The role of atrial fibrillation and aortic stiffness in brain structure and function

Maríanna Garðarsdóttir

Thesis for the degree of Philosophiae Doctor

March 2026

School of Health Sciences

FACULTY OF MEDICINE

UNIVERSITY OF ICELAND

The role of atrial fibrillation and aortic stiffness in brain structure and function

Maríanna Garðarsdóttir

Thesis for the degree of Philosophiae Doctor

Supervisor

Davíð O. Arnar

Doctoral committee

Davíð O. Arnar
Sigurður Sigurðsson, co-supervisor
Thor Aspelund
Vilmundur Guðnason

March 2026

School of Health Sciences
FACULTY OF MEDICINE
UNIVERSITY OF ICELAND

Þáttur gáttatifs og ósæðarstífleika í formgerð og starfsemi heilans

Maríanna Garðarsdóttir

Ritgerð til doktorsgráðu

Leiðbeinandi/umsjónarkennari

Davíð O. Arnar

Doktorsnefnd

Davíð O. Arnar
Sigurður Sigurðsson, meðleiðbeinandi
Thor Aspelund
Vilmundur Guðnason

Mars 2026

Heilbrigðisvísindasvið

LÆKNADEILD

HÁSKÓLI ÍSLANDS

ISBN 978-9935-567-03-1

ORCID: orcid.org/0000-0002-0460-726X

Reykjavik, Iceland 2026

Ágrip

Gáttatif er algengasta viðvarandi hjartsláttartruflunin og getur gáttatif leitt til heilablóðfalls og hjartabilunar. Einnig hefur gáttatif verið tengt minnkuðu heilarúmmáli og vitrænni skerðingu. Hluta þessara áhrifa gáttatifs á heilarúmmál og vitræna getu er hægt að skýra með heilaáföllum en vaxandi vitneskja bendir til annarra þátta tengdum æðakerfi, bólgu og blóðflæði sem gera heilann viðkvæman fyrir þessum áhrifum gáttatifs. Ósæðarstífleiki, birtingarmynd aldursbundinnar hrörnun í æðakerfinu, tengist einnig breytingum á formgerð heilans og vitrænni starfsemi. Markmið þessarar ritgerðar var að rannsaka hvort breytingar eða truflun á miðlægu blóðflæði geti verið sameiginlegur farvegur sem tengi gáttatif og ósæðarstífleika við breytingar á gegnflæði blóðs um heila, formgerð heilans og vitræna getu.

Heilablóðflæði og gegnflæði blóðs um heila metið með segulómun var lægra hjá einstaklingum með langvarandi gáttatif samanborið við þá sem voru í eðlilegum sínus takti í þýðisrannsókn eldri einstaklinga, en þeir sem einhvern tímann höfðu verið í gáttatifi höfðu sambærilegt blóðflæði við þá sem aldrei höfðu fengið gáttatif. Langvarandi gáttatif tengdist einnig skerðingu á rúmmáli heilans, metið með segulómun, en ekki var munur á vitrænni getu milli hópanna.

Til að skoða hvort þessi áhrif gáttatifs á blóðflæði væru afturkræf voru heilablóðflæði og gegnflæði blóðs um um heilann mæld með tveimur aðferðum í segulómun fyrir og eftir valkvæða rafvendingu vegna gáttatifs. Bæði heilablóðflæði og gegnflæði blóðs um heilann jukust hjá þeim sem fóru í eðlilegan sínus takt við rafvendinguna og héldust áfram í réttum takti, en engin marktæk breyting sást hjá þeim sem voru áfram í gáttatifi þegar rafvending tókst ekki.

Í öðru þýði kom í ljós að þeir einstaklingar sem höfðu meiri stífleika í ósæð, metinn með þrýstingsnema sem hraði þrýstingsbylgju í ósæð milli hálsslagæða og náraslagæða, höfðu lægra gegnflæði blóðs um heila mælt með segulómun. Gegnflæðið blóðs um heila var lægra þegar um meiri stífleika var að ræða í öllum heilanum og í gráa og í hvíta vef heilans. Einnig var heilarúmmál lægra hjá þeim sem höfðu aukinn ósæðarstífleika, auk þess sem hvítavefsbreytingar voru meiri. Vitræn geta var sambærileg milli hópanna. Ósæðastífleiki hafði forspárgildi fyrir lægra gegnumstreymi blóðs um heila en lífaldur tengdist frekar heilarúmmáli.

Samantekið, þá tengdust bæði gáttatif og aukinn ósæðarstífleiki lægra gegnflæði blóðs um heila og merkjum um viðkvæma formgerð heilans. Að komast í eðlilegan sínus takt við rafvendingu við gáttatifi jók gegnflæði blóðs um heilann sem styður það að skerðing á miðlægu blóðflæði geti verið afturkræf. Saman benda þessar niðurstöður til

þess að breytingar á miðlægu blóðflæði séu hluti af ferli sem tengi öldrunarbreytingar í hjarta- og æðakerfinu við heilaheilsu, og varpa ljósi á að truflun á gegnflæði blóðs um heila geti verið snemmkominn mælikvarði fyrir heilaáhættu.

Lykilorð:

Gáttatif, ósæðarstífleiki, heilablóðflæði, heilarúmmál, vitræn skerðing.

Abstract

Atrial fibrillation is the most common sustained cardiac arrhythmia and is associated not only with stroke and heart failure, but also with reduced brain volume and cognitive impairment. While thromboembolism explains part of this relationship, growing evidence suggests that additional mechanisms, including vascular, inflammatory, and hemodynamic processes, contribute to brain vulnerability in atrial fibrillation. Aortic stiffness, a manifestation of vascular aging, has similarly been linked to structural brain changes and cognitive decline. The overall aim of this thesis was to investigate whether disturbances in central hemodynamics represent a common pathway linking AF and aortic stiffness to alterations in brain perfusion, brain structure, and cognitive performance.

In a population-based cohort of older adults, total cerebral blood flow measured by phase-contrast magnetic resonance imaging and estimated brain perfusion were significantly lower in individuals with persistent atrial fibrillation compared with those in sinus rhythm. Individuals with paroxysmal atrial fibrillation had similar cerebral blood flow to those in sinus rhythm. Persistent atrial fibrillation was also associated with smaller relative brain volume assessed by magnetic resonance imaging, whereas cognitive performance did not differ significantly between groups.

To explore whether atrial fibrillation-related hypoperfusion might be reversible, total cerebral blood flow and brain perfusion were measured before and after electrical cardioversion using phase contrast and arterial spin labeling magnetic resonance imaging. Brain perfusion increased significantly in individuals who achieved and maintained sinus rhythm, whereas no significant change was observed in those who remained in atrial fibrillation.

In a separate cohort, aortic stiffness assessed as carotid-femoral pulse wave velocity measured by applanation tonometry was inversely associated with brain perfusion measured with arterial spin labeling magnetic resonance imaging. Higher aortic stiffness was also associated with smaller relative total brain, grey matter, and white matter volumes, and with greater white matter hyperintensity burden. In multivariable analyses, aortic stiffness independently predicted lower brain perfusion whereas chronological age was the strongest determinant of structural brain measures.

In conclusion, both atrial fibrillation and increased aortic stiffness were associated with reduced brain perfusion and markers of structural brain vulnerability. Restoration of sinus rhythm was accompanied by improvement in brain perfusion, supporting a dynamic hemodynamic mechanism. Together, these findings suggest that hemodynamic alterations represent an important pathway linking cardiovascular aging to brain vulnerability and highlight brain perfusion as a potential early marker of brain risk.

Keywords:

Atrial fibrillation, aortic stiffness, brain perfusion, brain volume, cognitive impairment.

Acknowledgements

First, I want to thank my supervisor and dear colleague, Professor Davíð O. Arnar, for initiating our scientific co-operation since he could not make me a cardiologist and for guiding me through this empowering process. Thank you for being both patient and pushy and a great mentor. You know I need my time to grow! I sincerely want to thank my amazing research group: Siggi—Sigurður Sigurðsson for being a fantastic role model and a vast source of knowledge in all things MRI, I hope to become at some point an inch of what you already are; Thor—Professor Thor Aspelund, my lifesaver and the coolest statistician there is in the whole world, and Villi—Professor Vilmundur Guðnason for being hugely inspiring and a great conversationalist, offering knife-sharp comments and clever suggestions during the process. Thanks to Valdís Arna Garðarsdóttir, R.N., who with endless patience and precision mastered the role of study coordinator in the cardioversion study, keeping both the study and me together during those busy two years. Thanks to Landspítali, my workplace on and off for over 35 years, for being a continuous place for inspiration even at 3 am; to my co-workers and precious work family in Diagnostic Imaging for their patience and kind personal support through the years, and to my close co-workers for the support and the patience during the past year, you know who you are. Thanks to Hjartavernd-the Icelandic Heart Association and AGES for allowing use of their material and to the staff at Hjartavernd for their kind assistance and professionalism. Thanks to Vísindasjóður Landspítala—Science Fund of Landspitali, to Minningarsjóður Helgu Jónsdóttur og Sigurliða Kristjánssonar—Helga Jónsdóttir and Sigurliði Kristjánsson Memorial Fund, to the National Institute of Health and National Institute of Aging Intramural Research Program, and again to Hjartavernd—the Icelandic Heart Association and to Alþingi-the Icelandic Parliament for financial support to the studies.

My heartfelt thanks to my family, my parents; my father Garðar for his support, especially during my time in medical school, and my dear late mother Maia who always encouraged me in her wise way, especially during the toughest times. Thanks to my brothers, especially my twin Kristján, who knows me so well and makes my life always much easier and more amusing. My eternal love and gratitude to my lovely, wonderful daughters Maia and Arna for putting up with me and my crazy ideas, for being there and being fabulous. Thank you to my dear "uncle" Sveinn, for the fruitful discussions and the "injections" of encouragement. Thanks to the cousin group; Ásta, Ingunn and Anna Helga for late night discussions on all things important in life. Thanks to my gym coach for not letting me get away with missing many early-morning sessions and thanks to my dearest and best friend Ingibjörg, a fellow PhD student and sufferer, for the encouragement and always having my six. To all my great friends; I hope I will see more of you now!

I also want to thank Professor Marcus F. Müller, my clinical mentor during my residency at Sahlgrenska University Hospital for providing me with the opportunity to learn MRI diagnostics, and Professors Þórður Harðarson and Guðmundur Þorgeirsson, my teachers at Landspitali and the Faculty of Medicine for mentoring me in my very first study as a medical student back in 1997. I am grateful for the trust in presenting my study at my very first congress of the European Society of Cardiology in Stockholm during my fourth year of medical school. That was the first step of a long journey that later led me to the wonderful cities of Amsterdam, Vienna, Barcelona, Milan, Prague and Paris during the work on this thesis.

To the participants in the AGES Reykjavik Study, the cardioversion study and the OffGen study, my heartfelt thanks, without all of you none of this would have been possible.

Finally, to Sveinbjörn, the love of my life, thank you for the support from the first moment and for taking part in this journey with me. You have made every day wonderful in your kind, humorous and clever way and kept me together during the lows and the highs. Also, I would not have survived without all the late-night ice cream.

Contents

List of Abbreviations

AF: atrial fibrillation, a rapid and irregular cardiac arrhythmia originating in the fore chambers of the heart.

AGES-RS: Age, Gene/Environment Susceptibility-Reykjavik Study, an epidemiologic study conducted by the Icelandic Heart Association.

ASL: arterial spin labeling, a technique to quantify brain perfusion in a non-invasive manner with magnetic resonance imaging.

ASL-MRI: arterial spin labeling magnetic resonance imaging, a technique of quantifying brain perfusion.

BMI: body mass index, a measure of body fat content in adults based on height and weight.

BV: brain volume, in this thesis quantified by magnetic resonance imaging.

BP: brain perfusion, the delivery of oxygen and nutrients to brain tissue.

CBF: cerebral blood flow, the flow of blood to the brain through the cervical arteries.

CFPWV: carotid-femoral pulse wave velocity, a measure of the speed of the aortic pressure wave traveling between the carotid and the femoral arteries, indicating central arterial stiffness.

$CHADS_2$: a risk score used to estimate the 1-year risk of stroke in patients with clinical atrial fibrillation and to guide decisions on initializing anticoagulation therapy.

CHA_2DS_2-VA: a risk score used to estimate the 1-year risk of stroke in patients with clinical atrial fibrillation and to guide decisions on initializing anticoagulation therapy.

CHA_2DS_2-VASc: a risk score used to estimate the 1-year risk of stroke in patients with clinical atrial fibrillation and to guide decisions on initializing anticoagulation therapy.

CI: cognitive impairment, decline from a previous level of performance in one or more cognitive domains. Given the substantial variability in the terminology and diagnostic criteria found in the literature, the broad term "cognitive impairment" is used in this thesis, encompassing cognitive dysfunction and cognitive decline.

CSF: cerebrospinal fluid, the fluid in the ventricles of the brain surrounding the brain and the spinal cord.

DOACs: direct anticoagulants, also known as novel anticoagulants (**NOACs**), a class of medications that prevent blood clots by directly inhibiting specific clotting factors in the blood.

DM: diabetes mellitus, a group of metabolic diseases characterized by high blood sugar levels, resulting from either the body not producing enough insulin or the body's cells being resistant to insulin.

DSST: digit symbol substitution test, a neuropsychological test that assesses cognitive functions like attention, processing speed, and executive function, a test that is sensitive to various conditions like brain damage, dementia, and depression, as well as the effects of aging.

ECG (EKG): electrocardiogram, a recording of the electrical activity of the heart.

ESC: European Society of Cardiology, a medical society in all fields of cardiology with the mission to reduce the burden of cardiovascular disease.

GM: the grey matter of the brain, where the neural cells of the brain process and interpret information.

HF: heart failure, the heart´s inability to fill with and pump blood.

HR: heart rate.

ICV: intracranial volume, the sum of total brain volume (**TBV**) and cerebrospinal fluid (**CSF**) volume.

INR: international normalized ratio, a blood test for measuring how long it takes for blood to clot, used to test clotting times for administering doses in individuals taking warfarin.

MAP: mean arterial pressure, (systolic blood pressure+2(diastolic blood pressure))/3

MI: myocardial infarction, damage to the heart muscle (myocardium) caused by decreased or complete cessation of blood flow in the coronary arteries to a portion of the myocardium.

MMSE: Mini-Mental State Examination, a brief cognitive assessment tool used to screen for cognitive impairment in older adults and to assess the severity of dementia.

MR: magnetic resonance, physical excitation (resonance) induced by magnetic fields that is the basis for magnetic resonance imaging and describes how certain materials interact with magnetic fields.

MRI: magnetic resonance imaging, an imaging method that uses strong magnetic fields, magnetic field gradients and radio waves to generate detailed images of the body´s internal structure.

NIH: National Institute of Health, a federal agency for medical research in the United States of America.

NOACs: novel anticoagulants, also known as direct anticoagulants (DOACs), a class of medications that prevent blood clots by directly inhibiting specific clotting factors in the blood.

NT-proBNP: N-terminal prohormone of brain natriuretic peptide, a biomarker used in the diagnosis of heart failure.

OAC: oral anticoagulation, the administration of drugs to prevent clots from forming in the blood.

P-CASL: pseudo-continuous arterial spin labeling, one method of arterial spin labeling measuring brain perfusion.

PC: phase contrast, an MRI imaging method visualizing and quantifying velocity.

PC MRI: phase contrast magnetic resonance imaging, the use of phase contrast imaging in magnetic resonance imaging.

PWV: pulse wave velocity, a measure of the speed of the aortic pressure wave, indicating arterial stiffness.

SBI: silent brain infarction, see SCI.

SCI: silent cerebral infarction, the presence of focal cerebral infarcts in the absence of clinical neurological signs and symptoms, observed in neuroimaging studies.

sNfL: serum neurofilaments, a biomarker for neuronal injury in inflammatory, degenerative, traumatic and vascular neurological disorders.

SNR: signal-to-noise ratio, a measure comparing the level of a desired signal to the level of background noise in magnetic resonance imaging (**MRI**).

SR: sinus rhythm, a heart rhythm originating from the sinus node of the heart.

SV: stroke volume, the amount of blood pumped out of the heart's left ventricle with each heartbeat.

T: tesla, the strength of the magnetic field of a magnetic resonance imaging machine.

TCBF: total cerebral blood flow, the sum of measurement of blood flow in the cervical arteries, measured with phase contrast magnetic resonance imaging (**PC MRI**).

TBV: total brain volume, the sum of **GM**, white matter (**WM**), and white matter hyperintensities (**WMH**) in mL.

VSN: Vísindasiðanefnd, the Icelandic National Bioethics Committee.

WM: the white matter of the brain, where neural cells of the brain transmit information.

WMH: white matter hyperintensities, areas of increased signal intensity in the brain's white matter (**WM**), visible on magnetic resonance imaging (**MRI**) studies, associated with various conditions and often linked to vascular risk factors and small vessel disease presumably of vascular origin.

WML: white matter lesions, see **WMH**.

List of Figures

List of Tables

List of Original Papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Marianna Gardarsdottir, Sigurdur Sigurdsson, Thor Aspelund, Hrafnhildur Rokita, Lenore. J. Launer, Vilmundur Gudnason and David. O. Arnar. Arterial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. Europace (2018) 20, 1252–1258.

II. Marianna Gardarsdottir, Sigurdur Sigurdsson, Thor Aspelund, Valdis Anna Gardarsdottir, Lars Forsberg, Vilmundur Gudnason and David. O. Arnar. Improved brain perfusion after electrical cardioversion of atrial fibrillation. Europace (2020) 22, 530–537.

III. Marianna Gardarsdottir, Sigurdur Sigurdsson, Lars Forsberg, Gary F Mitchell, Lenore J. Launer, Thor Aspelund, Vilmundur Gudnason, David. O. Arnar. Aortic stiffness and brain perfusion in a population-based study. Submitted.

Declaration of Contribution

Initially, the candidate took part in applying to the Age, Gene/Environment Susceptibility (AGES) Executive Committee for permission to use AGES and Icelandic Heart Association data from the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-RS) in preparations for the first project. The candidate wrote the theoretical background of the Paper I, analyzed the data with the research group, led the work presenting the data as with supervisor Davíð O. Arnar and the rest of the group, Sigurður Sigurðsson, Thor Aspelund and Vilmundur Guðnason and was the first author of the Paper I. The candidate prepared the design of the second study with the supervisor and the research group, established the database for the study and acquired data in co-operation with the study coordinator, Valdís A. Garðarsdóttir. The candidate analyzed the data, primarily with the research group statistician, Thor Aspelund, and Sigurður Sigurðsson. The candidate led the presentation of the data with supervisor Davíð O. Arnar and Sigurður Sigurðsson, Thor Aspelund and Vilmundur Guðnason and wrote Paper II as first author. The candidate researched and wrote the theoretical background for the third project, analyzed the data with Sigurður Sigurðsson and Thor Aspelund, and wrote the manuscript of Paper III as first author. The candidate also participated in grant applications to Landspítali Scientific Fund and the Helga Jónsdóttir and Sigurliði Kristjánsson memorial fund with supervisor Davíð O. Arnar.

1 Introduction

1.1 Atrial fibrillation

1.1.1 Definition of atrial fibrillation

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by rapid, disorganized electrical activation of the atria, resulting in ineffective mechanical contraction and loss of coordinated atrial systole. AF is the most common sustained arrhythmia and one of the most common cardiovascular conditions in older adults, with a continuing rise in prevalence driven by population aging, improved survival, greater awareness, and increasing cardiovascular comorbidity (1–4). In Europe, the lifetime risk of developing AF approaches one in three, increasing from approximately one in four at the beginning of the century (2,5–7). The number of adults over 55 years living with AF in Europe was estimated at 8.8 million in 2010 and is projected to increase to 17.9 million by 2060, underscoring the substantial and growing public health burden of this arrhythmia (8).

The pathophysiological basis of AF involves both structural and electrophysiological abnormalities. Structurally, atrial fibrosis, dilatation, and altered gap junction expression disrupt normal conduction pathways of atrial tissue. Electrophysiologically, abnormalities in impulse generation and conduction such as enhanced ectopic activity particularly occurring in the pulmonary veins, triggered depolarizations, and reentry circuits, facilitate the initiation and maintenance of AF (3,4,9). The disorganized atrial electrical activity results in irregular and often rapid ventricular response due to erratic conduction through the atrioventricular node. This irregular ventricular rate impairs diastolic filling and reduces cardiac output, particularly in individuals with pre-existing left ventricular dysfunction, and may contribute to the development or worsening of heart failure (4). AF was previously distinguished as valvular or non-valvular AF, primarily for stroke risk assessment and anticoagulation strategy. Recent guidelines emphasize describing the specific type of valve disease, rather than using the binary classification, and the term “valvular” is now obsolete (3,4,10).

AF is a complex and heterogeneous condition that, while presenting with shared clinical phenotypes, can develop through multiple and distinct etiological pathways. These include genetic predisposition, ethnic and environmental influences, and metabolic disturbances, in addition to the contribution of conventional cardiovascular risk factors (11–14).

