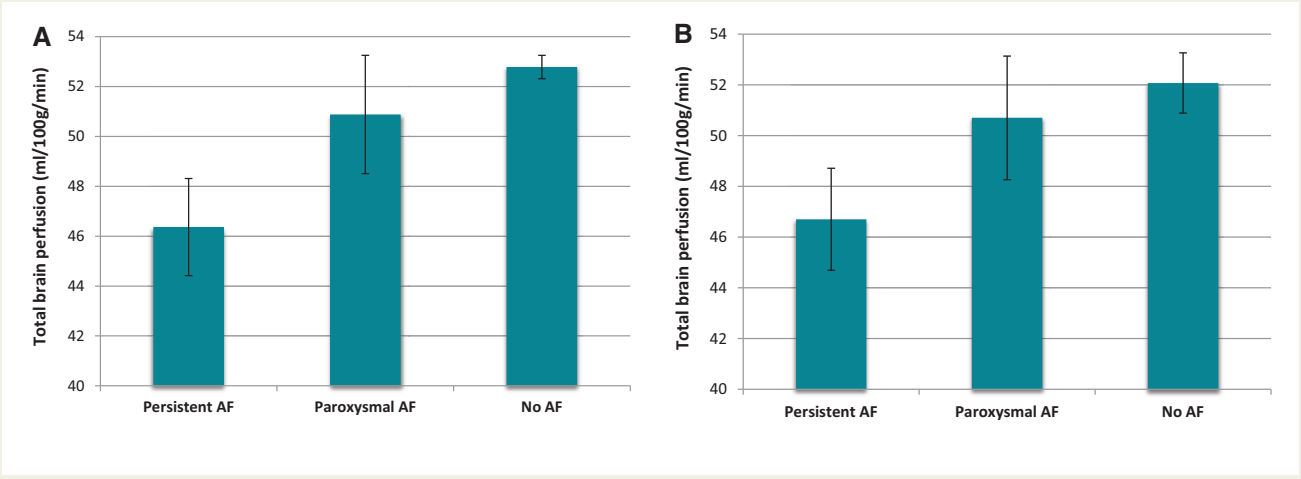

Figure 2 (*A*) Total brain perfusion in mL/100 g brain tissue/min in the three groups. Persistent AF: those with atrial fibrillation (AF) at the time of imaging; paroxysmal AF: those in sinus rhythm at imaging but with a previous history of AF; no AF: those in sinus rhythm and with no history of the arrhythmia. Adjustments were made for age and sex. Persistent AF vs. paroxysmal AF: $P < 0.01$; persistent vs. no AF: $P < 0.001$; paroxysmal AF vs. no AF: $P > 0.05$. (*B*) Total brain perfusion (mL/100 g brain tissue/min) in the three groups. Persistent AF: those with atrial fibrillation (AF) at the time of imaging; paroxysmal AF: those in sinus rhythm at imaging but with a previous history of AF; no AF: those in sinus rhythm and with no history of the arrhythmia. Adjustments were made for age, sex, use of anti-hypertensive medication and warfarin. Persistent AF vs. paroxysmal AF: $P < 0.05$; persistent vs. no AF: $P < 0.001$; paroxysmal AF vs. no AF: $P > 0.05$.

suggest that decreased cerebral blood flow may play an important role in diminished brain volume and the decline in cognitive function seen in individuals with AF.[4,7]

There have been a number of studies in recent years associating AF and cognitive impairment in individuals both with and without prior stroke suggesting a link between the two.[5,6,21] In this current study, we excluded people with dementia; among the relatively cognitively better performers there was no difference between the groups in cognitive function as measured by MMSE and DSST tests (*Table 1*).

A clear strength of the study is the large well-defined cohort and that brain imaging with MRI was available. The method of studying the blood flow by phase-contrast MRI is an accurate, reliable and highly reproducible method.[22] By measuring the total cerebral blood flow in the carotids and the basilar artery the sum of blood flowing to the brain through the cervical arteries is directly measured.[23] Phase-contrast imaging does not however assess the perfusion of the brain tissue directly, as first pass dynamic susceptibility contrast-enhanced magnetic resonance perfusion imaging and dynamic contrast-enhanced magnetic resonance perfusion imaging do, as well as the more recently developed method of arterial spin labelling magnetic resonance perfusion imaging. The limitations of our measurement is that perfusion is estimated rather than directly measured in the capillary bed of the brain, as would be done with arterial spin labelling and needs to be validated.

There are some additional limitations to this study. Of the original cohort in the AGES RS a number of individuals did not participate in this study. The reasons for this are numerous and are detailed in the methods section. Of the 648 individuals excluded from the study due to missing brain MRI data individuals with AF were more common as the main reason was inability to undergo the MRI study because of the presence of cardiac pacemakers and other medical devices that were felt to be a contraindication for the imaging study. Additionally the interpretation of the study results would have benefited from more detailed information on the AF burden of the paroxysmal group and the date of the last AF episode.