1.1.2 Risk factors and comorbidities in atrial fibrillation

Effective management of AF requires not only addressing the arrhythmia itself but also identifying and managing both associated risk factors and comorbidities. For example, hypertension is a risk factor for new-onset AF but once established, the hypertension becomes a comorbidity that increases the risk of stroke, heart failure, and recurrence of AF. Risk factors and comorbidities likely interact through shared pathophysiology by driving atrial remodeling that is a substrate for AF, by additive risk synergizing to increase AF burden (the overall time spent in AF during a clearly specified and reported period of monitoring, expressed as a percentage of time), and by having an impact on the management of AF if uncontrolled (4,15).

Personalized care supported by clinical decision tools can improve outcomes by targeting these underlying contributors and AF is best managed using the AF-CARE pathway (4):

- C – Comorbidity and risk factor management
- A – Avoid stroke and thromboembolism
- R – Reduce symptoms through rate and rhythm control
- E – Educate and enable patient-centered care

1.1.2.1 Risk factors

Among modifiable risk factors, elevated body mass index (BMI) and hypertension contribute the highest attributable risk for AF. Clinical guidelines emphasize optimal blood pressure control, as it reduces both AF recurrence and progression, and prevents related adverse cardiovascular events (1,3,4). In hypertensive patients, blood pressure reduction, especially when it leads to regression of left ventricular hypertrophy, has been associated with a decreased risk of developing AF (16). Controlling blood pressure may also prevent atrial remodeling, a key mechanism in AF pathogenesis (17,18). Other established modifiable risk factors include smoking, physical inactivity, excess alcohol consumption, and sleep apnea (4). These factors often precede AF and contribute to its development through structural or electrical remodeling of the atria.

1.1.2.2 Comorbidity and risk factors in atrial fibrillation

A comorbidity is a coexisting medical condition present in a patient who already has AF. Comorbidities may have contributed to AF onset or developed after AF and complicate its course or management. Comorbidities influence the risk of developing AF, as well as the progression and recurrence of AF and increase treatment complexity. Addressing these factors can improve AF-related outcomes and prevent recurrence,

and their management is essential to successful long-term AF control (4). Heart failure is the most common non-fatal outcome of AF and at the same time remains the leading cause of death among individuals with AF, highlighting the importance of coordinated disease management (4). The next most common adverse impacts of AF are ischemic stroke, ischemic heart disease, other thromboembolic events, and increased risk of cognitive impairment and dementia (4). Modifiable contributing factors associated with AF include coronary and valvular heart disease, stroke, history of cardiac surgery, chronic renal disease, heart failure, diabetes mellitus, obesity, obstructive sleep apnea, and unhealthy lifestyle behaviors (1,3,19–21).

With improved stroke prevention and heart failure therapy, patients with AF are living longer, but longevity brings increased exposure to the detrimental long-term effects of AF and its treatments, including progressive organ dysfunction (22).

1.1.3 Stroke risk in atrial fibrillation

AF is a major causal factor in cardioembolic and ischemic stroke with up to a five-fold increase in risk of various severity (5,9,21,23–26). The heart is a significant source of emboli caused by electromechanical dissociation and fibrillation of the left atrium with subsequent dilatation, abnormal contractility and impaired atrial emptying causing stasis of blood, particularly in the left atrial appendage, increasing risk of thrombus formation and subsequent cerebral embolization. Additional factors increasing risk of stroke in AF are older age, previous stroke or transient ischemic attack, vascular disease, renal dysfunction, low BMI, and surgery (2,27,28). At the same time oral anticoagulation reduces thromboembolic events and mortality, and because AF-related strokes are otherwise more disabling and often fatal, broader use of anticoagulation has contributed to declining stroke incidence in AF (21,29).

1.1.4 Risk score and anticoagulation in atrial fibrillation

Stroke and prevention of thromboembolism is a priority in the management of patients with AF and anticoagulation should be offered to all, unless the patient is identified at true low risk (4,5,21,30). Direct anticoagulants (DOACs) are preferred except in patients with mechanical heart valves due to the thrombogenic nature of the valves, and in moderate to severe mitral stenosis due to increased risk of atrial thrombus formation in the dilated atrium (4,29,31–36). Prior to commencing anticoagulation treatment with oral anti-coagulation (OAC), bleeding risk should be evaluated to identify and manage modifiable bleeding risk factors (4,21).

Before anticoagulation administration in individuals with clinical AF, individual assessment with validated stroke risk scores is needed (2,4,5,37). According to the 2024 ESC guidelines by Van Gelder et al. (2024), the CHA_2DS_2-VA score is proposed in the lack of other locally validated alternatives, excluding birth sex or gender criterion (4). The risk scores have a generally modest individual predictive value, but do lower

stroke risk following onset of AF, and reduce adverse outcomes with specific treatment (1,4,38). While prevention of thromboembolic stroke remains the cornerstone of AF management, increasing evidence indicates that AF contributes to structural and functional brain changes even in the absence of clinically apparent stroke.

1.2 Atrial fibrillation and brain volume

Growing evidence demonstrates an association between AF and reduced brain volume. In a study by Stefansdottir et al. (2013), persistent AF was associated with smaller total brain, grey matter (GM), and white matter (WM) volumes, with stronger effects observed with increasing arrhythmia burden, suggesting a dose-dependent impact on brain structure over time (39). Earlier studies were often small, conducted in younger populations or underpowered, possibly underestimating the cumulative effects of AF on brain volume (40–42). Similarly, Moazzami et al. (2020) reported later that age may amplify the adverse structural effects of AF, potentially reflecting longer exposure to arrhythmia burden (43).

Further supporting structural vulnerability, Polymeris et al. (2020) demonstrated an inverse relationship between serum neurofilament light chain (sNfL)—a biomarker of neuronal injury—and normalized brain volume in individuals with AF, independent of age, stroke history, and overt brain lesions (44). WM lesions and large infarcts were the strongest independent predictors of sNfL, suggesting subclinical vascular brain injury and covert neurodegeneration contributing to brain atrophy in AF (44).

Age and vascular comorbidities such as hypertension, diabetes, and heart failure may act both as confounders and mediators in this interplay between AF and brain atrophy. While silent infarction, microvascular injury, and systemic inflammation have been proposed as contributing mechanisms, subclinical hemodynamic compromise—such as chronic hypoperfusion or altered neurohormonal response—may also play a role (45).

Because structural brain alterations are closely linked to cognitive function, these findings raise the question of whether AF is associated not only with reduced brain volume but also with measurable cognitive decline and broader functional consequences.

1.3 Atrial fibrillation and cognition

AF has been consistently associated with cognitive impairment and dementia, further underscoring the clinical relevance of these structural findings. Several non-mutually exclusive mechanisms have been proposed to explain this relationship. A meta-analysis by Kalantarian et al. (2013) demonstrates an increased risk of both cognitive impairment and dementia in individuals with AF, despite heterogeneity in age, comorbidities, stroke ascertainment and AF classification across studies (46). Importantly, the association persisted beyond clinically overt stroke, implicating additional non-embolic pathways (46). Subsequent studies have confirmed that AF is

associated with both stroke-related and non-stroke-related cognitive decline, with particularly strong effects observed in vascular dementia (47,48). AF has indeed been associated with increased risk of cerebral small vessel disease, reduced brain volume, and cognitive impairment, reinforcing the hypothesis of a cerebrovascular and neurodegenerative continuum (49). Longitudinal data further suggest that subclinical infarction in AF contributes to cognitive decline, particularly in older individuals and in the presence of cumulative vascular burden (50–52). Overall, evidence suggests that vascular brain injury in AF contributes to cognitive decline, particularly in the presence of comorbidities such as hypertension and diabetes (49,53).

Collectively, these observations suggest that cognitive decline in AF is not solely a consequence of cerebrovascular events, but rather the cumulative result of subtle and potentially chronic disturbances in brain perfusion and structure. This perspective shifts attention from discrete embolic episodes toward broader hemodynamic and vascular mechanisms that operate silently over time.

1.4 Possible causes of altered brain structure and function in atrial fibrillation

Building on this concept, the impact of AF on brain structure and function likely reflects multiple interacting biological pathways (Figure 1). AF appears to influence the brain through converging embolic, vascular, inflammatory, and hemodynamic processes (52,54–58). Among these pathways, hemodynamic disturbance has emerged as a particularly compelling mechanism. AF is characterized by irregular ventricular rhythm, beat-to-beat variability in stroke volume, loss of atrioventricular synchrony, and reduced cardiac efficiency, all of which may compromise effective cerebral blood delivery even in the absence of overt stroke. Chronic alterations in central flow dynamics may impair microvascular integrity and promote progressive structural injury, particularly in the context of aging and vascular comorbidity.

Age and vascular risk factors further modify this relationship. Both AF and cognitive impairment increase with advancing age and cumulative vascular exposure, and hypertension, diabetes, heart failure, and obesity have been independently associated with brain atrophy, reduced GM volume, and WM injury (46,49,59). Thus, AF-related hemodynamic instability likely operates within a broader substrate of vascular aging, where cumulative vascular burden increases susceptibility to brain injury.

While AF contributes to brain injury through embolic and hemodynamic mechanisms, vascular aging and arterial stiffening represent parallel and potentially interacting pathways influencing brain perfusion and structural brain integrity. This raises the possibility that disturbances in central hemodynamics beyond rhythm irregularity—such as increased aortic stiffness and altered pulsatile energy transmission—may exert additive effects on the brain.

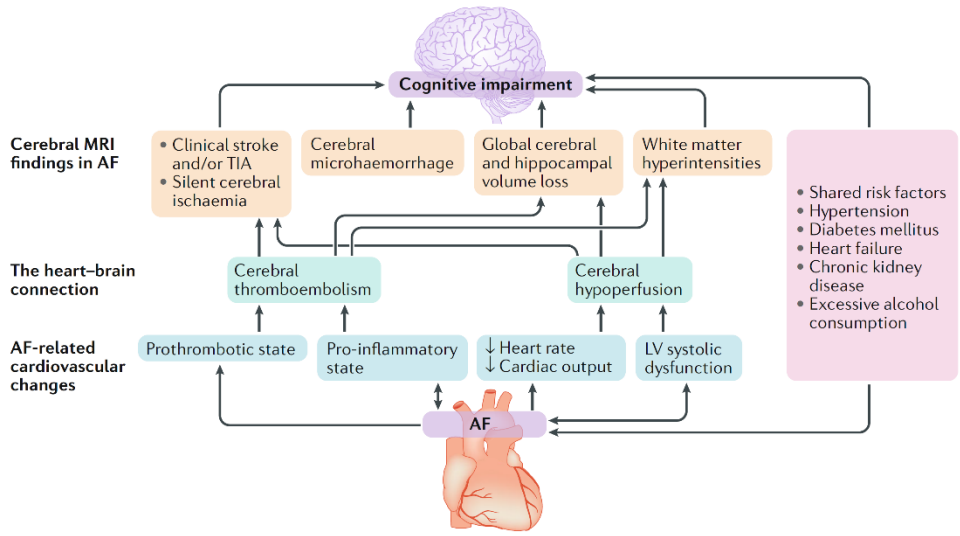

Figure 1 Proposed pathophysiology of cognitive impairment in atrial fibrillation.
Atrial fibrillation (AF) has a number of effects that predispose to cognitive impairment, including a prothrombotic state, a pro-inflammatory state, and reduced cardiac output. Final pathways leading to cognitive impairment potentially include cerebral embolism, hemorrhage, and volume loss. LV, left ventricular; TIA, transient ischemic attack. Reprinted with permission from M. Madhavan, J. Graff-Radford, J.P. Piccini, B.J. Gersh. Cognitive dysfunction in atrial fibrillation. Nature Reviews Cardiology 2018, vol. 15, p. 744–756. www.nature.com/nrcardio/.

1.5 Atherosclerosis and aortic stiffness

Vascular aging involves progressive structural remodeling of the arterial wall that leads to loss of elasticity and increasing arterial stiffness. Stiffening of the aorta, the principal elastic artery of the circulation and a key buffer of pulsatile cardiac output, represents a central manifestation of this process and has important implications for both cardiovascular and cerebrovascular health (60).

Atherosclerosis is a chronic inflammatory disease of the arterial wall that promotes progressive structural remodeling, luminal narrowing, and loss of arterial compliance, ultimately contributing to arterial stiffening and impaired tissue perfusion. The atherosclerotic process is accelerated by aging, vascular risk factors, and cumulative hemodynamic stress (61,62). In parallel, vascular aging is characterized by elastin fragmentation, increased collagen deposition, and medial calcification, further reducing arterial elasticity.

A functional consequence of these cumulative structural changes is increased aortic stiffness, reflecting the progressive loss of the aorta's normal cushioning function. This process can be quantified as pulse wave velocity (PWV), which reflects the intrinsic stiffness of the aortic wall and integrates the cumulative effects of vascular aging and cardiometabolic risk exposure, making it a central measure of arterial health (63,64).

Aortic stiffness reflects the loss of normal viscoelastic properties of the aortic wall and represents a maladaptive response to cumulative hemodynamic load and vascular risk exposures (62). Increasing evidence suggests that arterial stiffening may also represent a biological pathway through which these exposures contribute to cardiovascular and cerebrovascular disease (60). Elevated PWV is consistently associated with increased cardiovascular morbidity and mortality (65–68). Large population-based studies, including the Rotterdam and Framingham cohorts, demonstrate that PWV provides additive and independent prognostic information beyond traditional cardiovascular risk factors, supporting its role as a robust biomarker of vascular disease risk (69,70). In the Framingham Offspring Study, higher carotid-femoral PWV (CFPWV) and central pulse pressure were associated with increased risk of cardiovascular events and mortality, reinforcing the clinical and epidemiological relevance of central arterial stiffness (71–73).

Both atherosclerosis and arterial stiffening accelerate with age, and PWV can be viewed as an integrated marker of cumulative vascular injury across the life course. In contrast, the predictive value of several conventional cardiovascular risk factors diminishes in older age due to selective survival and increasing comorbidity (67,74,75). In the Framingham Offspring Study, Mitchell et al. (2004) demonstrates that aging is associated with a disproportionate increase in aortic stiffness relative to peripheral muscular arteries, resulting in reversal of the normal central-to-peripheral stiffness gradient (76). This age-related shift enhances transmission of pulsatile energy into the microcirculation, highlighting the pathophysiological significance of aortic stiffness.

Beyond its established association with cardiovascular morbidity and mortality, increased aortic stiffness may also have important implications for high-flow organs such as the brain. Increased transmission of pulsatile pressure into the distal circulation may expose the cerebral microvasculature to greater hemodynamic stress, providing a potential link between vascular aging and alterations in brain perfusion and structural brain integrity.

1.6 Aortic stiffness and the brain

The aorta plays a central role in buffering pulsatile cardiac output, protecting the distal microcirculation from excessive pressure and flow fluctuations. Aortic impedance reflects the opposition of the aorta to pulsatile blood flow. In healthy young adults, the compliant aorta exhibits low impedance, whereas first-generation branch arteries are relatively stiffer and display higher impedance. This transition creates an impedance mismatch that promotes partial reflection of pulsatile waves and limits transmission of pulsatile pressure into the distal arterial tree.

With aging and cumulative vascular exposure, aortic compliance declines, and central impedance rises. As a result, the normal impedance mismatch between the aorta and

its branch vessels is reduced, diminishing wave reflection and increasing transmission of pulsatile pressure into the microcirculation (76–78).

The resulting pulsatile load may damage cerebral small vessels and impair microvascular integrity, rendering the brain particularly vulnerable (72,79). Increased pulse pressure transmission has been associated with vascular remodeling, impaired cerebrovascular reactivity, and microvascular injury, processes that may contribute to alterations in cerebral perfusion and subsequent structural brain injury (80–83).

Consistent with this mechanistic framework, increased aortic stiffness measured by CFPWV has been associated with lower regional cerebral blood flow (84). Alterations in cerebral perfusion may therefore represent an early manifestation of vascular stiffening, potentially preceding detectable structural brain injury. Elevated PWV has also been linked to reduced total brain and GM perfusion, smaller total brain and GM volume, and increased risk of cognitive impairment (85). Furthermore, increased arterial stiffness has been associated with imaging markers of cerebral small vessel disease, including WMH, subcortical infarctions, and microinfarcts detected by MRI, suggesting an association with microvascular dysfunction and brain damage (86–88). In systematic reviews and meta-analyses, higher aortic stiffness has been consistently associated with poorer performance across multiple cognitive domains, independent of demographic and clinical characteristics (89,90). This framework provides a physiological basis for investigating how disturbances in central hemodynamics, arising from rhythm irregularity and arterial stiffening, may influence brain perfusion and structural brain vulnerability.

1.7 Assessment of brain perfusion and aortic stiffness

Detailed methodological descriptions are provided in Chapter 3. The following section outlines the theoretical principles underlying the assessment of brain perfusion and aortic stiffness used in this thesis.

1.7.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive imaging modality that exploits the magnetic properties of hydrogen protons to generate high-resolution anatomical and functional images without ionizing radiation. Owing to its superior soft-tissue contrast, MRI is particularly suited for assessment of brain structure and pathology. In addition to structural imaging, MRI enables quantitative evaluation of cerebral blood flow and brain perfusion using specialized techniques, including phase contrast (PC) and arterial spin labeling (ASL).

1.7.1.1 Phase contrast magnetic resonance imaging

PC MRI is a velocity-encoded technique that allows visualization and direct quantification of blood flow. By encoding flow velocity into phase shifts of moving spins, PC MRI enables measurement of the magnitude and direction of blood flow within selected vessels (91). When applied at the level of the cervical arteries, PC MRI permits calculation of total cerebral blood flow (TCBF) by combining flow velocities with vessel cross-sectional area (Figure 2) (92–95).

For accurate quantification, the imaging plane must be oriented perpendicular to the vessel of interest and the velocity encoding (v_{enc}) appropriately adjusted to avoid measurement error (91,96). PC MRI has demonstrated good reproducibility and feasibility even in elderly populations and provides a robust measure of global cerebral inflow (94).

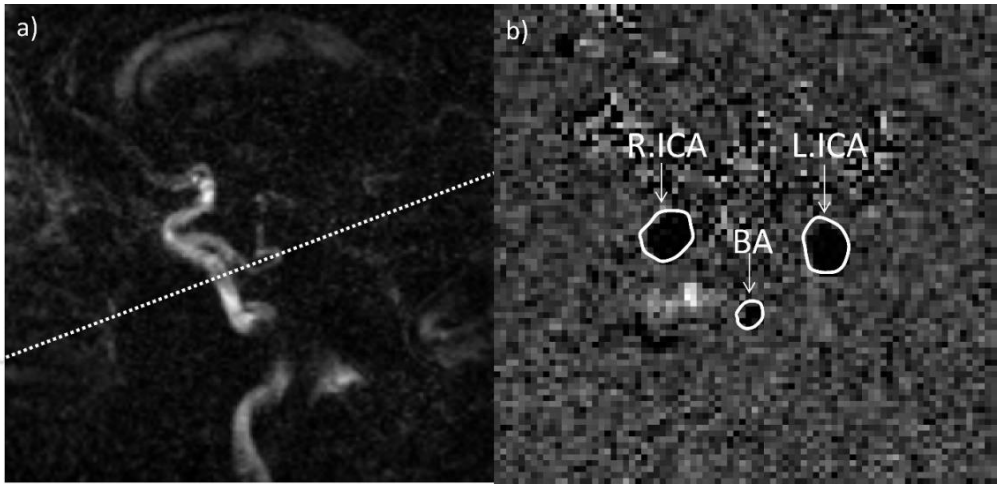

Figure 2 PC MRI for quantification of total cerebral blood flow.
a) A PC MRI scan for measuring mean TCBF was prescribed on a PC MRI sagittal localizer image perpendicular to the carotid arteries at the level of the mid-basilar artery. b) A representative phase image demonstrating the right and left internal carotid arteries (R.ICA and L.ICA) together with the basilar artery (BA). Reprinted with permission from S. Sigurdsson, L. Forsberg, T. Aspelund, R.J. var der Geest, M.A. van Buchem, L.J: Launer, V. Gudnason, M.J. van Osch. Feasibility of Using Pseudo-Continuous Arterial Spin Labeling Perfusion in a Geriatric Population at 1.5 Tesla. PLOS One 2015. vol. 10 (12), e0144743. journals.plos.org/plosone/.

1.7.1.2 Arterial spin labeling magnetic resonance imaging

ASL is a non-invasive MRI technique that quantifies brain perfusion at the tissue level without the need for exogenous contrast agents (97,98). In ASL, inflowing arterial blood water is magnetically labeled proximal to the imaging region and used as an endogenous tracer. After a defined transit time, labeled blood reaches the capillary bed, allowing quantification of brain perfusion in units of milliliters per gram of tissue per minute (mL/g/min) (Figure 3) (99,100).

Figure 3 ASL planning with labeling plane at the upper cervical spine (orange) perpendicular to the carotid and basilar artery and image volume (green).
PCASL: pseudo-continuous arterial spin labeling.

The inflow of inverted spins alters total tissue magnetization and consequently the tissue magnetization as well as image intensity, creating the tag image. The final product, the perfusion image, will reflect the amount of arterial blood delivered to each voxel within the slice during the transit time, determining the delivery rate of oxygen and nutrients to the microcirculation (94,101). Perfusion is a fundamental quantitative physiological parameter, referring to the delivery of nutrients and oxygen to tissues (99,100).

ASL enables regional and whole brain perfusion assessment and is particularly suitable for repeated measurements due to its non-invasive nature (100). Pseudo-continuous ASL has been shown to be feasible and reliable in elderly populations at 1.5 Tesla, with good agreement compared to PC MRI measurements (94). As brain perfusion is influenced by age-related vascular changes, careful consideration of acquisition parameters is required in older individuals. There are three main approaches to ASL labeling; continuous labeling, pulsed labeling, and velocity selective labeling. Pseudo-continuous ASL is one form of continuous labeling and recommended for clinical imaging by a consensus expert group due to its robustness and simplicity (102).

1.7.2 Applanation tonometry

Atherosclerosis and vascular aging can be assessed as aortic stiffness non-invasively with arterial tonometry, the reference non-invasive method for measuring CFPWV (Figure 4) (103). This technique involves recording arterial pressure waveforms at the carotid and femoral arteries using a high-fidelity pressure sensor. The time delay between the foot of the two waveforms, combined with the measured transit distance, yields CFPWV, an established measure of aortic stiffness (70,104). CFPWV reflects

stiffness of the central elastic arteries and is considered the gold standard for epidemiological and clinical studies of arterial stiffness. CFPWV demonstrates strong predictive value for cardiovascular events and mortality independent of conventional risk factors (68,103,104). Importantly, central arterial stiffness precedes overt hypertension, providing complementary information beyond brachial blood pressure measurement (62,105).

Some technical limitations should be acknowledged. Accurate femoral waveform acquisition may be challenging in individuals with obesity, metabolic syndrome, diabetes or peripheral arterial disease, and proximal arterial stenosis can affect waveform transmission (104,106).

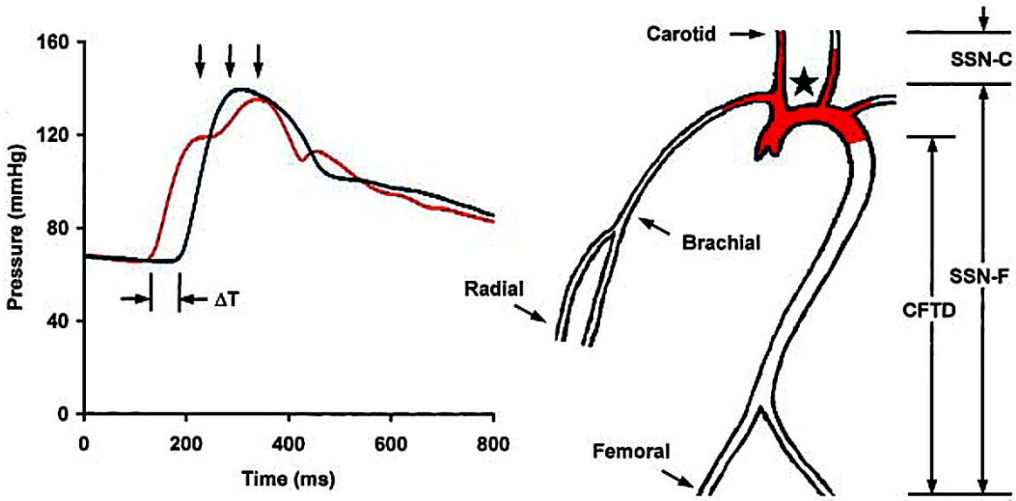

Figure 4 Measurement of carotid-femoral pulse wave velocity.
Time delay, ΔT, between the foot of the carotid (red waveform) and femoral waveforms was measured. Carotid-femoral transit distance (CFTD) was estimated by measuring the distance from the suprasternal notch (SSN, ★) to the carotid (SSN-C) and femoral (SSN-F) sites and taking the difference to account for parallel transmission along the brachiocephalic and carotid arteries and around the aortic arch (red shading). This corrected distance is divided by transit time delay to give PWV. Note that carotid-femoral PWV fails to assess stiffness of the proximal aorta (red shading). Reprinted with permission from G.F. Mitchell, J.L. Izzo Jr., Y. Lacourciere, J.P. Ouellet, J. Neutel, C. Qian, L.J. Kerwin, A.J. Block, M.A. Pfeffer. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. Circulation 2002, vol. 105 (25), p. 2955-–2961. https://www.ahajournals.org/.

To summarize Chapter 1, AF and aortic stiffness represent prevalent manifestations of cardiovascular aging that may converge on the brain through shared disturbances in central hemodynamics. While thromboembolism and overt stroke remain established mechanisms of brain injury in AF, accumulating evidence indicates that chronic

alterations in flow dynamics, impaired brain perfusion, and enhanced pulsatile energy transmission may contribute to structural brain changes and cognitive impairment even in the absence of clinically apparent cerebrovascular events. Progressive arterial stiffening further alters aortic buffering capacity and increases pulsatile load within the cerebral microcirculation, raising the possibility that rhythm-related irregularity and vascular stiffening interact to influence brain integrity. However, the extent to which these mechanisms independently or jointly affect brain perfusion and subsequent structural and cognitive outcomes remains uncertain. Clarifying these relationships defines the central research problem addressed in this thesis.

2 Aims and hypotheses

2.1 Aims

The overall aim of this thesis was to examine whether disturbances in central hemodynamics represent a unifying pathway linking AF and aortic stiffness to alterations in brain perfusion, brain structure, and cognitive performance.

In Paper I, the aim was to evaluate the association between AF and TCBF, estimated brain perfusion, brain volume, and cognitive performance in elderly individuals.

In Paper II, the aim was to evaluate changes in TCBF and brain perfusion following electrical cardioversion to sinus rhythm (SR) in individuals with AF.

In Paper III, the aim was to evaluate the associations of age and aortic stiffness with brain perfusion, brain volume, and cognitive performance.

2.2 Hypotheses

The hypotheses of this thesis were:

- Total cerebral blood flow and estimated brain perfusion are lower in elderly individuals with permanent AF compared with those in SR.
- Brain volume and cognitive performance are reduced in elderly individuals with permanent AF compared with those in SR.
- Brain perfusion improves following successful restoration of SR by electrical cardioversion.
- Brain perfusion is inversely associated with aortic stiffness.
- Increased aortic stiffness is associated with reduced brain volume and poorer cognitive performance.

3 Materials and Methods

The following chapter describes the methods used in the three studies included in this thesis. More detailed methods and protocols are provided in the individual papers included in this thesis.

3.1 Paper I

The cohort in the study on TCBF and estimated brain perfusion comes from AGES II, a follow up visit of 3316 surviving participants from the multidisciplinary AGES Reykjavik Study (AGES-RS) who gave consent for participation, conducted in 2007-2011 (107). The AGES-RS, initiated in 2002, was designed to examine genetic and environmental factors contributing to clinical and subclinical disability in old age (108). The AGES-RS cohort consists of 6000 elderly subjects and is a random recruitment of survivors from the previous Reykjavik Study that commenced in 1967, collecting midlife data on cardiovascular traits (109,110). The Reykjavik Study is a total population study of men and women born in 1907-1935 who were residents of the greater Reykjavik area in 1967, and the cohort has been followed since the beginning by the Icelandic Heart Association.

Data collection included a questionnaire, clinical examination, brain, musculoskeletal system, heart and vasculature imaging, measurement of body composition and metabolic regulation as well as cognitive testing to provide detailed phenotypes related to neurocognitive, cardiovascular, and musculoskeletal systems. Individuals with diagnosis of dementia and heart failure were excluded in the current study. After excluding individuals with contraindications for MRI (claustrophobia, physical inability to undergo the investigation, pacemaker), participants underwent brain MRI on a 1.5-T Signa Excite Twinspeed system (General Electric Medical Systems, Waukesha, WI). The scan protocol included PC scan for TCBF measurements, and anatomical imaging sequences of the whole brain for calculations of brain tissue volumes and estimation of brain perfusion, including cerebrospinal fluid (CSF), GM, WM, and white matter hyperintensities (WMH) that were segmented with a validated automatic image tissue post-processing pipeline (111,112). The AGES-Reykjavik brain MRI image acquisition protocol has previously been described in detail (112). In brief, the protocol included a T1-weighted 3-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.

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

TCBF was measured using PC 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. PC MRI does not measure perfusion directly in the microcirculation, and therefore average brain perfusion of each group was estimated. This approach allowed indirect estimation of perfusion at the tissue level. The average blood flow volume was divided by whole brain volume to generate the average estimated whole brain perfusion, expressed in units of mL/100g brain tissue/min, assuming an average brain density of 1.05 g/mL (113). Details on the analysis of the images as well as calculation of cerebral blood flow and average estimated perfusion have previously been described by Sigurdsson et al. (2015) (94). The operators of the MRI system performing the acquisitions and the MR image analysts were blinded to all clinical information on the study participants, including the AF status of each participant. Stroke was determined from 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 multi-detector scanner with prospective ECG triggering (Siemens Healthcare, Erlangen). For cognitive testing, the Mini-Mental State Examination and the Digit Symbol Substitution Test were administered to all participants. Cognitive impairment was classified as 23 points or lower on the Mini-Mental State Examination score (MMSE) and 17 or lower on the digit symbol substitution test score (DSST).

Participants were divided into three groups according to presence of AF at the time of MRI imaging and previous history of AF; AF on electrocardiogram (ECG) (persistent AF group), those in SR on ECG but with previous history of AF from hospital records or medical history (paroxysmal AF group), and those in SR on ECG and with no previous history of AF (no AF group). Of the 2291 participants, 117 had persistent AF and 78 individuals had a prior history of the arrhythmia but were in SR at the time of the examination. For statistical analysis, generalized linear models were used to compare characteristics between groups with age and sex adjustment. The assumption of a normal distribution of the residuals from the continuous perfusion measures was verified by inspecting qq-plots of residuals from the regression models. Generalized linear models were used to perform analysis of TCBF difference between groups with age and sex adjustments, as well as adjustments for brain volume, warfarin use, and use of antihypertensive medication. Similarly, analysis of brain perfusion was done with adjustments for warfarin use and use of antihypertensive medication, but adjustments for brain volume were not needed as the outcome was already standardized by total brain volume. All analyses were done using SAS System software version 9.2 (SAS Institute Inc., Cary, NC, USA). Data was presented as mean (standard deviation) for

continuous variables and as percentages for categorical variables. A P-value <0.05 was considered statistically significant.

The AGES-Reykjavik study was 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.

3.2 Paper II

To investigate TCBF and brain perfusion before and after elective direct-current cardioversion, all individuals between the age of 18 to 75 scheduled for cardioversion for AF at Landspitali–University Hospital in Reykjavik, Iceland were invited to participate in the study (114). A letter was sent to individuals on the waiting list with an offer to receive more information on the study. They were contacted via phone by a study coordinator 10–14 days after the letter was sent, and an appointment made if they wished to participate. During the interview, the study coordinator collected demographic information on the participants, and blood pressure and heart rate were recorded. Collected information also included cardiovascular risk factors and past medical history, information on the nature (paroxysmal AF or persistent AF) and length of AF episodes, medication use and history (beta blockers, antihypertensive medication, anticoagulation medication; warfarin or novel oral anticoagulants, aspirin or platelet inhibitors, diabetes medication, lipid lowering medication, and digoxin) as well as history of previous cardioversion, if present. Information was also obtained from participants´ medical records if needed regarding biochemistry, medication, and past medical history, and results of echocardiography studies were registered if done within 6 months prior to entering the study.

Exclusion criteria included former stroke, severe claustrophobia, contraindications for MRI (pacemaker, implantable cardioverter defibrillator or other contraindications for MRI). The study coordinator went through a safety questionnaire regarding MRI compatibility after obtaining informed written consent from each participant, and participants were advised not to use caffeine or tobacco at least 4 hours before the MRI examination. When the date of the cardioversion was set, the first MRI study was scheduled by the study coordinator to be done prior to the cardioversion, either the day before or preferably on the same day according to the study protocol (Figure 5). Biochemistry tests (N-terminal probrain natriuretic peptide (NT-proBNP)) were done the day before the cardioversion and INR had to have been stable at >2.0 for more than 3 weeks prior to the cardioversion. At the day of the cardioversion, an ECG was done to confirm AF, and electrical cardioversion was performed under brief anesthesia according to clinical hospital protocol. The use of anticoagulation pre- and post-

cardioversion is mandatory. Although electrical systole in the atria is induced immediately after successful cardioversion to SR, mechanical atrial systole may be delayed for a few weeks. Therefore, it is reasonable to consider that it takes more than a few weeks for normal hemodynamics to be fully restored after successful cardioversion. Indeed, in the study, the follow up MRI was performed at least ten weeks after the procedure, to allow the atria to mechanically recover. Cognitive testing was not performed, as cognitive function was not a main outcome in the study and changes in cognitive performance were not expected to be affected during the short observation period.

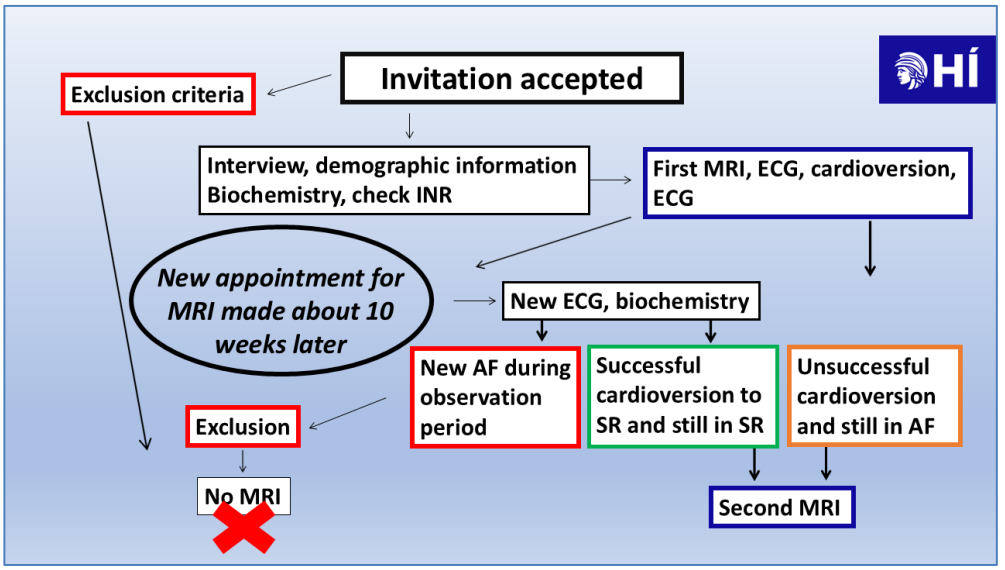

Figure 5 A diagram showing the cardioversion study protocol in Paper II.
Individuals with contraindication for MRI were excluded from the study. Baseline information was collected and informed consent obtained. The day before the cardioversion, ECG and biochemistry test were done and the first MRI was performed on the day of the cardioversion. An appointment was made for the second MRI at least 10 weeks after the cardioversion and approximately a week before, a new ECG was done and the patient asked about symptoms of recurrent AF. If recurrence had occurred, the patient was excluded from the second MRI, but those that achieved and maintained continued SR after a successful cardioversion or maintained AF after an unsuccessful cardioversion went for the MRI as planned.

After the cardioversion was done, ECG-verified results were registered, and the second MRI examination was scheduled. Before the follow-up visit, a biochemistry test (NT-proBNP) and an ECG was performed a few days before the follow-up visit to confirm SR after successful cardioversion or continued AF if unsuccessful, and the patient asked about symptoms of recurrent AF. Patients with recurrence of AF on ECG after a previously successful cardioversion to SR were excluded from further participation in the study, as the time from cardioversion to recurrence was uncertain, and the second

MRI was cancelled. Without knowledge of the interim between cardioversion to SR and recurrence of AF, the results would have been very difficult to interpret. No 24-hour Holter monitoring was performed between the cardioversion and the follow-up visit. Those that achieved and maintained SR after a successful cardioversion, or continued in AF after unsuccessful cardioversion, that is maintained unchanged rhythm on the day of the second MRI, went for the imaging procedure as planned.

MRI acquisition and image processing as well as measurement of TCBF were performed as described in Section 3.1. The ASL perfusion scan protocol included acquisition of 3-dimensional pCASL perfusion sequences for calculating brain perfusion, with post-labeling delay of 1525 milliseconds (112). Quantitative ASL perfusion maps were calculated for the whole brain, global GM, global WM, and multiple cortical and subcortical brain regions using a validated automated image post-processing pipeline (94,112). PC measurements for cerebral blood flow measurements were done for comparison with ASL. The operators of the MRI system performing the acquisitions and the MR image analysts were blinded to all clinical information on the study participants, including the AF status of each participant.

Participants were divided into three groups, those that were cardioverted into SR and remained in SR during the observation period (SR group), those who remained in AF after an unsuccessful attempt at cardioversion (AF group), and those who had a recurrence of AF during the observation period after a successful cardioversion to SR (recurrent AF group). Those in the recurrent AF group were excluded from further evaluation with a second MRI according to the study protocol as previously described (Figure 5). Data were presented as mean (standard deviation) for continuous variables and as percentage for categorical variables. A P-value of <0.05 was considered statistically significant. Characteristics between groups were compared using t-tests and X^2 tests. The assumption of normal distribution of the two continuous blood flow measures was verified by inspecting qq-plots of residuals from the regression models. All analyses were performed using R version 3.5.5. Changes in TCBF over time and between groups were analyzed with linear mixed models using the lme4 package in R, with age and sex adjustment, as well as adjustment for brain volume. Adjustment for brain volume was not performed because perfusion was quantified independently of total brain volume. Adjusted marginal means at each time-point and change between time-points were estimated using the emmeans package in R.

The study was approved by the Icelandic National Bioethics Committee, which acts as the Institutional Review Board for the Icelandic Heart Association and the National University Hospital (VSN-13-043) and by the Icelandic Data Protection Authority.

3.3 Paper III

The sample in Paper III on aortic stiffness and brain perfusion came from the OffGen population. The OffGen study was designed to investigate neurologic, cardiovascular,

sensory, lifestyle, and medical history differences in offspring of AGES-Reykjavik Study parents, previously described in Section 3.1. The OffGen study involved selective analysis of subclinical disease and traits such as brain morphology and function, based on genetics and other profiles in parents. The cohort consisted of 956 participants that were recruited in 2011–2015 (mean age 62 years, range 55-81 years) and the current sample consists of 269 OffGen participants aged 58 to 74 years who were randomly selected from the cohort and specifically recruited for PWV measurements using tonometry, measurement of brain perfusion and structural brain imaging with MRI, and cognitive evaluation.

The hemodynamic acquisition, calculations of PWV, and analysis protocol of CFPWV have already been described in detail (115,116). Blood pressure was measured following 15–20 minutes of supine posture, using a computer-controlled device that automatically inflated the cuff to a user preset maximum pressure, and then precisely controlled deflation at 2 mmHg/second. This device digitized and recorded cuff pressure, electrocardiogram, and a cuff microphone channel throughout the inflation and deflation sequence. Applanation tonometry with ECG for assessment of regional PWV was obtained with a custom transducer from the carotid, brachial, radial, and femoral arteries. Body surface measurements from suprasternal notch to pulse recording sites were obtained by using a fiberglass tape measure for carotid, brachial, and radial sites, and a caliper for the femoral site (115).

The MRI scan protocols, PC acquisition, ASL acquisition, and anatomical imaging acquisition as well as tissue segmentation and calculations of brain tissue volumes have already been described in Sections 3.1 and 3.2. The operators of the MRI system performing the acquisitions and the MR image analysts were blinded to all clinical information on the study participants. The Mini-Mental State Examination and the Digit Symbol Substitution Test were administered to all participants for cognitive testing. Cognitive impairment was classified as 23 points or lower on the Mini-Mental State Examination score (MMSE) and 17 or lower on the digit symbol substitution test score (DSST).

This study was a cross-sectional observational analysis. For comparison of characteristics, participants were divided into two groups (lower and higher aortic stiffness) by median arterial stiffness, 8.6 m/s. For regression models, the negative inverse transformation of CFPWV (niCFPWV) was used to normalize the right-skewed distribution due to non-linear age- and pressure-related aortic stiffening and to reduce heteroskedasticity of CFPWV (niCFPWV= -1000/CFPWV). Analysis of brain perfusion difference between groups was performed using generalized linear models with age and sex adjustment, as well as adjustment for heart rate, mean arterial pressure (MAP), and use of antihypertensive medication. The assumption of a normal distribution of the continuous perfusion measures was verified by inspecting qq-plots of residuals from the regression models. All analyses were performed using R Statistical Software version

4.4.2. Data were presented as mean (standard deviation) for continuous variables and as percentage for categorical variables. A P-value <0.05 was considered statistically significant.

The study was approved by the Icelandic National Bioethics Committee, which acts as the Institutional Review Board for the Icelandic Heart Association and the National University Hospital, as well as the Icelandic Data Protection Authority (VSN 11-047). Informed written consent was obtained from all participants.

4 Results

This thesis is based on the three papers listed on page XVII. Paper I begins by evaluating cerebral blood flow and estimated brain perfusion, brain volumes and cognitive performance by AF status in a population study. In Paper II, direct measures of brain perfusion and cerebral blood flow are evaluated in individuals undergoing elective cardioversion for AF, and in Paper III, brain perfusion is evaluated by aortic stiffness, assessed as PWV by tonometry.