The results also raise some important clinical questions. It would be interesting to evaluate whether restoration of sinus rhythm in individuals with AF would lead to improved blood flow to the brain. Such a study would have to be done in a prospective manner. Likewise a follow-up of the cohort may be of potential value regarding cognitive outcome over time in order to support the hypothesis that AF affects brain volume and cognition by causing reduced blood flow to the brain and decreased brain perfusion.

The results, while intriguing, therefore need to be validated in a longitudinal manner, preferably with measurements of total cerebral blood flow and brain perfusion in AF and then by repeated measurements after restoration of sinus rhythm in the same individuals.

Conclusions

Atrial fibrillation was associated with decrease in total cerebral blood flow and brain perfusion in an unselected elderly cohort. These results may, at least in part, explain the association of AF with reduced relative brain volume and cognitive impairment. There is growing data that AF may adversely affect the brain in other ways than by increasing the risk of cerebral infarcts. The association between persistent AF and diminished cerebral blood flow and brain perfusion are of particular interest as the consequences may potentially influence treatment decisions in AF.

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Conflict of interest: none declared.

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References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
2. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med* 2013;**158**:338–46.
3. Dietzel J, Haeusler KG, Endres M Does atrial fibrillation cause cognitive decline and dementia? Europace. 2017 Apr 6. doi: 10.1093/europace/eux031. [Epub ahead of print]
4. Stefansdottir H, Arnar DO, Aspelund T, Sigurdsson S, Jonsdottir MK, Hjaltason H *et al*. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. *Stroke* 2013;**44**:1020–5.
5. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* 1997;**28**:316–21.
6. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C *et al*. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;**29**:2125–32.
7. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS *et al*. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm* 2010;**7**:433–7.
8. Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G *et al*. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol* 2007;**165**:1076–87.
9. Sigurdsson S, Aspelund T, Forsberg L, Fredriksson J, Kjartansson O, Oskarsdottir B *et al*. Brain tissue volumes in the general population of the elderly: the AGES-Reykjavik study. *Neuroimage* 2012;**59**:3862–70.
10. Sigurdsson S, Forsberg L, Aspelund T, van der Geest RJ, van Buchem MA, Launer LJ *et al*. Feasibility of using pseudo-continuous arterial spin labeling perfusion in a geriatric population at 1.5 Tesla. *PLoS One* 2015;**10**:e0144743.
11. Ikram MA, Vrooman HA, Vernooij MW, den Heijer T, Hofman A, Niessen WJ *et al*. Brain tissue volumes in relation to cognitive function and risk of dementia. *Neurobiol Aging* 2010;**31**:378–86.
12. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. *Lancet Neurol* 2012;**11**:272–82.
13. Marcoux FW, Morawetz RB, Crowell RM, DeGirolami U, Halsey JH. Differential regional vulnerability in transient focal cerebral ischemia. *Stroke* 1982;**13**:339–46.
14. Efimova I, Efimova N, Chernov V, Popov S, Lishmanov Y. Ablation and pacing: improving brain perfusion and cognitive function in patients with atrial fibrillation and uncontrolled ventricular rates. Pacing. *Clin Electrophysiol* 2012;**35**:320–6.
15. Totaro R, Corridoni C, Marini C, Marsili R, Prencipe M. Transcranial Doppler evaluation of cerebral blood flow in patients with paroxysmal atrial fibrillation. *Ital J Neurol Sci* 1993;**14**:451–4.
16. Lavy S, Stern S, Melamed E, Cooper G, Keren A, Levy P. Effect of chronic atrial fibrillation on regional cerebral blood flow. *Stroke* 1980;**11**:35–8.
17. Petersen P, Kastrup J, Videbaek R, Boysen G. Cerebral blood flow before and after cardioversion of atrial fibrillation. *J Cereb Blood Flow Metab* 1989;**9**:422–5.
18. Porebska A, Nowacki P, Safranow K, Drechsler H. Nonembolic, hemodynamic blood flow disturbances in the middle cerebral arteries in patients with paroxysmal atrial fibrillation without significant carotid stenosis. *Clin Neurol Neurosurg* 2007;**109**:753–7.
19. Wutzler A, Nee J, Boldt LH, Kühnle Y, Gräser S, Schröder T *et al*. Improvement of cerebral oxygen saturation after successful electrical cardioversion of atrial fibrillation. *Europace* 2014;**16**:189–94.
20. Elbers PW, Prins WB, Plokker HW, van Dongen EP, van Iterson M, Ince C. Electrical cardioversion for atrial fibrillation improves microvascular flow independent of blood pressure changes. *J Cardiothorac Vasc Anesth* 2012;**26**:799–803.
21. Hui DS, Morley JE, Mikolajczak PC, Lee R. Atrial fibrillation: a major risk factor for cognitive decline. *Am Heart J* 2015;**169**:448–56.
22. Barkhof F, Tas MW, Frequin ST, Scheltens P, Hommes OR, Nauta JJ *et al*. Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis. *Neuroradiology* 1994;**36**:382–7.
23. Bonekamp D, Degaonkar M, Barker PB. Quantitative cerebral blood flow in dynamic susceptibility contrast MRI using total cerebral flow from phase contrast magnetic resonance angiography. *Magn Reson Med* 2011;**66**:57–66.