4.1 Study populations and patient characteristics

4.1.1 Study population and characteristics in a population-based cohort in Paper I

The study on cerebral blood flow and estimated brain perfusion (Paper I) included 2291 men and women (mean age 80 years, range 71-95 years) from AGES II, a follow up visit from the multidisciplinary AGES-RS, described in Section 3.1. Of the 2291 individuals, 117 had AF (persistent AF group) and 78 had a prior history of the arrhythmia but were in SR at the time of imaging (paroxysmal AF group) (Table 1) (107). The remaining 2096 individuals had no known history of the arrhythmia (no AF group).

Individuals with persistent AF were older when compared to those with paroxysmal AF or no AF (81.2 years versus 79.6 and 79.4 years, respectively), included more men (63.3% versus 52.6% and 38.8%, respectively), and had lower measured systolic blood pressure (141.3 mm Hg versus 142.7 mm Hg and 145.3 mm Hg, respectively). Those with paroxysmal AF used antihypertensive medication and aspirin most frequently, while those with permanent AF used warfarin most frequently (Table 1). Measured cholesterol was highest in the no AF group and lowest in the paroxysmal AF group (5.3 mmol/L versus 4.7 mmol/L). History of coronary heart disease was most frequent in the paroxysmal AF group and least frequent in the no AF group (42.3% versus 24.2%). Other demographic factors and cardiovascular risk factors, including education, smoking status, alcohol consumption, BMI, self-reported or history of hypertension, diabetes type 2 or myocardial infarction, and calculated coronary artery calcium from computed tomography examination of the coronary arteries were similar between all groups (Table 1).

Table 1 Characteristics of individuals in Paper I.

Patient characteristics				**All groups**
	Persistent AF (n=117)	**Paroxysmal AF (n=78)**	**No AF (n=2096)**	**P-value**
Age, years	*81.2 (5.1)*	*79.6 (4.3)*	*79.4 (4.5)*	*p<0.001*
Sex, % men	*63.3*	*52.6*	*38.8*	*p<0.001*
Education, % primary	*12.0*	*20.5*	*20.1*	*p=0.16*
Ever smoker, former or current, %	*49.6*	*57.1*	*47.4*	*p=0.40*
Alcohol consumption, g/week[a]	*6.4 (1.6-26.4)*	*3.2 (1.6-16.1)*	*3.2 (0-16.1)*	*p=0.91*
Height, cm	*171.6 (9.9)*	*169.4 (9.8)*	*167.0 (9.1)*	*p<0.01*
BMI	*27.0 (3.9)*	*27.3 (4.3)*	*26.8 (4.3)*	*p=0.18*
HTN history	*94.0*	*94.9*	*88.7*	*p=0.06*
SBP mm Hg	*141.3 (22.8)*	*142.7 (22.6)*	*145.3 (20.7)*	*p<0.05*
MI history	*13.7*	*16.7*	*12.3*	*p=0.63*
CHD	*28.2*	*42.3*	*24.2*	*p<0.01*
Cholesterol	*4.9 (1.1)*	*4.7 (1.1)*	*5.3 (1.1)*	*p<0.001*
DM type 2	*15.4*	*15.4*	*11.7*	*p=0.58*
HTN med	*84.6*	*91.0*	*69.5*	*p<0.001*
Warfarin use	*67.5*	*33.3*	*2.2*	*p<0.001*
Aspirin use	*31.6*	*51.3*	*42.2*	*p<0.01*
CAC[a]	*671 (197-2027)*	*630 (126-1974)*	*404 (78-1173)*	*p=0.57*

Data are shown as mean (standard deviation) for continuous variables and as % for categorical variables. [a]Median and quartiles. Persistent AF: those with 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. AF: atrial fibrillation, BMI: body mass index in kg/m^2, HTN history: history of hypertension, SBP: systolic blood pressure, MI history: history of myocardial infarction, CHD: history of coronary heart disease, DM type 2: diabetes mellitus type 2, HTN med: antihypertensive medication use, CAC: coronary artery calcium.

4.1.2 Study population and characteristics before cardioversion in Paper II

In the cardioversion study, 44 men (n=35, 80%) and women (mean age 64 years at entry, range 36-74 years) were enrolled in total (Table 2) (114). A total of 27 individuals (21 men) completed the study with two MRI examinations, 17 that were cardioverted to SR and remained in SR during the study period (SR group) and 10 who remained in AF after an unsuccessful cardioversion attempt (AF group). The remaining 17 had a recurrence of AF during the observation period and were therefore excluded from the second MRI according to the study protocol (recurrent AF group) (Figure 5, Section 3.2). One individual in the AF group had missing PC MRI due to technical failure during the follow up visit.

There was no significant difference in baseline characteristics between the three groups with regards to age, BMI, systolic or diastolic blood pressure, heart rate, or previous smoking status, but those in the SR group reported more often that they had never smoked (Table 2). There was no significant difference between the three groups with regards to self-reported or history of hypertension, lipid disorders, coronary heart disease, coronary interventions or surgery, valve disease, or heart failure (114). With regards to medication, there was no significant difference in warfarin use, thrombin or antiplatelet medication use, lipid lowering medication or diabetes medication, digoxin or antiarrhythmic medication use, but those in the AF group used more often aspirin (Table 2) (114). All individuals were taking oral anticoagulation medication, and the proportion of those taking novel oral anticoagulation was similar in all three groups. Measured NT-proBNP was similar prior to cardioversion across the three outcome groups and left ventricular ejection fraction measured by echocardiography prior to cardioversion was also similar between the groups. (Table 2) (114).

Table 2 Characteristics of individuals at baseline before cardioversion in Paper II.

Patient characteristics				
	SR groups (n=17)	**AF group (n=10)**	**Recurrent AF group (n=17)**	**P-value all groups**
Age, years	*62.6 (9.8)*	*65.9 (6.3)*	*65.3 (7.6)*	*p=0.53*
Height, cm	*177.2 (10.2)*	*175.9 (7.9)*	*179.8 (8.6)*	*p=0.53*
Weight, kg	*94.4 (19.5)*	*95.3 (10.6)*	*92.1 (13.2)*	*p=0.86*
BMI	*29.8 (4.61)*	*30.8 (2.3)*	*28.5 (3.8)*	*p=0.33*
SBP (mm Hg)	*132.3 (16.8)*	*134.0 (15.7)*	*133.3 (19.3)*	*p=0.97*
DBP (mm Hg)	*82.9 (11.9)*	*85.6 (7.0)*	*89.2 (15.3)*	*p=0.37*
HR before cardioversion	*77.6 (14.5)*	*80.2 (12.4)*	*78.8 (9.8)*	*p=0.87*
Ever smoker, former or current	*10 (58.8)*	*10 (100.0)*	*12 (70.6)*	*p=0.07*
Smoking (never)	*7 (41.2)*	*0 (0.0)*	*5 (29.4)*	*p<0.01*
HTN	*13 (76.5)*	*6 (60.0)*	*9 (52.9)*	*p=0.35*
Lipid disorder	*3 (17.6)*	*6 (60.0)*	*4 (23.5)*	*p=0.052*
CHD	*2 (11.8)*	*5 (50.5)*	*4 (23.5)*	*p=0.09*
PCI or CABG	*1 (5.9)*	*3 (30.0)*	*1 (5.9)*	*p=0.11*
Valve or other cardiac disease	*8 (47.1)*	*4 (40.0)*	*7 (41.2)*	*p=0.78*
Other cardiac surgery/intervention	*1 (5.9)*	*0 (0.0)*	*1 (5.9)*	*p=0.74*
Reduced contractility, HF	*4 (23.5)*	*5 (50.0)*	*9 (52.9)*	*p=0.18*
Other cardiac disease	*0 (0.0)*	*0 (0.0)*	*2 (11.8)*	*p=0.19*
Stroke	*2 (11.8)*	*0 (0.0)*	*0 (0.0)*	*p=0.19*
Anti-hypertensive medication	*14 (82.4)*	*9 (90.0)*	*14 (82.4)*	*p=0.85*

Beta-blocker use	*13 (76.5)*	*8 (80.0)*	*10 (58.8)*	*p=0.40*
Warfarin use	*5 (29.4)*	*4 (40.0)*	*3 (17.6)*	*p=0.44*
Thrombin/Xa use	*12 (70.6)*	*5 (50.5)*	*13 (76.5)*	*p=0.35*
Aspirin use	*0 (0.0)*	*4 (40.0)*	*2 (11.8)*	*p<0.05*
Lipid medication	*1 (5.9)*	*7 (70.0)*	*3 (17.6)*	*p<0.01*
Diabetes medication	*1 (5.9)*	*0 (0.0)*	*1 (5.9)*	*p=0.74*
Digoxin	*4 (23.5)*	*1 (10.0)*	*2 (11.8)*	*p=0.54*
Class III use	*4 (23.5)*	*0 (0.0)*	*3 (17.6)*	*p=0.26*

Data are shown as mean (standard deviation) for continuous variables and % for categorical variables. SR group: those successfully converted to sinus rhythm, AF group: those that were not converted into sinus rhythm, recurrent AF: those that were successfully converted into sinus rhythm but had recurrent atrial fibrillation at follow up. AF: atrial fibrillation, SR: sinus rhythm, BMI: body mass index as kg/m^2, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, HTN: hypertension, CHD: coronary heart disease, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, HF: heart failure. Xa: Xa inhibitor, Class III: Class III antiarrhythmic.

4.1.3 Study population and characteristics in aortic stiffness in Paper III

The sample consisted of 269 men and women (mean age 62 years, range 58-76 years). Subjects were stratified according to mean CFPWV, 8.6 m/s. In unadjusted analyses, individuals with higher CFPWV (>8.6 m/s, n=135) were significantly older (63.7 versus 61.9 years, P<0.001) when compared to those with lower aortic stiffness (<8.6 m/s, n=134), had higher measured systolic and diastolic blood pressure (130.0 mm Hg versus 118.5 mm Hg (P<0.001) and 65.2 mmHg versus 61.2 mm Hg (P<0.001), respectively) higher MAP (90.2 mm Hg versus 83.0 mm Hg (P<0.001)), and higher heart rate (66.1 beats per minute versus 59.8 beats per minute (P<0.05)), and used antihypertensive medication more often (Table 3).

Table 3 Characteristics of individuals with lower and higer aortic stiffness in Paper III.

Characteristics stratified by median CFPWV (8.6 m/s)	Lower CFPWV group 1 (<8.6 m/s) n=134	Higher CFPWV group 2 (>8.6 m/s) n=135	P-value
Age (years)	61.9 (3.7)	63.7 (4.2)	<0.001
Sex (% men)	58	47	>0.05
Systolic BP (mm Hg)	118.5 (12.9)	130.0 (14.3)	<0.001
Diastolic BP (mm Hg)	61.2 (8.4)	65.2 (8.7)	<0.001
MAP (mm Hg)	83.0 (9.4)	90.2 10.4)	<0.001
Heart rate	59.8 (8.2)	66.1 (9.7)	<0.001
Anti-hypertension medication use	41	59	<0.05

Data are shown as mean (standard deviation) for continuous variables and % for categorical variables. CFPWV: carotid-femoral pulse wave velocity, BP: blood pressure, MAP: mean arterial pressure.

4.2 Total cerebral blood flow and brain perfusion in AF and aortic stiffness

4.2.1 Total cerebral blood flow and average estimated brain perfusion in a population-based cohort in Paper I

TCBF, adjusted for age and sex, was on average lowest in the persistent AF group (472.1 mL/min), intermediate in the paroxysmal group (512.3 mL/min) and highest in the no AF group (541.0 mL/min) (Table 4), with significant differences between persistent AF and both comparison groups (P<0.05 and P<0.001, respectively) (107). TCBF in the paroxysmal group was lower than in the no AF group (P<0.05). After additionally adjusting for relative brain volume, antihypertensive medication and warfarin use, the difference between persistent AF (487.3 mL/min) and no AF (535.5 mL/min) remained significant, whereas the difference between paroxysmal AF (520.0 mL/min) and no AF groups was attenuated (Table 4, Figure 6) (107).

Table 4 Total cerebral blood flow and averave estimated brain perfusion of individials in Paper I.

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

Persistent AF: those with 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]Difference between persistent AF and no AF. [b]Adjusted for brain volume. [c]Adjusted for brain volume, use of anti-hypertensive medication and warfarin use. [d]Adjusted for use of anti-hypertensive medication and warfarin use. AF: atrial fibrillation, ML/min: flow in cervical arteries in milliliters per minute; ml/100g/min: brain perfusion in milliliters per 100 grams of brain tissue per minute.

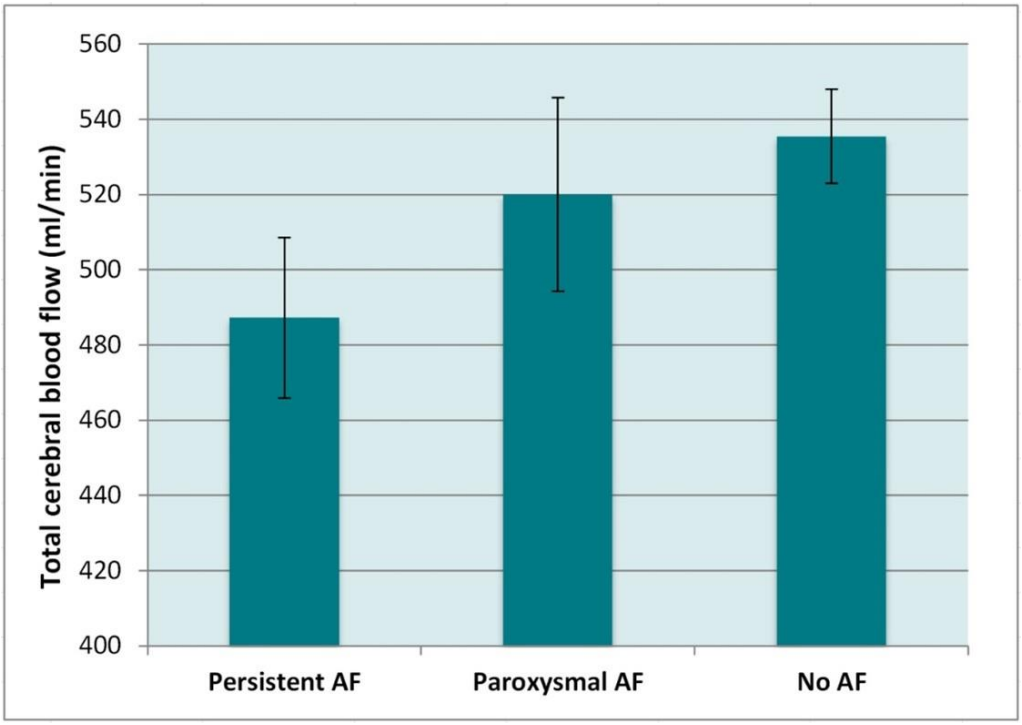

Figure 6 Total cerebral blood flow (mL/min) in the cervical arteries in the three groups in Paper I.

Persistent AF: those with 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. Adjustments were made for age, sex, brain volume, use of anti-hypertensive medication and warfarin use. Persistent AF versus paroxysmal AF: p=0.05; persistent versus no AF: p<0.001; paroxysmal AF versus no AF: p>0.05. AF: atrial fibrillation.

Estimated whole brain perfusion, adjusted for age and sex, was on average significantly the lowest in the persistent AF group (46.4 mL/100g/min), intermediate in the paroxysmal AF group (50.9 mL/100g/min, P<0.05 when compared to persistent AF group) and highest in the no AF group (52.8 mL/100g/min, P<0.001 when compared to the persistent AF group) (Table 4) (107). Estimated brain perfusion remained significantly reduced in the persistent AF group (46.7 mL/100g/min) after additional adjustment for medication use (Table 4). No significant difference in estimated perfusion was observed between paroxysmal AF and no AF, neither before (50.9 mL/100g/min versus 52.8 mL/100g/min) nor after adjustment for medication use (50.7 mL/100g/min versus 50.7 mL/100g/min) (Table 4, Figure 7) (107).

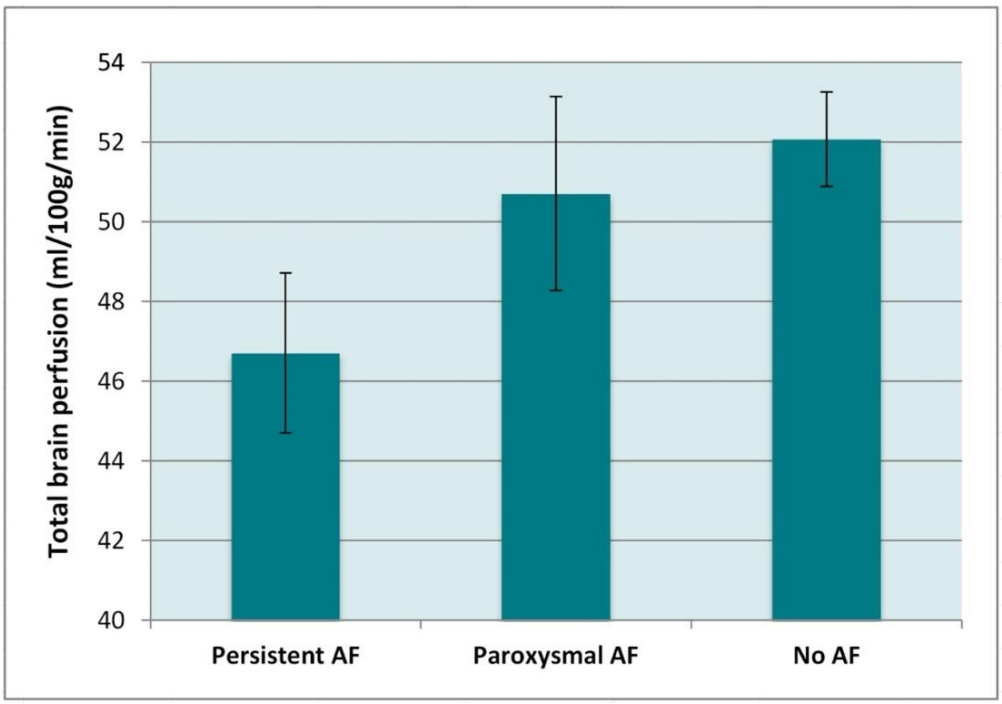

Figure 7 Average estimated brain perfusion (mL/100g brain tissue/min) in the three groups in Paper I.

Persistent AF: those with 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. Adjustments were made for age, sex, use of anti-hypertensive medication and warfarin. Persistent AF versus paroxysmal AF: $p<0.05$; persistent versus no AF: $p<0.001$; paroxysmal AF versus no AF: $p>0.05$. AF: atrial fibrillation.

4.2.2 Brain perfusion and total cerebral blood flow before and after cardioversion in Paper II

At baseline, there was no significant difference in whole brain perfusion, GM perfusion, or TCBF between the three outcome groups (Table 5) (114). Brain perfusion measured in the whole brain with ASL MRI was 36.6 mL/100g/min in the SR group, 34.0 mL/100g/min in the AF group and 36.1 mL/100g/min in the recurrent AF group ($P>0.05$). GM perfusion measured 40.2 mL/100g/min in the SR group, 37.2 mL/100g/min in the AF group and 39.8 mL/100g/min in the recurrent AF group ($P>0.05$) (114). TCBF measured 557.4 mL/min in the SR group, 588.8 mL/min in the AF group and 528.2 mL/min in the recurrent AF group ($P>0.05$). Left ventricular ejection fraction was similar between the groups and measured NT-pro BNP values were also in similar ranges (Table 5) (114).

Table 5 Brain perfusion and total cerebral blood flow at baseline in Paper II.

Brain perfusion and cerebral blood flow at baseline				
Baseline value	**SR group (n=17)**	**AF group (n=10)**	**Recurrent AF group (n=17)**	**P-value**
ASL Whole Brain mL/100g/min	*36.6 (8.2)*	*34.0 (7.9)*	*36.1 (8.6)*	*p=0.73*
ASL Grey Matter mL/100g/min	*40.2 (9.6)*	*37.2 (9.4)*	*39.8 (10.3)*	*p=0.72*
Total CBF[a] mL/min	*557.4 (109.9)*	*588.8 (144.2)*	*528.2 (110.5)*	*p=0.45*
Relative BV %	*71.4 (4.6)*	*69.9 (2.3)*	*69.1 (3.7)*	*p=0.32*
EF %	*57.6 8.1)*	*57.6 (9.1)*	*55.5 (8.6)*	*p=0.83*
BNP pg/mL	*1172.6 (950.1)*	*437.3 (236.6)*	*927.3 (584.2)*	*p=0.06*

Data are age and sex adjusted and shown as mean (standard deviation). [a]Adjusted for brain volume. SR group: those successfully converted to sinus rhythm, AF group: those that were not converted into sinus rhythm, recurrent AF: those that were successfully converted into sinus rhythm but had recurrent atrial fibrillation at follow up. AF: atrial fibrillation, SR: sinus rhythm, ASL: arterial spin labelling, CBF: cerebral blood flow, BP: brain perfusion, BV: brain volume, EF: ejection fraction, BNP: brain natriuretic peptide.

Following successful restoration of SR, brain perfusion measured with ASL MRI increased significantly in the whole brain in the SR group (4.9 mL/100g/min, P<0.001), and in the GM in the SR group (5.6 mL/100g/min, P<0.001), whereas no significant change was observed in individuals who remained in AF (AF group, -1.6 mL/100g/min, P>0.05), (Table 6, Figures 8 and 9) (114). Total cerebral blood flow measured with PC MRI similarly increased after successful cardioversion in the SR group (58.6 mL/min) but remained unchanged in those that remained in AF (AF group, -20.8 mL/min, P>0.05) (Table 6, Figure 8) (114). Heart rate lowered significantly in those that were cardioverted to SR from 80.5 ±15.0 beats per minute to 58.1 ±7.1 (P<0.001), while no significant change was seen in the AF group. The interval between baseline and follow-up MRI did not differ between the SR and the AF groups, 20.7 weeks and 24.5 weeks, respectively (P>0.05) (114).

Table 6 Brain perfusion and total cerebral blood flow before and after cardioversion.

TCBF and average estimated BP before and after cardioversion					
		First visit	**Second visit**	**Change**	**P-value[b]**
ASL WB mL/min	**SR group (n=17)**	*36.3 (1.9)*	*41.2 (1.9)*	*+4.9 (1.3)*	*p<0.001*
	AF group (n=10)	*34.4 (2.6)*	*32.8 (2.6)*	*-1.6 (1.7)*	*p=0.36*
ASL GM mL/min	**SR group (n=17)**	*39.9 (2.3)*	*45.5 (2.3)*	*+5.6 (1.4)*	*p<0.001*
	AF group (n=10)	*37.8 (2.9)*	*35.9 (3.0)*	*-1.9 (2.0)*	*p=0.34*
TCBF mL[a]	**SR group (n=17)**	*555.2 (29.2)*	*613.8 (29.5)[§]*	*+58.6 (24.1)*	*p<0.05*
	AF group (n=10)	*586.8 (38.2)*	*566.0 (39.9)[§]*	*-20.8 (32.0)*	*p=0.52*

Data are age and sex adjusted and shown as estimated marginal means (standard errors) using Kenward-Roger Degrees of Freedom Approximation. [a]Adjusted for brain volume. [b]: change between visits. [§]N=9. SR group: those successfully converted to sinus rhythm, AF group: those that were not converted into sinus rhythm, recurrent AF: those that were successfully converted into sinus rhythm but had atrial fibrillation at follow up. TCBF: total cerebral blood flow, BP: brain perfusion, ASL: arterial spin labelling, WB: whole brain, SR: sinus rhythm, AF: atrial fibrillation, GM: grey matter.

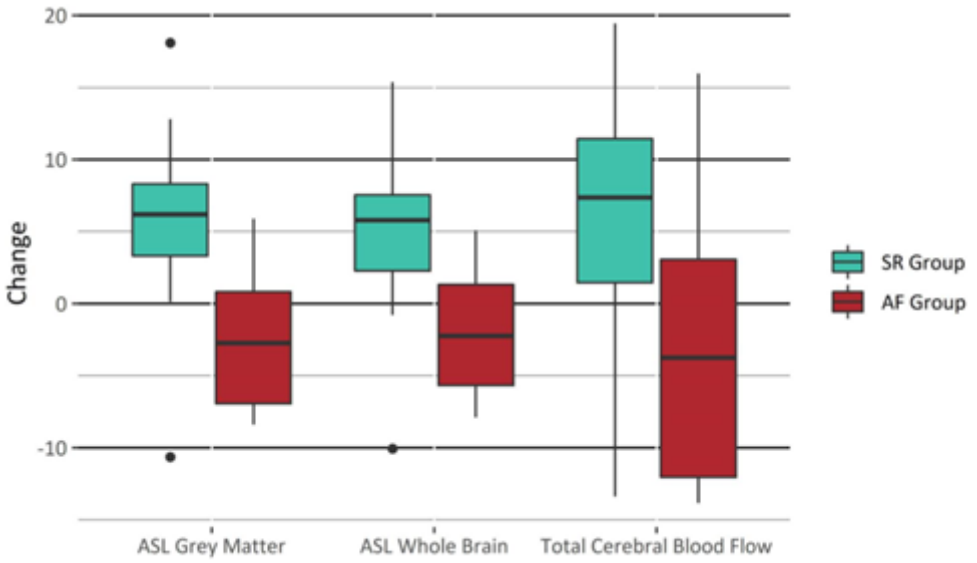

Figure 8 Box whisker plot showing the change in brain perfusion in the grey matter and the whole brain and the change in total cerebral blood flow in the SR group and the AF group after cardioversion in Paper II.
The upper columns show a positive change in perfusion and cerebral blood flow in the SR group after a successful cardioversion, whereas the lower columns show no change in the AF group after an unsuccessful cardioversion. Total cerebral blood flow measurements were scaled by a factor of 10. SR: sinus rhythm, AF: atrial fibrillation, ASL: arterial spin labeling. Reprinted with permission from M. Gardarsdottir, S. Sigurdsson, T. Aspelund, V.A. Gardarsdottir, L. Forsberg, V. Gudnason, D.O. Arnar. Improved brain perfusion after electrical cardioversion of atrial fibrillation. Europace 2020, vol. 22 (4), p. 530-–537. https://www.academic.oup.europace.

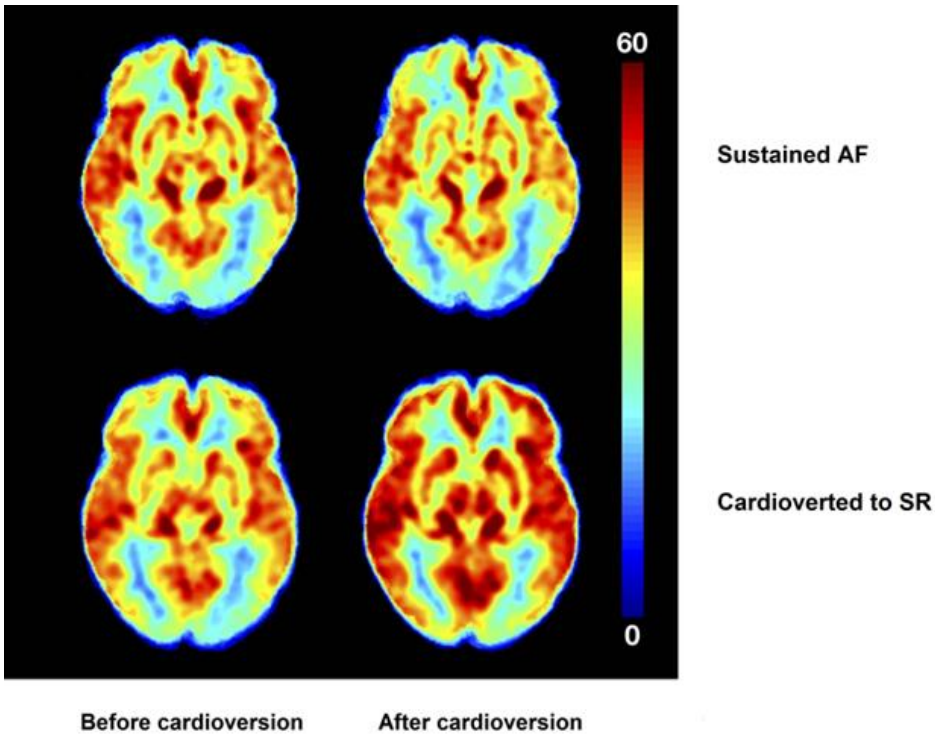

Figure 9 Average brain perfusion map of the whole brain before and after cardioversion measured by ASL MRI in Paper II.
Upper panel shows average baseline brain perfusion of the AF group before cardioversion (left) and no detectable change after an unsuccessful cardioversion (right). Lower panel shows baseline brain perfusion in the SR groups before cardioversion (right) and visible improvement of perfusion after restoration of SR after a successful cardioversion (left). The perfusion is most prominent in the cortex of the brain where perfusion is naturally most apparent. The scale on the right shows color coded perfusion, with the lowest value (0 mL/100g/min) being blue and the highest (60 mL/100g/min) being red. AF: atrial fibrillation, ASL: arterial spin labeling, MRI: magnetic resonance imaging: SR; sinus rhythm. Reprinted with permission from M. Gardarsdottir, S. Sigurdsson, T. Aspelund, V.A. Gardarsdottir, L. Forsberg, V. Gudnason, D.O. Arnar. Improved brain perfusion after electrical cardioversion of atrial fibrillation. Europace 2020, vol. 22 (4), p. 530-–537. https://www.academic.oup.europace.

4.2.3 Brain perfusion in aortic stiffness in Paper III

Individuals with higher aortic stiffness (>8.6 m/s) exhibited significantly lower global brain perfusion measured by ASL MRI (46.7 mL/100g/min versus 51.0 mL/100g/min, P<0.001), GM perfusion (52.0 mL/100g/min versus 57.0 mL/100g/min, P<0.001), and WM perfusion (39.4 mL/100g/min versus 42.6 mL/100g/min, P<0.001) (Table 7, Figure 10). Across increasing quintiles of niCFPWV, a gradual downward shift in median global brain perfusion was observed, from those in the lowest quintile demonstrating the highest perfusion to those in the higher quintiles showing lower values (Figure 11).

Table 7 Brain perfusion stratified by median CFPWV in Paper III.

Brain perfusion stratified by median CFPWV (8.6 m/s)	Lower CFPWV group 1 (<8.6 m/s) n=134	Higher CFPWV group 2 (>8.6 m/s) n=135	P-value
Total BP (ml/100g/min)	51.0 (9.3)	46.7 (9.9)	<0.001
GM perfusion (ml/100g/min)	57.0 (10.7)	52.0 (11.3)	<0.001
WM perfusion (ml/100g/min) unit	42.6 (7.7)	39.4 (7.9)	<0.001

Data are shown as mean (standard deviation) for continuous variables and % for categorical variables. CFPWV: carotid-femoral pulse wave velocity, BP: brain perfusion, GM: grey matter, WM: white matter.

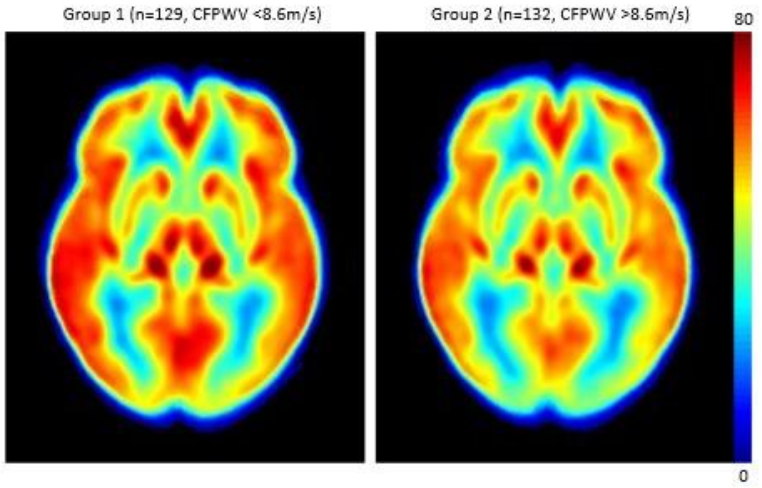

Figure 10 Average total brain perfusion map split by median CFPWV (8.6 m/s) measured by ASL MRI in Paper III.
On the left, the group with lower CFPWV (<8.6 m/s) is pictured, and on the right the group with higher CFPWV (>8.6 m/s) is pictured. The perfusion is most prominent in the cortex of the brain where perfusion is naturally most apparent. The scale on the right shows color coded perfusion, with the lowest value (0 mL/100g/min) being blue and the highest (60 mL/100g/min) being red. CFPWV: carotid-femoral pulse wave velocity, ASL: arterial spin labeling, MRI: magnetic resonance imaging.

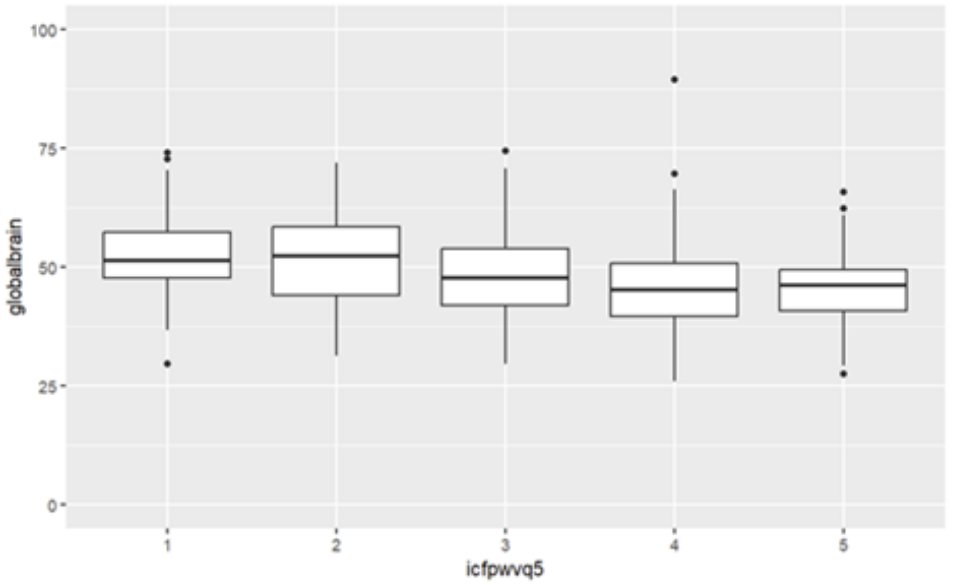

Figure 11 Global brain perfusion across quintiles of negative inverse carotid-femoral pulse wave velocity (niCFPWV) in Paper III.
Globalbrain: total brain perfusion, icfpwvq5: aortic stiffness as negative inverse carotid-femoral pulse wave velocity across increasing quartiles of negative inverse carotid-femoral pulse wave velocity.

In multivariable regression analyses, increased aortic stiffness was independently associated with lower global brain perfusion (β=-0.08, P<0.01) after adjustment for age, sex, heart rate, MAP, and antihypertensive medication use, but not with total, GM, WM relative brain volume or WMH volume (Table 8). Older age was not independently associated with global brain perfusion but was independently associated with lower relative total brain (β=-0.26, P<0.001), GM (β=-0.19, P<0.001), and WM volume (β=-0.07, P<0.01) and increased WMH volume (β=0.31, P<0.001). MAP was neither associated with brain perfusion nor volume metrics, but heart rate was associated with increased global brain perfusion (β=-0.22, P<0.05) and lower relative GM volume (β=-0.04, P<0.05).

Table 8 Multivariable associations of aortic stiffness with brain perfusion and brain volumes in Paper III.

Total brain perfusion	**Variable**	**β**	**Standard error**	**P-value**
	Age	-0.22	0.15	>0.05
	Sex	5.10	1.15	<0.001
	HR	0.17	0.07	<0.05
	MAP	-0.03	0.06	>0.05
	HTN med	-1.84	1.28	>0.05
	niCFPWV	-0.08	0.03	<0.01
Relative total brain volume	**Variable**	**β**	**Standard error**	**P-value**
	Age	-0.26	0.04	<0.001
	Sex	1.41	0.30	<0.001
	HR	-0.03	0.02	>0.05
	MAP	-0.01	0.02	>0.05
	HTN med	-0.20	0.31	>0.05
	niCFPWV	0.003	0.01	>0.05
Relative GM volume	**Variable**	**β**	**Standard error**	**P-value**
	Age	-0.19	0.03	<0.001
	Sex	1.17	0.21	<0.001
	HR	-0.04	0.01	<0.05
	MAP	0.004	0.01	>0.05
	HTN med	-0.37	0.21	>0.05
	niCFPWV	0.0001	0.01	>0.05

Relative WM volume	Variable	β	Standard error	P-value
	Age	-0.07	0.03	<0.01
	Sex	0.25	0.21	>0.05
	HR	-0.002	0.01	>0.05
	MAP	-0.009	0.01	>0.05
	HTN med	0.18	0.21	>0.05
	niCFPWV	0.002	0.01	>0.05
WMH volume	**Variable**	**β**	**Standard error**	**P-value**
	Age	0.31	0.07	<0.001
	Sex	0.07	0.55	>0.05
	HR	-0.02	0.03	>0.05
	MAP	-0.01	0.03	>0.05
	HTN med	0.22	0.56	>0.05
	niCFPWV	0.02	0.01	>0.05

Adjustments were made for age, sex, heart rate, mean arterial pressure and antihypertensive medication use. HR: heart rate, MAP: arterial pressure, HTN med: antihypertensive medication, niCFPWV: negative inverse carotid-femoral pulse wave velocity, GM: grey matter, WM: white matter, WMH: white matter hyperintensities.

4.3 Brain volumes and cognitive performance

4.3.1 Brain volume and cognitive performance in atrial fibrillation in a population-based cohort in Paper I

There was no significant difference in TBV (total brain volume, the sum of GM, white matter (WM), and white matter hyperintensities (WMH) in mL) between the three groups in Paper I (Table 9) (107). Relative brain volume (TBV/ICV*100) was smallest in individuals with persistent AF (69.3%), intermediate in individuals with paroxysmal AF (70.3%) and largest in those without AF (71.7%) (P<0.001) (107). Stroke was more frequent in both persistent and paroxysmal AF groups (P<0.001) (Table 9). Cognitive scores did not differ significantly between the groups, but GDS scale measures varied between the groups (P<0.05) (107).

Table 9 Brain volumes and cognitive measures in Paper I.

Brain volumes and cognitive measures				**All groups**
	Persistent AF (n=117)	**Paroxysmal AF (n=78)**	**No AF (n=2096)**	**P-value**
TBV, ml	*1073.2 (103.1)*	*1061.3 (109.6)*	*1066.1 (98.3)*	*p=0.09*
ICV, ml	*1550.7 (157.6)*	*1510.9 (151.6)*	*1490.2 (146.7)*	*p=0.35*
Relative BV (%)	*69.3 (3.6)*	*70.3 (4.0)*	*71.7 (3.8)*	*p<0.001*
Stroke	*16.2*	*19.2*	*6.4*	*p<0.001*
GDS scale	*2.4 (1.9)*	*2.6 (1.9)*	*2.1 (2.0)*	*p<0.05*
MMSE score	*26.2 (2.4)*	*26.3 (3.7)*	*26.6 (2.6)*	*p=0.85*
DSST score	*27.4 (9.6)*	*29.4 (9.4)*	*30.6 (10.1)*	*p=0.30*

Data are shown as mean (standard deviation) for continuous variables and as % for categorical variables. Persistent AF: those with atrial fibrillation 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. AF: atrial fibrillation, TBV: total brain volume, ICV: intracranial volume, BV: relative brain volume, GDS: geriatric depression scale, MMSE: mini mental-state examination, DSST: digit symbol substitution test.

4.3.2 Brain volume and cognitive performance before cardioversion for atrial fibrillation in Paper II

There was no significant difference in stroke between the three groups; SR group, AF group and recurrent AF (Table 2, Section 4.1.2) (114). No significant difference was observed in relative brain volume at baseline between the three outcome groups (Table 5, Section 4.2.2) (114). As described in Section 3.2, cognitive testing was not performed in the study.

4.3.3 Brain volume and cognitive performance in aortic stiffness in a population-based sample in Paper III

Relative total brain volume and relative GM were smaller in those participants with increased aortic stiffness (80.9% versus 81.8% (P<0.01), and 48.7% versus 49.3% (P<0.05), respectively), while WMH volume was increased in the high-stiffness group (1.0% versus 0.4%, P<0.05) (Table 10). Cognitive performance did not differ significantly between the two groups (Table 10).

Table 10 Brain volumes and cognitive performance by median aortic stiffness in Paper III.

Characteristics stratified by median CFPWV (8.6 m/s)	Lower CFPWV group 1 (<8.6 m/s) n=134	Higher CFPWV group 2 (>8.6 m/s) n=135	P-value
Relative total brain volume (%)	81.8 (2.5)	80.9 (2.7)	<0.01
Relative GM volume (%)	49.3 (1.8)	48.7 (1.9)	<0.05
Relative WM volume (%)	32.5 (1.6)	32.2 (1.6)	>0.05
WMH volume* (%)	0.39	1.01	<0.05
MMSE score	28.2 (1.6)	28.3 (1.6)	>0.05
DSST score	48.4 (10.5)	47.0 (11.0)	>0.05

Values are shown as mean (*median) (standard deviation) for continuous variables and % for categorical variables. CFPWV: carotid-femoral pulse wave velocity, GM: grey matter, WM: white matter, WMH: white matter hyperintensities, MMSE: mini mental-state examination, DSST: digit symbol substitution test.

5 Discussion

5.1 Main findings

Permanent AF was associated with lower TCBF and reduced estimated brain perfusion compared with SR. Individuals with permanent AF also exhibited smaller relative brain volume, while no difference in cognitive function was observed in the studied population. Brain perfusion improved following successful electrical cardioversion to SR, whereas no significant change was observed in those who remained in AF.

Higher aortic stiffness was associated with lower total brain, GM and WM perfusion and with smaller relative total brain and GM volume, and greater WMH burden. In multivariable analysis, increased aortic stiffness independently predicted lower total brain perfusion, whereas older age was associated with smaller relative total brain, GM, and WM volume and greater WMH burden.

5.2 Hemodynamic determinants of brain perfusion: effects of atrial fibrillation and aortic stiffness

In the present studies, both AF and increased aortic stiffness were associated with reduced brain perfusion, supporting the concept that central hemodynamics influence cerebral blood flow. Individuals with persistent AF exhibited the lowest TCBF and lowest estimated brain perfusion measured with MRI, whereas those without a prior history of AF had the highest values. These differences persisted after adjustment for age, sex and relevant structural and clinical covariates, indicating that AF at the time of imaging is an important determinant of cerebral blood flow and estimated brain perfusion, independent of prior arrhythmia history.

Brain perfusion improved following successful electrical cardioversion to SR, whereas no improvement was observed in individuals who remained in AF. This observation suggests that AF-related cerebral hypoperfusion is dynamic and consistent with impaired effective cerebral blood delivery, reflecting beat-to-beat variability in stroke volume, altered autoregulatory responses, or neurohumoral influences.

A comparable pattern of cerebral hypoperfusion was observed in relation to increased aortic stiffness. Greater aortic stiffness, assessed by tonometric CFPWV, was associated with lower brain perfusion and independently predicted reduced perfusion in multivariable analyses. These findings indicate that cerebral blood flow is sensitive to proximal aortic stiffening and are consistent with prior studies demonstrating inverse associations between aortic stiffness and brain perfusion measured with ASL-MRI (84,117).

Taken together, the associations of AF and aortic stiffness with reduced brain perfusion point toward a dynamic mechanism affecting the cerebral microcirculation. In AF, irregular ventricular rhythm and impaired cardiac efficiency disrupt effective forward flow. In contrast, aortic stiffening reduces the buffering capacity of the proximal aorta, increasing forward pressure and transmission of pulsatile stress into the cerebral microcirculation, which may compromise microvascular regulation, promote cerebral hypoperfusion, and contribute to subsequent cumulative structural brain changes. Thus, rhythm irregularity and arterial stiffening appear to influence brain perfusion through distinct but converging hemodynamic pathways.

5.3 Structural and functional consequences of atrial fibrillation and aortic stiffness

AF has been associated with smaller brain volume and cognitive impairment independent of overt stroke. In Paper I, individuals with persistent AF exhibited the smallest relative brain volume, supporting the possibility that sustained hemodynamic disturbances associated with AF contribute to adverse structural brain changes. Although individuals with persistent AF were older, and age is a well-established determinant of brain atrophy, adjustment for age indicated that the observed differences in brain volume were related to the presence of persistent AF itself.

In the study by Stefansdottir et al. (2013), AF was associated with smaller total brain, GM, and WM volumes, and the strongest effects were observed for total brain and GM matter volume and in individuals with persistent or long-standing AF. These findings suggested a dose-response relationship, with greater structural brain changes observed with increasing AF burden (39). Information on AF duration was not available in Paper I, limiting assessment of cumulative exposure.

In Paper III, aortic stiffness showed a similar pattern of association with brain structure. Higher aortic stiffness was associated with smaller relative total brain and GM volume and greater WMH burden. However, in multivariable analyses, aortic stiffness independently predicted lower total brain perfusion, whereas age was associated with smaller relative total brain, GM, and WM volumes and greater WMH burden. These findings suggest that perfusion measures may be more sensitive to vascular stiffening than structural brain measures and support the concept that hemodynamic alterations may precede detectable structural brain injury, that rather reflect cumulative and long-term processes (81,118).

In Paper I, cognitive performance did not differ significantly between groups, possibly reflecting exclusion of individuals diagnosed with dementia. No association with cognitive measures was observed in Paper III either. This absence of detectable cognitive differences may partly reflect the relatively young age of the sample in Paper III. Nevertheless, several previous studies have linked increased aortic stiffness to

reduced brain perfusion, structural brain injury, and poorer cognitive performance (85,103,119–121). Large population-based studies, including the Cardiovascular Health Study and the Whitehall II imaging study, further support an association between aortic stiffness and cognitive impairment and risk of dementia, independent of traditional vascular risk factors (88,122).

Together, these observations suggest that AF and arterial stiffening influence brain structure and cognitive function through partially overlapping hemodynamic pathways, in which alterations in cerebral perfusion may represent an early and potentially reversible stage preceding structural brain injury and cognitive decline.

5.4 Effects of rhythm restoration and implications for central hemodynamics

Previous small studies reported reduced cerebral blood flow in individuals with AF and increased cerebral blood flow following restoration of SR with electrical cardioversion (123–125). In Paper II, cerebral blood flow and brain perfusion increased significantly following successful cardioversion to SR, whereas no change was observed when the cardioversion was unsuccessful. Rate control was adequate prior to the procedure, and no differences in blood pressure or heart rate were observed between groups at baseline, indicating that the observed improvement was unlikely to be explained by systemic hemodynamic changes. Rather, restoration of coordinated atrial and ventricular activity and function appears to enhance effective forward flow and stabilize brain perfusion.

No differences in relative brain volume were observed at baseline, and structural measures were not reassessed following cardioversion, as the observation period was insufficient to detect structural change. Together, these findings suggest that AF-related cerebral hypoperfusion represents a dynamic and potentially reversible component of brain vulnerability, in contrast to structural alterations that likely develop over longer time scales. This observation also highlights the importance of temporal dynamics, whereby hemodynamic disturbances may influence cerebral perfusion early, whereas structural brain changes likely reflect cumulative exposure to these alterations.

Later studies have confirmed improvements in cerebral blood flow and cardiac output following restoration of SR, attributed in part to reduced beat-to-beat variability in stroke volume, improved ventricular filling, and stabilization of microvascular flow (126–128). High-temporal-resolution studies using near-infrared spectroscopy have further shown that AF is characterized by frequent extreme single-beat hemodynamic variations within the cerebral microcirculation, which are attenuated following cardioversion (129). Although ASL MRI does not capture beat-to-beat fluctuations, the observed increase in mean perfusion is consistent with improved overall hemodynamic stability.

These findings are also consistent with other studies suggesting improved cerebral blood flow following restoration of SR and a lower long-term risk of cognitive impairment in individuals undergoing rhythm control strategies (130–135). However, most available data remains observational, and causal inference regarding long-term structural or cognitive benefit is limited (136–138).

While cerebral hypoperfusion provides a plausible mechanistic link between AF and adverse brain outcomes, additional contributors including thromboembolism, microinfarction, small vessel disease, systemic inflammation, and shared vascular risk factors likely act in parallel. Nonetheless, the present findings indicate that rhythm-related hemodynamic instability represents a measurable and potentially modifiable determinant of cerebral blood flow and brain perfusion in the aging brain.

5.5 Comorbidity and cumulative vascular exposure

AF, aortic stiffness, and structural and functional brain alterations share a broad cluster of cardiovascular risk factors, including hypertension, diabetes mellitus, atherosclerosis, dyslipidemia, obesity, smoking, and chronic kidney disease. These conditions promote atrial remodeling, arterial stiffening, endothelial dysfunction, and cerebral small vessel disease, linking rhythm disturbances and vascular aging to brain injury through overlapping biological pathways. Rather than acting independently, these processes frequently coexist and likely exert additive or synergistic effects on brain perfusion and brain integrity (45).

Hypertension represents a central driver within this axis by increasing the risk of AF and accelerating arterial stiffening through vascular remodeling and inflammation, contributing directly to cerebral small vessel disease and vascular cognitive impairment (62,83,139,140). Diabetes similarly promotes atrial remodeling and arterial stiffening in a proinflammatory milieu and is independently associated with microvascular dysfunction and brain atrophy (44,141,142). Together, these metabolic and hemodynamic exposures increase susceptibility to cerebral injury. Within this context, aortic stiffness may be viewed both as a consequence of cumulative comorbidity and as a mediator of further vascular and cerebral dysfunction. This concept is supported by the recent work of Hamel-Sellman et al. (2026), demonstrating bidirectional relationships between vascular age, cardiometabolic risk factors, and incident cardiometabolic disease, ultimately contributing to cardiovascular disease development (60). By increasing transmission of pulsatile pressure into the cerebral circulation, aortic stiffness likely amplifies the impact of shared risk factors on microvascular injury and vascular remodeling. In this way, aortic stiffness functions both as a marker and a mechanism of systemic vascular aging, highlighting the importance of early identification and management of vascular risk factors (60,73,143).

Age remains the strongest non-modifiable determinant across these processes. AF prevalence rises steeply with advancing age, and aging is closely associated with

progressive arterial stiffening, reduced cerebrovascular reserve, and brain atrophy (70,144,145). In the present studies, although age was associated with structural brain measures in Papers I and III, multivariable analyses demonstrated independent associations between AF or aortic stiffness and brain perfusion. These findings suggest that aging, with its cumulative burden of vascular and cardiometabolic exposures, primarily shapes the structural substrate over time, whereas disturbances in central hemodynamics exert additional effects on brain perfusion.

Taken together, AF and aortic stiffness become prevalent with aging and cumulative vascular exposure, yet they represent distinct pathophysiological processes that converge at the level of the cerebral microcirculation. Against a background of age-related vascular vulnerability, rhythm-related flow irregularity and stiffness-related pulsatile stress may act as distinct but converging hemodynamic stressors, influencing brain perfusion and increasing vulnerability to cerebral injury over time.

5.6 Study strengths and limitations

5.6.1 Strengths

The present thesis has several strengths. First, brain perfusion was quantified using validated MRI techniques, including PC MRI and ASL MRI, enabling direct, non-invasive assessment of global and regional brain perfusion rather than relying on indirect or surrogate measures. The combination of perfusion imaging, structural brain imaging, and cognitive evaluation allowed simultaneous assessment of both dynamic and cumulative markers of brain vulnerability.

Second, the inclusion of a cardioversion study provided a unique opportunity to examine within-individual changes in brain perfusion following restoration of SR. This longitudinal component strengthens the mechanistic interpretation of the cross-sectional findings and supports the concept of perfusion as a dynamic hemodynamic marker.

Third, aortic stiffness was assessed using CFPWV measured by applanation tonometry, the reference standard for non-invasive assessment of central arterial stiffness. The use of tonometric CFPWV enhances the validity of the observed associations between vascular stiffening and brain perfusion.

Finally, the studies were conducted within well-characterized cohorts with detailed clinical phenotyping, standardized imaging protocols, and blinded image analysis. These methodological features reduce measurement bias and strengthen internal validity, providing a robust framework for examining the interplay between central hemodynamics and brain health.

5.6.2 Limitations

Several methodological limitations should be considered when interpreting the findings of the present work.

Selection and Participation Bias

In Papers I and II, several individuals were excluded due to contraindications for MRI, most commonly pacemakers and implantable cardioverter-defibrillators. In Paper I, participants were survivors of the AGES-Reykjavik Study who agreed to follow-up examination; death prior to examination, refusal, and loss to follow-up were major causes of non-participation. Additional exclusions included missing MRI data, claustrophobia, physical inability to undergo imaging, prevalent heart failure, and diagnosed dementia.

In Paper II, recruitment proved challenging for logistical reasons, including non-response to invitation, spontaneous restoration of SR prior to cardioversion, arrhythmia reclassification, MRI contraindications, and equipment malfunction. Recurrence of AF during follow-up led to further exclusions from repeat imaging. These factors may introduce selection bias and limit generalizability.

Sample Size and Statistical Power

The sample size in Paper II was modest, limiting statistical power, particularly for TCBF, which demonstrated substantial variability. Although TCBF correlates strongly with ASL-derived perfusion measures, limited power may have reduced the ability to detect smaller effects.

Cross-Sectional Design and Causality

Papers I and III were cross-sectional in design. Consequently, causal relationships or temporal sequencing between AF, aortic stiffness, brain perfusion, and structural brain changes cannot be inferred. Longitudinal studies assessing brain perfusion, brain volume, and cognitive function over time would be required to clarify these relationships.

Measurement Limitations

In Paper I, estimated perfusion was indirectly estimated rather than directly measured with ASL MRI, as ASL was not available at the time of examination. Consequently, GM-specific perfusion could not be assessed. Additionally, detailed information on AF burden and timing of the last AF episode was lacking in Paper I, and continuous rhythm monitoring was not performed during follow-up in Paper II. Intermittent AF episodes during the observation period therefore cannot be excluded. In Paper III, AF status was not systematically ascertained, limiting evaluation of potential interaction between AF and aortic stiffness. Information on AF duration in Paper I was not available, preventing assessment of cumulative exposure to rhythm-related hemodynamic disturbances.

Confounding and Residual Bias

Although statistical adjustments were performed for major cardiovascular risk factors, residual confounding cannot be excluded. Unmeasured or incompletely characterized comorbidities may have influenced the observed associations.

Cognitive Assessment

Individuals diagnosed with dementia were excluded in Paper I, which may have reduced variability in cognitive measures. The relatively young age of the cohort may also partly explain the absence of detectable cognitive differences despite perfusion and structural findings.

5.7 Future perspectives

The present findings suggest that disturbances in central hemodynamics represent a potentially modifiable pathway linking cardiovascular aging to brain vulnerability. Several key directions for future investigation emerge.

Randomized rhythm-control trials with brain endpoints

If AF-related hypoperfusion is dynamic and reversible, future randomized trials comparing rhythm control with rate control should incorporate brain perfusion, structural MRI markers, and cognitive performance as predefined outcomes. Inclusion of individuals without established cognitive impairment would allow assessment of prevention rather than late-stage mitigation. Continuous rhythm monitoring, ideally with implantable devices, would enable quantification of AF burden and clarify whether sustained SR translates into durable preservation of brain perfusion and structural brain integrity.

Long-term hemodynamic trajectories

Longitudinal cohort studies with repeated measurements of brain perfusion, aortic stiffness, brain structure, and cognition are needed to establish temporal relationships. Such designs would clarify whether alterations in cerebral perfusion precede measurable structural decline and whether progression of arterial stiffening parallels cognitive deterioration or further propagation of cardiovascular risk. Integration of AF burden, vascular risk exposure, and treatment status would help disentangle rhythm-related from vascular-mediated effects.

Aortic stiffness as a modifiable target

While CFPWV independently predicted reduced brain perfusion, its potential as an intervention target remains incompletely explored. Prospective studies should evaluate whether strategies that reduce arterial stiffness or pulsatile load can mitigate microvascular brain injury and cognitive decline. Because arterial stiffening often precedes overt hypertension, CFPWV may serve as an early marker of vascular vulnerability and aid in risk stratification.

Anticoagulation and microvascular brain injury

Although anticoagulation reduces overt thromboembolic events, its influence on structural brain measures and cognitive trajectories requires further study. Comparative investigations between anticoagulation strategies may clarify whether prevention of subclinical embolic injury translates into measurable preservation of brain structure.

Integrative hemodynamic models

Future research should move beyond isolated cardiovascular exposures toward integrative models incorporating rhythm irregularity, pulsatile pressure transmission, cerebrovascular autoregulation, microvascular resilience, and cumulative comorbidity. Advanced imaging and computational approaches may further elucidate how central hemodynamic disturbances interact with age-related susceptibility to produce progressive brain injury.

Taken together, advancing this field requires a transition from cross-sectional association to mechanistic and interventional studies. By positioning central hemodynamics as a shared pathway linking AF and arterial stiffening to cerebral vulnerability, future research may inform strategies aimed at preserving cognitive health in aging populations.

6 Conclusions

This thesis demonstrates that disturbances in central hemodynamics represent an important pathway linking AF and aortic stiffness to alterations in brain perfusion and structural brain integrity. Permanent AF was associated with lower TCBF and reduced estimated brain perfusion, and restoration of SR was accompanied by measurable improvement in perfusion, supporting a dynamic and partly reversible hemodynamic mechanism. Similarly, increased aortic stiffness was independently associated with reduced brain perfusion, with accompanying differences in structural brain markers, underscoring the vulnerability of the cerebral microcirculation to altered pulsatile load.

While aging remains the dominant determinant of brain atrophy, both rhythm-related flow irregularity and vascular stiffening exert additional and potentially modifiable effects on brain perfusion. These hemodynamic disturbances operate within a broader context of cumulative vascular risk exposure, thereby increasing the susceptibility of the cerebral microcirculation to injury. Together, the findings support the concept that cardiovascular aging affects brain health not only through overt thromboembolism and clinical stroke, but also through chronic alterations in central blood flow and pulsatile dynamics.

By integrating rhythm disturbances and arterial stiffening within a shared hemodynamic framework, this work highlights central hemodynamics as an important link between cardiovascular disease and brain health and further underscore its relevance as a potential therapeutic target for preserving cognitive function in aging populations.

References

1. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet. 2015 Jul 11; 386(9989): 154–62. doi:10.1016/S0140-6736(14)61774-8 PubMed Central PMCID: PMC4553037

2. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Fugar S, Generoso G, Heard DG, Hiremath S, Ho JE, ... Martin SS. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. 2023 Feb 21; 147(8): e93–621. doi:10.1161/CIR.0000000000001123

3. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, Deswal A, Eckhardt LL, Goldberger ZD, Gopinathannair R, Gorenek B, Hess PL, Hlatky M, Hogan G, Ibeh C, Indik JH, Kido K, Kusumoto F, Link MS, ... Wan Wagoner DR. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024 Jan 2; 149(1): e1–156. doi:10.1161/CIR.0000000000001193 PubMed Central PMCID: PMC11095842

4. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns H, De Potter TJR, Dwight J, Guasti L, Hanke T, Jaarsma T, Lettino M, Lochen ML, Lumbers RT, Maesen B, Molgaard I, Rosano GMC, Sanders P, Schnabel RB, ... Kotecha D. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2024 Sep 29; 45(36): 3314–414. doi:10.1093/eurheartj/ehae176

5. Lip GYH, Proietti M, Potpara T, Mansour M, Savelieva I, Tse HF, Goette A, Camm AJ, Blomstrom-Lundqvist C, Gupta D, Boriani G. Atrial fibrillation and stroke prevention: 25 years of research at EP Europace journal. Europace. 2023 Aug 2; 25(9). doi:10.1093/europace/euad226 PubMed Central PMCID: PMC10451006

6. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D´Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjmain EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004 Aug 31; 110(9): 1042–6. doi:10.1161/01.CIR.0000140263.20897.42

7. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. European Heart Journal. 2006 Apr; 27(8): 949–53. doi:10.1093/eurheartj/ehi825

8. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. European Heart Journal. 2013 Sep; 34(35): 2746–51. doi:10.1093/eurheartj/eht280 PubMed Central PMCID: PMC3858024

9. Migdady I, Russman A, Buletko AB. Atrial Fibrillation and Ischemic Stroke: A Clinical Review. Seminars in Neurology. 2021 Aug; 41(4): 348–64. doi:10.1055/s-0041-1726332

10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYP, Pinto FJ, … Watkins CL. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European Heart Journal. 2021 Feb 1; 42(5): 373–498. doi:10.1093/eurheartj/ehaa612

11. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, Trinquart L, McManus DD, Staerk L, Lin H, Lunetta KL, Ellinor PT, Benjamin EJ, Lubitz SA. Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation. Circulation. 2018 Mar 6; 137(10): 1027–38. doi:10.1161/CIRCULATIONAHA.117.031431 PubMed Central PMCID: PMC5840011

12. Belbasis L, Mavrogiannis MC, Emfietzoglou M, Evangelou E. Environmental factors, serum biomarkers and risk of atrial fibrillation: an exposure-wide umbrella review of meta-analyses. European Journal of Epidemiology. 2020 Mar; 35(3): 223–39. doi:10.1007/s10654-020-00618-3

13. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ, Alonso A. Lifetime Risk of Atrial Fibrillation by Race and Socioeconomic Status: ARIC Study (Atherosclerosis Risk in Communities). Circulation: Arrhythmia and Electrophysiology. 2018 Jul; 11(7): e006350. doi:10.1161/CIRCEP.118.006350 PubMed Central PMCID: PMC6053683

14. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, Almgren P, Alonso A, Anderson CD, Aragam KG, Arking DE, Barnard J, Bartz TM, Benjamin EJ, Bihlmeyer NA, Bis JC, Bloom HL, Boerwinkle E, Bottinger EB, … Ellinor PT. Multi-ethnic genome-wide association study for atrial fibrillation. Nature Genetics. 2018 Jun 11; 50(9): 1225–33. doi:10.1038/s41588-018-0133-9 PubMed Central PMCID: PMC6136836

15. Rosner GF, Reiffel JA, Hickey K. The Concept of "Burden" in Atrial Fibrillation. Journal of Atrial Fibrillation. 2012; 4(5): 400. doi:10.4022/jafib.400 PubMed PMID: 28496712; PubMed Central PMCID: PMC5153001

16. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlof B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. Journal of the American College of Cardiology. 2005 Mar 1; 45(5): 712–9. doi:10.1016/j.jacc.2004.10.068

17. Okin PM, Wachtell K, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, Lindholm LH, Nieminen MS, Edelman JM, Hille DA, Dahlof B. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. The Journal of the American Medical Association. 2006 Sep 13; 296(10): 1242–8. doi:10.1001/jama.296.10.1242

18. Johnson LS, Platonov PG, Conen D, Kennback C, Jujic A, Healey JS, Holm H, Sundstrom J, Engstrom G. Markers of Atrial Myopathy in the General Population: Prevalence, Predictors, and Inter-Relations. Journal of the American College of Cardiology: Clinical Electrophysiology. 2023 Nov; 9(11): 2240–9. doi:10.1016/j.jacep.2023.07.012

19. Chung MK, Eckhardt LL, Chen LY, Ahmed HM, Gopinathannair R, Joglar JA, Noseworthy PA, Pack QR, Sanders P, Trulock KM. Lifestyle and Risk Factor Modification for Reduction of Atrial Fibrillation: A Scientific Statement From the American Heart Association. Circulation. 2020 Apr 21; 141(16): e750–72. doi:10.1161/CIR.0000000000000748

20. Zhao E, Chen S, Du Y, Zhang Y. Association between Sleep Apnea Hypopnea Syndrome and the Risk of Atrial Fibrillation: A Meta-Analysis of Cohort Study. Biomed Research International. 2018; 2018: 5215868. doi:10.1155/2018/5215868 PubMed Central PMCID: PMC5822830

21. Choi SE, Sagris D, Hill A, Lip GYH, Abdul-Rahim AH. Atrial fibrillation and stroke. Expert Review of Cardiovascular Therapy. 2023 Jan; 21(1): 35–56. doi:10.1080/14779072.2023.2160319

22. Bunch TJ, Galenko O, Graves KG, Jacobs V, May HT. Atrial Fibrillation and Dementia: Exploring the Association, Defining Risks and Improving Outcomes. Arrhythmia & Electrophysiology Review. 2019 Mar; 8(1): 8–12. doi:10.15420/aer.2018.75.2 PubMed Central PMCID: PMC6434510

23. Best JG, Bell R, Haque M, Chandratheva A, Werring DJ. Atrial fibrillation and stroke: a practical guide. Practical Neurology. 2019 Jun; 19(3): 208–24. doi:10.1136/practneurol-2018-002089

24. Luscher TF. The heart and the brain: cardiovascular risk factors, atrial fibrillation, and dementia. European Heart Journal. 2019 Jul 21; 40(28): 2271–5. doi:10.1093/eurheartj/ehz508

25. Shah R, Wilkins E, Nichols M, Kelly P, El-Sadi F, Wright FL, Townsend N. Epidemiology report: trends in sex-specific cerebrovascular disease mortality in Europe based on WHO mortality data. European Heart Journal. 2019 Mar 1; 40(9): 755–64. doi:10.1093/eurheartj/ehy378 PubMed Central PMCID: PMC6396027

26. Norris JW, Froggatt GM, Hachinski VC. Cardiac arrhythmias in acute stroke. Stroke. 1978 Aug; 9(4): 392–6. doi:10.1161/01.str.9.4.392

27. G. B. D. Diseases, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Oct 17; 396(10258): 1204–22. doi:10.1016/S0140-6736(20)30925-9 PubMed Central PMCID: PMC7567026

28. G. B. D. Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Oct 17; 396(10258): 1223–49. doi:10.1016/S0140-6736(20)30752-2 PubMed Central PMCID: PMC7566194

29. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, … Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2011 Sep 15; 365(11): 981–92. doi:10.1056/NEJMoa1107039

30. Kim TH, Yang PS, Kim D, Yu HT, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. CHA(2)DS(2)-VASc Score for Identifying Truly Low-Risk Atrial Fibrillation for Stroke: A Korean Nationwide Cohort Study. Stroke. 2017 Nov; 48(11): 2984–90. doi:10.1161/STROKEAHA.117.018551

31. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, … Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2009 Sep 17; 361(12): 1139–51. doi:10.1056/NEJMoa0905561

32. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, … Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2013 Nov 28; 369(22): 2093–104. doi:10.1056/NEJMoa1310907

33. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011 Sep 8; 365(10): 883–91. doi:10.1056/NEJMoa1009638

34. Carnicelli AP, Hong H, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, Patel MR, Wallentin L, Alexander JH, Cecilia Bahit M, Benz AP, Bohula EA, Chao TF, Dyal L, Ezekowitz M, AA Fox K, Gencer B, Halperin JL, Hijazi Z, ... Granger CB. Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex. Circulation. 2022 Jan 25; 145(4): 242–55. doi:10.1161/CIRCULATIONAHA.121.056355 PubMed Central PMCID: PMC8800560

35. Kotecha D, Pollack CV, De Caterina R, Renda G, Kirchhof P. Direct Oral Anticoagulants Halve Thromboembolic Events After Cardioversion of AF Compared With Warfarin. Journal of the American College of Cardiology. 2018 Oct 16; 72(16): 1984–6. doi:10.1016/j.jacc.2018.07.083

36. Connolly SJ, Karthikeyan G, Ntsekhe M, Haileamlak A, El Sayed A, El Ghamrawy A, Damasceno A, Avezum A, Dans AML, Gitura B, Hu D, Kamanzi ER, Maklady F, Fana G, Gonzalez-Hermosillo JA, Musuku J, Kazmi K, Zuhlke L, Gondwe L, ... Yusuf S. Rivaroxaban in Rheumatic Heart Disease-Associated Atrial Fibrillation. New England Journal of Medicine. 2022 Sep 15; 387(11): 978–88. doi:10.1056/NEJMoa2209051

37. Escudero-Martinez I, Morales-Caba L, Segura T. Atrial fibrillation and stroke: A review and new insights. Trends in Cardiovascular Medicine. 2023 Jan; 33(1): 23–9. doi:10.1016/j.tcm.2021.12.001

38. van der Endt VHW, Milders J, Penning de Vries BBL, Trines SA, Groenwold RHH, Dekkers OM, Trevisan M, Carrero JJ, van Diepen M, Dekker FW, de Jong Y. Comprehensive comparison of stroke risk score performance: a systematic review and meta-analysis among 6 267 728 patients with atrial fibrillation. EP Europace. 2022 Nov 22; 24(11): 1739–53. doi:10.1093/europace/euac096 PubMed Central PMCID: PMC9681133

39. Stefansdottir H, Arnar DO, Aspelund T, Sigurdsson S, Jonsdottir MK, Hjaltason H, Launer LJ, Gudnason V. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. Stroke. 2013 Apr; 44(4): 1020–5. doi:10.1161/STROKEAHA.12.679381 PubMed Central PMCID: PMC3632359

40. Manolio TA, Kronmal RA, Burke GL, Poirier V, O'Leary DH, Gardin JM, Fried LP, Steinberg EP, Bryan RN. Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. Stroke. 1994 Feb; 25(2): 318–27. doi:10.1161/01.str.25.2.318

41. Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, D´Agostino RB, DeCarli C. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. Neurology. 2004 Nov; 63(9): 1591–9.

42. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C, Heindel W, Breithardt G, Berger K, Ringelstein EB, Kirchhof P, Wersching H. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. European Heart Journal. 2008 Sep; 29(17): 2125–32. doi:10.1093/eurheartj/ehn341

43. Moazzami K, Shao IY, Chen LY, Lutsey PL, Jack CR, Mosley T, Joyner DA, Gottesman R, Alonso A. Atrial Fibrillation, Brain Volumes, and Subclinical Cerebrovascular Disease (from the Atherosclerosis Risk in Communities Neurocognitive Study [ARIC-NCS]). The Americal Journal of Cardiology. 2020 Jan 15; 125(2): 222–8. doi:10.1016/j.amjcard.2019.10.010 PubMed Central PMCID: PMC6942172

44. Polymeris AA, Coslovksy M, Aeschbacher S, Sinnecker T, Benkert P, Kobza R, Beer J, Rodondi N, Fischer U, Moschovitis G, Monsch AU, Springer A, Schwenkglenks M, Wuerfel J, De Marchis GM, Lyrer PA, Kuhne M, Osswald S, Conen D, ... Bonati LH. Serum neurofilament light in atrial fibrillation: clinical, neuroimaging and cognitive correlates. Brain Communications. 2020; 2(2): fcaa166. doi:10.1093/braincomms/fcaa166 PubMed Central PMCID: PMC7753055

45. Park S, Lee S, Kim Y, Cho S, Kim K, Kim YC, Han SS, Lee H, Lee JP, Lee S, Choi EK, Joo KW, Lim CS, Kim YS, Kim DK. Causal effects of atrial fibrillation on brain white and gray matter volume: a Mendelian randomization study. BMC Medicine. 2021 Nov 24; 19(1): 274. doi:10.1186/s12916-021-02152-9 PubMed Central PMCID: PMC8611907

46. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Annals of Internal Medicine. 2013 Mar; 158(5 Pt 1): 338–46. doi:10.7326/0003-4819-158-5-201303050-00007 PubMed Central PMCID: PMC4465526

47. Mobley AR, Subramanian A, Champsi A, Wang X, Myles P, McGreavy P, Bunting KV, Shukla D, Nirantharakumar K, Kotecha Det al. Thromboembolic events and vascular dementia in patients with atrial fibrillation and low apparent stroke risk. Nature Medicine. 2024 Aug; 30(8): 2288–94. doi:10.1038/s41591-024-03049-9 PubMed Central PMCID: PMC11333279

48. Kim D, Yang PS, Yu HT, Kim TH, Jang E, Sung JH, Pak HN, Lee MY, Lee MH, Lip GYH, Joung B. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. European Heart Journal. 2019 Jul 21; 40(28): 2313–23. doi:10.1093/eurheartj/ehz386

49. Koh YH, Lew LZW, Franke KB, Elliott AD, Lau DH, Thiyagarajah A, Linz D, Arstall M, Tully PJ, Baune BT, Munawar DA, Mahajan R. Predictive role of atrial fibrillation in cognitive decline: a systematic review and meta-analysis of 2.8 million individuals. EP Europace. 2022 Sep 1; 24(8): 1229–39. doi:10.1093/europace/euac003 PubMed Central PMCID: PMC9435641

50. Singh-Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, Kivimaki M, Dugravot A. Atrial fibrillation as a risk factor for cognitive decline and dementia. European Heart Journal. 2017 Sep 7; 38(34): 2612–8. doi:10.1093/eurheartj/ehx208 PubMed Central PMCID: PMC5837240

51. Kobayashi A, Iguchi M, Shimizu S, Uchiyama S. Silent cerebral infarcts and cerebral white matter lesions in patients with nonvalvular atrial fibrillation. Journal of Stroke and Cerebrovascular Diseases. 2012 May; 21(4): 310–7. doi:10.1016/j.jstrokecerebrovasdis.2010.09.004

52. Chen LY, Lopez FL, Gottesman RF, Huxley RR, Agarwal SK, Loehr L, Mosley T, Alonso A. Atrial fibrillation and cognitive decline-the role of subclinical cerebral infarcts: the atherosclerosis risk in communities study. Stroke. 2014 Sep; 45(9): 2568–74. doi:10.1161/STROKEAHA.114.005243 PubMed Central PMCID: PMC4146651

53. Testai FD, Gorelick PB, Chuang PY, Dai X, Furie KL, Gottesman RF, Iturrizaga JC, Lazar RM, Russo AM, Seshadri S, Wan EY. Cardiac Contributions to Brain Health: A Scientific Statement From the American Heart Association. Stroke. 2024 Dec; 55(12): e425–38. doi:10.1161/STR.0000000000000476

54. Madhavan M, Graff-Radford J, Piccini JP, Gersh BJ. Cognitive dysfunction in atrial fibrillation. Nature Reviews Cardiology. 2018 Dec; 15(12): 744–56. doi:10.1038/s41569-018-0075-z

55. Conen D, Rodondi N, Muller A, Beer JH, Ammann P, Moschovitis G, Auricchio A, Hayoz D, Kobza R, Shah D, Novak J, Schlapfer J, Di Valentino M, Aeschbacher S, Blum S, Meyre P, Sticherling C, Bonati LH, Ehret G, ... Osswald S. Relationships of Overt and Silent Brain Lesions With Cognitive Function in Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2019 Mar 12; 73(9): 989–99. doi:10.1016/j.jacc.2018.12.039

56. Wolters FJ, Zonneveld HI, Hofman A, van der Lugt A, Koudstaal PJ, Vernooij MW, Ikram MA. Cerebral Perfusion and the Risk of Dementia: A Population-Based Study. Circulation. 2017 Aug 22; 136(8): 719–28. doi:10.1161/CIRCULATIONAHA.117.027448

57. Marshall RS. Effects of altered cerebral hemodynamics on cognitive function. Journal of Alzheimer´s Disease. 2012; 32(3): 633–42. doi:10.3233/JAD-2012-120949

58. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. Journal of the American College of Cardiology. 2012 Dec; 60(22): 2263–70. doi:10.1016/j.jacc.2012.04.063

59. Cox SR, Lyall DM, Ritchie SJ, Bastin ME, Harris MA, Buchanan CR, Fawns-Ritchie C, Barby MC, de Nooij L, Reus LM, Alloza C, Shen X, Neilson E, Alderson HL Hunter S, Liewald DC, Whalley HC, McIntosh AM, Lawrie SM, ... Deary IJ. Associations between vascular risk factors and brain MRI indices in UK Biobank. European Heart Journal. 2019 Jul 21; 40(28): 2290–300. doi:10.1093/eurheartj/ehz100 PubMed Central PMCID: PMC6642726

60. Hamel-Sellman DJ, Prescott BR, Korzinski TJ, Xanthakis V, Cooper LL, Hamburg NM, Tsao CW, Benjamin EJ, Vasan RS, Mitchell GF. Relations of Artificial Intelligence Vascular Age With Cardiometabolic Disease Progression: The Framingham Heart Study. Journal of the American Heart Association. 2025 Dec 16; 14(24): e044872. doi:10.1161/JAHA.125.044872

61. Sethi S, Rivera O, Oliveros R, Chilton R. Aortic stiffness: pathophysiology, clinical implications, and approach to treatment. Integrated Blood Pressure Control. 2014; 7: 29–34. doi:10.2147/IBPC.S59535 PubMed Central PMCID: PMC4046515

62. Angoff R, Mosarla RC, Tsao CW. Aortic Stiffness: Epidemiology, Risk Factors, and Relevant Biomarkers. Frontiers in Cardiovascular Medicine. 2021; 8: 709396. doi:10.3389/fcvm.2021.709396 PubMed Central PMCID: PMC8606645

63. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Cheng S, Aragam J, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Relations of Central Hemodynamics and Aortic Stiffness with Left Ventricular Structure and Function: The Framingham Heart Study. Journal of the American Heart Association. 2016 Mar 9; 5(3): e002693. doi:10.1161/JAHA.115.002693

64. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber T. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension. 2015 Sep; 66(3): 698–722. doi:10.1161/HYP.0000000000000033

65. Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, Boutouyrie P. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke. 2003 May; 34(5): 1203–6. doi:10.1161/01.STR.0000065428.03209.64

66. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension. 2002 Jan; 39(1): 10–5. doi:10.1161/hy0102.099031

67. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006 Feb 7; 113(5): 657–63. doi:10.1161/CIRCULATIONAHA.105.555235

68. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. Journal of the American College of Cardiology. 2010 Mar 30; 55(13): 1318–27. doi:10.1016/j.jacc.2009.10.061

69. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation. 2006 Feb 7; 113(5): 664–70. doi:10.1161/CIRCULATIONAHA.105.579342

70. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation. 2010 Feb 2; 121(4): 505–11. doi:10.1161/CIRCULATIONAHA.109.886655 PubMed Central PMCID: PMC2836717

71. Niiranen TJ, Kalesan B, Mitchell GF, Vasan RS. Relative Contributions of Pulse Pressure and Arterial Stiffness to Cardiovascular Disease. Hypertension. 2019 Mar; 73(3): 712–7. doi:10.1161/HYPERTENSIONAHA.118.12289 PubMed Central PMCID: PMC6374179

72. Vasan RS, Pan S, Xanthakis V, Beiser A, Larson MG, Seshadri S, Mitchell GF. Arterial Stiffness and Long-Term Risk of Health Outcomes: The Framingham Heart Study. Hypertension. 2022 May; 79(5): 1045–56. doi:10.1161/HYPERTENSIONAHA.121.18776 PubMed Central PMCID: PMC9009137

73. Mitchell GF, Rong J, Larson MG, Korzinski TJ, Xanthakis V, Sigurdsson S, Gudnason V, Launer LJ, Aspelund T, Hamburg NM, Gotal JD, Vasan RS. Vascular Age Assessed From an Uncalibrated, Noninvasive Pressure Waveform by Using a Deep Learning Approach: The AI-VascularAge Model. Hypertension. 2024 Jan; 81(1): 193–201. doi:10.1161/HYPERTENSIONAHA.123.21638

74. Glynn RJ, Field TS, Rosner B, Hebert PR, Taylor JO, Hennekens CH. Evidence for a positive linear relation between blood pressure and mortality in elderly people. Lancet. 1995 Apr 1; 345(8953): 825–9. doi:10.1016/s0140-6736(95)92964-9

75. Kannel WB, D'Agostino RB, Silbershatz H. Blood pressure and cardiovascular morbidity and mortality rates in the elderly. American Heart Journal. 1997 Oct; 134(4): 758–63. doi:10.1016/s0002-8703(97)70061-9

76. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004 Jun; 43(6): 1239–45. doi:10.1161/01.HYP.0000128420.01881.aa

77. Mitchell GF, Gudnason V, Launer LJ, Aspelund T, Harris TB. Hemodynamics of increased pulse pressure in older women in the community-based Age, Gene/Environment Susceptibility-Reykjavik Study. Hypertension. 2008 Apr; 51(4): 1123–8. doi:10.1161/HYPERTENSIONAHA.107.108175 PubMed Central PMCID: PMC11106724

78. Mitchell GF. Reflections on reflected waves in 'YoungAdult.' The Journal of Physiology. 2022 Oct; 600(20): 4381–2. doi:10.1113/JP283599

79. O'Rourke MF, Safar ME. Relationship Between Aortic Stiffening and Microvascular Disease in Brain and Kidney: Cause and Logic of Therapy. Hypertension. 2005 Jul; 46(1): 200–4. doi:10.1161/01.HYP.0000168052.00426.65

80. Climie RE, Gallo A, Picone DS, Di Lascio N, van Sloten TT, Guala A, Mayer CC, Hametner B, Bruno RM. Measuring the Interaction Between the Macro- and Micro-Vasculature. Frontiers in Cardiovascular Medicine. 2019; 6: 169. doi:10.3389/fcvm.2019.00169 PubMed Central PMCID: PMC6882776

81. Tsao CW, Himali JJ, Beiser AS, Larson MG, DeCarli C, Vasan RS, Mitchell GF, Seshadri S. Association of arterial stiffness with progression of subclinical brain and cognitive disease. Neurology. 2016 Feb 16; 86(7): 619–26. doi:10.1212/WNL.0000000000002368 PubMed Central PMCID: PMC4762417

82. Mitchell GF. Aortic Stiffness and Cerebral Blood Flow. American Journal of Hypertension. 2011 Oct 1; 24(10): 1056–1056. doi:10.1038/ajh.2011.112

83. Muela HCS, Costa-Hong VA, Yassuda MS, Moraes NC, Memoria CM, Machado MF, Bor-Seng-Shu E, Nogueira RC, Mansur AJ, Massaro AR, Nitrini R, Macedo TA, Bortolotto LA. Higher arterial stiffness is associated with lower cognitive performance in patients with hypertension. The Journal of Clinical Hypertension Greenwich. 2018 Jan; 20(1): 22–30. doi:10.1111/jch.13129 PubMed Central PMCID: PMC8031309

84. Tarumi T, Shah F, Tanaka H, Haley AP. Association Between Central Elastic Artery Stiffness and Cerebral Perfusion in Deep Subcortical Gray and White Matter. American Journal of Hypertension. 2011 Oct 1; 24(10): 1108–13. doi:10.1038/ajh.2011.101

85. Li X, Xing J, Hui Y, Shi H, Li R, Zhang S, Chen S, Li J, Liang X, Wu Y, Zhao P, Wu S, Wang Z. Hippocampal volume mediates the association of arterial stiffness with cognitive impairment in adult population. Journal of Hypertension. 2024 Sep 1; 42(9): 1566–72. doi:10.1097/HJH.0000000000003760 PubMed Central PMCID: PMC11296271

86. Henskens LHG, Kroon AA, Van Oostenbrugge RJ, Gronenschild EHBM, Fuss-Lejeune MMJJ, Hofman PAM, Lodder J, De Leeuw PW. Increased Aortic Pulse Wave Velocity Is Associated With Silent Cerebral Small-Vessel Disease in Hypertensive Patients. Hypertension. 2008 Dec; 52(6): 1120–6. doi:10.1161/HYPERTENSIONAHA.108.119024

87. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E. Arterial stiffness, the brain and cognition: A systematic review. Ageing Research Review. 2014 May; 15: 16–27. doi:10.1016/j.arr.2014.02.002

88. Cui C, Sekikawa A, Kuller LH, Lopez OL, Newman AB, Kuipers AL, Mackey RH. Aortic Stiffness is Associated with Increased Risk of Incident Dementia in Older Adults. Journal of Alzheimer´s Disease. 2018; 66(1): 297–306. doi:10.3233/JAD-180449 PubMed Central PMCID: PMC6313252

89. Alvarez-Bueno C, Cunha PG, Martinez-Vizcaino V, Pozuelo-Carrascosa DP, Visier-Alfonso ME, Jimenez-Lopez E, Cavero-Redondo I. Arterial Stiffness and Cognition Among Adults: A Systematic Review and Meta-Analysis of Observational and Longitudinal Studies. Journal of the American Heart Association. 2020 Mar 3; 9(5): e014621. doi:10.1161/JAHA.119.014621 PubMed Central PMCID: PMC7335587

90. Pase MP, Herbert A, Grima NA, Pipingas A, O'Rourke MF. Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis. Internal Medicine Journal. 2012 Jul; 42(7): 808–15. doi:10.1111/j.1445-5994.2011.02645.x

91. Wymer DT, Patel KP, Burke WF, Bhatia VK. Phase-Contrast MRI: Physics, Techniques, and Clinical Applications. Radiographics. 2020 Feb; 40(1): 122–40. doi:10.1148/rg.2020190039

92. Barkhof F, Kouwenhoven M, Scheltens P, Sprenger M, Algra P, Valk J. Phase-contrast cine MR imaging of normal aqueductal CSF flow. Effect of aging and relation to CSF void on modulus MR. Acta Radiologica. 1994 Mar; 35(2): 123–30.

93. 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. Magnetic Resonance in Medicine. 2011 Jul; 66(1): 57–66. doi:10.1002/mrm.22776 PubMed Central PMCID: PMC3140063

94. Sigurdsson S, Forsberg L, Aspelund T, van der Geest RJ, van Buchem MA, Launer LJ, Gudnason V, van Osch MJ. Feasibility of Using Pseudo-Continuous Arterial Spin Labeling Perfusion in a Geriatric Population at 1.5 Tesla. PLOS One. 2015; 10(12): e0144743. doi:10.1371/journal.pone.0144743 PubMed Central PMCID: PMC4687637

95. Han H, Lin Z, Soldan A, Pettigrew C, Betz JF, Oishi K, Li Y, Liu P, Albert M, Lu H. Longitudinal Changes in Global Cerebral Blood Flow in Cognitively Normal Older Adults: A Phase-Contrast MRI Study. Journal of Magnetic Resonance Imaging. 2022 Nov; 56(5): 1538–45. doi:10.1002/jmri.28133 PubMed Central PMCID: PMC9411265

96. Lotz J, Meier C, Leppert A, Galanski M. Cardiovascular flow measurement with phase-contrast MR imaging: basic facts and implementation. Radiographics. 2002 Jun; 22(3): 651–71. doi:10.1148/radiographics.22.3.g02ma11651

97. Deibler AR, Pollock JM, Kraft RA, Tan H, Burdette JH, Maldjian JA. Arterial spin-labeling in routine clinical practice, part 1: technique and artifacts. AJNR American Journal of Neuroradiology. 2008 Aug; 29(7): 1228–34. doi:10.3174/ajnr.A1030 PubMed Central PMCID: PMC4686140

98. Haller S, Zaharchuk G, Thomas DL, Lovblad KO, Barkhof F, Golay X. Arterial Spin Labeling Perfusion of the Brain: Emerging Clinical Applications. Radiology. 2016 Nov; 281(2): 337–56. doi:10.1148/radiol.2016150789

99. Detre John A. Magnetom Flash Clinical Neurology [Internet]. 2008 Jan. Available from: www.siemens.com/magnetom-world.

100. Wintermark M, Sesay M, Barbier E, Borbely K, Dillon WP, Eastwood JD, Glenn TC, Grandin CB, Pedraza S, Soustiel JF, Nariai T, Zaharchuk G, Caille JM, Dousset V, Yonas H. Comparative overview of brain perfusion imaging techniques. Stroke. 2005 Sep; 36(9): e83-99. doi:10.1161/01.STR.0000177884.72657.8b

101. Calamante F, Thomas DL, Pell GS, Wiersma J, Turner R. Measuring cerebral blood flow using magnetic resonance imaging techniques. Journal of Cerebral Blood Flow & Metabolism. 1999 Jul; 19(7): 701–35. doi:10.1097/00004647-199907000-00001

102. Alsop DC, Detre JA, Golay X, Gunther M, Hendrikse J, Hernandez-Garcia L, Lu H, MacIntosh BJ, Parkes LM, Smits M, van Osch MJ, Wang DJ, Wong EC, Zaharchuk G. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magnetic Resonance in Medicine. 2015 Jan; 73(1): 102–16. doi:10.1002/mrm.25197 PubMed Central PMCID: PMC4190138

103. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. Brain. 2011 Nov; 134(Pt 11): 3398–407. doi:10.1093/brain/awr253 PubMed Central PMCID: PMC3212721

104. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. Expert consensus document on arterial stiffness: methodological issues and clinical applications. European Heart Journal. 2006 Nov; 27(21): 2588–605. doi:10.1093/eurheartj/ehl254

105. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. The Journal of the American Medical Association. 2012 Sep 5; 308(9): 875–81. doi:10.1001/2012.jama.10503 PubMed Central PMCID: PMC3594687

106. Van Bortel LM, Duprez D, Starmans-Kool MJ, Safar ME, Giannattasio C, Cockcroft J, Kaiser DR, Thuillez C. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. American Journal of Hypertension. 2002 May; 15(5): 445–52. doi:10.1016/s0895-7061(01)02326-3

107. Gardarsdottir M, Sigurdsson S, Aspelund T, Rokita H, Launer LJ, Gudnason V, Arnar DO. Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. EP Europace. 2018; 20(8): 1252–8. doi:10.1093/europace/eux220 PubMed Central PMCID: PMC6075509

108. Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, Thorgeirsson G, Aspelund T, Garcia ME, Cotch MF, Hoffman HJ, Gudnason V. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. American Journal of Epidemiology. 2007 May; 165(9): 1076–87. doi:10.1093/aje/kwk115 PubMed Central PMCID: PMC2723948

109. Bjornsson OG, Davidsson D, Olafsson H, Olafsson O, Sigfusson N, Thorsteinsson T. Stages I-III, 1967-1969, 1970-1971 and 1974-1976. Participants, Invitation, Response etc. The Icelandic Heart Association; Reykjavik: 1979. Report ABC XVIII. Health Survey in the Reykjavik Area-Men. 1979.

110. Bjornsson G, Bjornsson OJ, Davidsson D, Kristjansson BT, Olafsson O, Sigfusson N, Thorsteinsson T. Stages I-III, 1968-1969, 1971-1972 and 1976-1978. Participants, Invitation, Response etc. The Icelandic Heart Association; Reykjavík: 1982. Report ABC XXIV. Health Survey in the Reykjavik Area-Women. 1982.

111. Zijdenbos AP, Forghani R, Evans AC. Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. IEEE Transactions on Medical Imaging. 2002 Oct; 21(10): 1280–91. doi:10.1109/TMI.2002.806283

112. Sigurdsson S, Aspelund T, Forsberg L, Fredriksson J, Kjartansson O, Oskarsdottir B, Jonsson PV, Eiriksdottir G, Harris TB, Zijdenbos A, van Buchem MA, Launer LJ, Gudnason V. Brain tissue volumes in the general population of the elderly: the AGES-Reykjavik study. Neuroimage. 2012 Feb; 59(4): 3862–70. doi:10.1016/j.neuroimage.2011.11.024 PubMed Central PMCID: PMC4712156

113. Herscovitch P, Raichle ME. What is the correct value for the brain–blood partition coefficient for water? Journal of Cerebral Blood Flow & Metabolism. 1985 Mar; 5(1): 65–9. doi:10.1038/jcbfm.1985.9

113. Gardarsdottir M, Sigurdsson S, Aspelund T, Gardarsdottir VA, Forsberg L, Gudnason V, Arnar DO. Improved brain perfusion after electrical cardioversion of atrial fibrillation. EP Europace. 2020; 22(4): 530-537. doi:10.1093/europace/euz336

114. Mitchell GF, Izzo JL, Lacourciere Y, Ouellet JP, Neutel J, Qian C, Kerwin LJ, Block AJ, Pfeffer MA. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. Circulation. 2002 Jun 25; 105(25): 2955–61. doi:10.1161/01.cir.0000020500.77568.3c

115. Mitchell GF, Lacourcière Y, Ouellet JP, Izzo JL, Neutel J, Kerwin LJ, Block AJ, Pfeffer MA. Determinants of Elevated Pulse Pressure in Middle-Aged and Older Subjects With Uncomplicated Systolic Hypertension: The Role of Proximal Aortic Diameter and the Aortic Pressure-Flow Relationship. Circulation. 2003 Sep 30; 108(13): 1592–8. doi:10.1161/01.CIR.0000093435.04334.1F

116. Suri S, Chiesa ST, Zsoldos E, Mackay CE, Filippini N, Griffanti L, Mahmood A, Singh-Manoux A, Shipley MJ, Brunner EJ, Kivimaki M, Deanfield JE, Ebmeier KP. Associations between arterial stiffening and brain structure, perfusion, and cognition in the Whitehall II Imaging Sub-study: A retrospective cohort study. PLOS Medicine. 2020 Dec; 17(12): e1003467. doi:10.1371/journal.pmed.1003467 PubMed Central PMCID: PMC7771705

117. Benetos A. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. American Journal of Hypertension. 2002 Dec; 15(12): 1101–8. doi:10.1016/S0895-7061(02)03029-7

118. Tsao CW, Seshadri S, Beiser AS, Westwood AJ, Decarli C, Au R, Himali JJ, Hamburg NM, Vita JA, Levy D, Larson MG, Benjamin EJ, Wolf PA, Vasan RS, Mitchell GF. Relations of arterial stiffness and endothelial function to brain aging in the community. Neurology. 2013 Sep 10; 81(11): 984–91. doi:10.1212/WNL.0b013e3182a43e1c PubMed Central PMCID: PMC3888200

119. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, Wong D, Zhou Y, Knopman D, Mosley TH, Gottesman RF. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. Neurology. 2018 Apr 3; 90(14): e1248–56. doi:10.1212/WNL.0000000000005259 PubMed Central PMCID: PMC5890613

120. Tomoto T, Tarumi T, Zhang R. Central arterial stiffness, brain white matter hyperintensity and total brain volume across the adult lifespan. Journal of Hypertension. 2023 May; 41(5): 819–29. doi:10.1097/HJH.0000000000003404

121. Hobden G, Reid G, Chiesa ST, Wang C, Jobbins L, Mackay CE, Hughes AD, Ebmeier KP, Pitt J, Kivimaki M, Singh-Manoux A, Suri S. Associations of aortic and carotid artery health with cerebrovascular markers and cognition in older adults from the Whitehall II imaging study. BMC Medicine. 2025 Jun 3 ;23(1): 330. doi:10.1186/s12916-025-04105-y PubMed Central PMCID: PMC12135225

122. Wutzler A, Nee J, Boldt LH, Kühnle Y, Gräser S, Schröder T, Haverkamp W, Storm C. Improvement of cerebral oxygen saturation after successful electrical cardioversion of atrial fibrillation. EP Europace. 2014 Feb; 16(2): 189–94. doi:10.1093/europace/eut246

123. Lavy S, Stern S, Melamed E, Cooper G, Keren A, Levy P. Effect of chronic atrial fibrillation on regional cerebral blood flow. Stroke. 1980 Feb; 11(1): 35–8.

124. Petersen P, Kastrup J, Videbaek R, Boysen G. Cerebral blood flow before and after cardioversion of atrial fibrillation. Journal of Cerebral Blood Flow & Metabolism. 1989 Jun; 9(3): 422–5. doi:10.1038/jcbfm.1989.62

125. He X, Xiao H, Guo H, Weng Y, Zhang L, Fang Q, Tang X. Atrial fibrillation-related ischemic stroke and cognitive impairment: Research progress on the characteristics and pathogenesis. Brain Research Bulletin. 2025 Jul; 227: 111392. doi:10.1016/j.brainresbull.2025.111392

126. Rasti SD, Sugiarto AAR, Nuryandi APA, Arvianti MZ, Yomara RT, Nagasastra J, Julario R, Fagi RA, Windrati DMH. Revitalizing brain perfusion: Unveiling advancements through rhythm control strategies in atrial fibrillation-A systematic review. Journal of Arrhythmia. 2024 Jun; 40(3): 411–22. doi:10.1002/joa3.13056 PubMed Central PMCID: PMC11199798

127. Kedzo J, Lovric Kojundzic S, Marinovic Guic M, Tandara L, Breskovic T, Jurisic Z. Association of Electrical Cardioversion with Brain Perfusion and Cognitive Function in Patients with Atrial Fibrillation. Life Basel. 2023 Apr 3; 13(4). doi:10.3390/life13040935 PubMed Central PMCID: PMC10142430

128. Saglietto A, Scarsoglio S, Canova D, Roatta S, Gianotto N, Piccotti A, Franzin S, Gaita F, De Ferrari GM, Ridolfi L, Anselmino M. Increased beat-to-beat variability of cerebral microcirculatory perfusion during atrial fibrillation: a near-infrared spectroscopy study. EP Europace. 2021 Aug 6; 23(8): 1219–26. doi:10.1093/europace/euab070

129. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, Day JD. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2011 Aug; 22(8): 839–45. doi:10.1111/j.1540-8167.2011.02035.x

130. Damanti S, Pasina L, Cortesi L, Rossi PD, Cesari M. Atrial Fibrillation: Possible Influences of Rate and Rhythm Control Strategy on Cognitive Performance. Journal of the American Geriatric Society. 2018 Nov; 66(11): 2178–82. doi:10.1111/jgs.15568

131. Kim D, Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Lip GYH, Joung B. Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study. European Heart Journal. 2020 Dec 14; 41(47): 4483–93. doi:10.1093/eurheartj/ehaa726

132. Jin MN, Kim TH, Kang KW, Yu HT, Uhm JS, Joung B, Lee MH, Kim E, Pak HN. Atrial Fibrillation Catheter Ablation Improves 1-Year Follow-Up Cognitive Function, Especially in Patients With Impaired Cognitive Function. Circulation: Arrhythmia and Electrophysiology. 2019 Jul; 12(7): e007197. doi:10.1161/CIRCEP.119.007197

133. Harrison SL, Buckley BJR, Austin P, Lane DA, Lip GYH. Catheter ablation and lower risk of incident dementia and mortality in older adults with atrial fibrillation. Journal of the American Geriatric Society. 2023 Nov; 71(11): 3357–66. doi:10.1111/jgs.18538

134. Saglietto A, Ballatore A, Xhakupi H, De Ferrari GM, Anselmino M. Association of Catheter Ablation and Reduced Incidence of Dementia among Patients with Atrial Fibrillation during Long-Term Follow-Up: A Systematic Review and Meta-Analysis of Observational Studies. Journal of Cardiovascular Development and Disease. 2022 Apr 30; 9(5). doi:10.3390/jcdd9050140 PubMed Central PMCID: PMC9143892

135. Bodagh N, Yap R, Kotadia I, Sim I, Bhalla A, Somerville P, O´Neill M, Williams SE. Impact of catheter ablation versus medical therapy on cognitive function in atrial fibrillation: a systematic review. Journal of Interventional Cardiac Electrophysiology. 2022 Oct; 65(1): 271–86. doi:10.1007/s10840-022-01196-y PubMed Central PMCID: PMC9550702

136. Burnham TS, Scott ML, Steinberg BA, Varela DL, Zenger B, Bunch TJ. Impact of Catheter Ablation on Stroke, Cognitive Decline and Dementia. Arrhythmia & Electrophysiology Review. 2021 Oct 27; 10(3): 205–10. doi:10.15420/aer.2021.42

137. Gallinoro E, D'Elia S, Prozzo D, Lioncino M, Natale F, Golino P, Cimmino G. Cognitive Function and Atrial Fibrillation: From the Strength of Relationship to the Dark Side of Prevention. Is There a Contribution from Sinus Rhythm Restoration and Maintenance? Medicina Kaunas. 2019 Sep 13; 55(9). doi:10.3390/medicina55090587 PubMed Central PMCID: PMC6780629

138. Kalantarian S, Ruskin JN. Atrial Fibrillation and Cognitive Decline: Phenomenon or Epiphenomenon? Cardiology Clinics. 2016 May; 34(2): 279–85. doi:10.1016/j.ccl.2015.12.011

139. Abell JG, Kivimaki M, Dugravot A, Tabak AG, Fayosse A, Shipley M, Sabia S, Singh-Manoux A. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. European Heart Journal. 2018 Sep 1; 39(33): 3119–25. doi:10.1093/eurheartj/ehy288 PubMed Central PMCID: PMC6122131

140. Niiranen TJ, Lyass A, Larson MG, Hamburg NM, Benjamin EJ, Mitchell GF, Vasan RS. Prevalence, Correlates, and Prognosis of Healthy Vascular Aging in a Western Community-Dwelling Cohort: The Framingham Heart Study. Hypertension. 2017 Aug; 70(2): 267–74. doi:10.1161/HYPERTENSIONAHA.117.09026 PubMed Central PMCID: PMC5509504

141. Wang A, Green JB, Halperin JL, Piccini JP. Atrial Fibrillation and Diabetes Mellitus. Journal of the American College of Cardiology. 2019 Aug; 74(8): 1107–15. doi:10.1016/j.jacc.2019.07.020

142. Cooper LL, Palmisano JN, Benjamin EJ, Larson MG, Vasan RS, Mitchell GF, Hamburg NM. Microvascular Function Contributes to the Relation Between Aortic Stiffness and Cardiovascular Events: The Framingham Heart Study. Circulation: Cardiovascular Imaging. 2016 Dec; 9(12): e004979. doi:10.1161/CIRCIMAGING.116.004979

143. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006 Jul 11; 114(2): 119–25. doi:10.1161/CIRCULATIONAHA.105.595140

144. Tarumi T, Zhang R. Cerebral hemodynamics of the aging brain: risk of Alzheimer disease and benefit of aerobic exercise. Frontiers in Physiology. 2014; 5. doi:10.3389/fphys.2014.00006

Original Publications

Paper I

ESC European Society of Cardiology

Europace (2018) **20**, 1252–1258
doi:10.1093/europace/eux220

CLINICAL RESEARCH
Atrial fibrillation

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

Marianna Gardarsdottir[1], Sigurdur Sigurdsson[2], Thor Aspelund[2,3], Hrafnhildur Rokita[4], Lenore J. Launer[5], Vilmundur Gudnason[2,3], and David O. Arnar[3,6]*

[1]Department of Radiology, Landspitali—The National University Hospital of Iceland, Hringbraut, 101 Reykjavik, Iceland; [2]Icelandic Heart Association, Holtasmari 1, 201 Kopavogur, Iceland; [3]Faculty of Medicine, School of Health Sciences, University of Iceland, Vatnsmyrarvegur 16, 101 Reykjavik, Iceland; [4]Department of Internal Medicine II, Regensburg University Hospital, Franz-Josef-Strauss-Allee 11, 93042, Regensburg, Germany; [5]Laboratory of Epidemiology and Population Sciences, National Institute of Ageing, National Institutes of Health, 7201 Gateway Building, Bethesda, MD 20892, USA; and [6]Department of Cardiology, Landspitali - The National University Hospital of Iceland, Hringbraut, 101 Reykjavik, Iceland.

Received 1 April 2017; revised 3 June 2017; editorial decision 16 April 2017; accepted 13 June 2017; online publish-ahead-of-print 9 August 2017

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

* Corresponding author. Tel: +354 543 1000; fax: +354 543 6467. *E-mail address:* davidar@landspitali.is

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 $\geq$140 mmHg systolic or diastolic blood pressure $\geq$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.

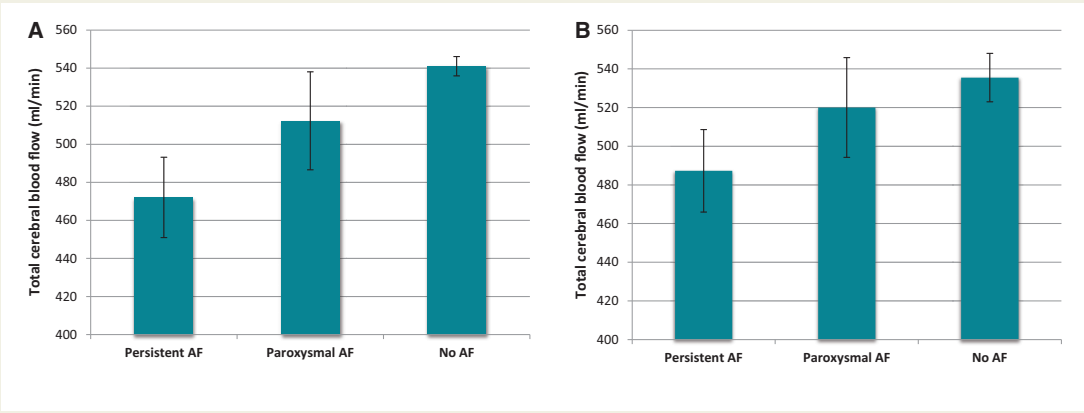

Figure 1 (*A*) Total cerebral blood flow in the cervical arteries in mL/min in the three groups. Persistent AF: those with atrial fibrillation (AF) at the time of imaging; paroxysmal AF: those in sinus rhythm at imaging but with a previous history of AF; no AF: those in sinus rhythm and with no history 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

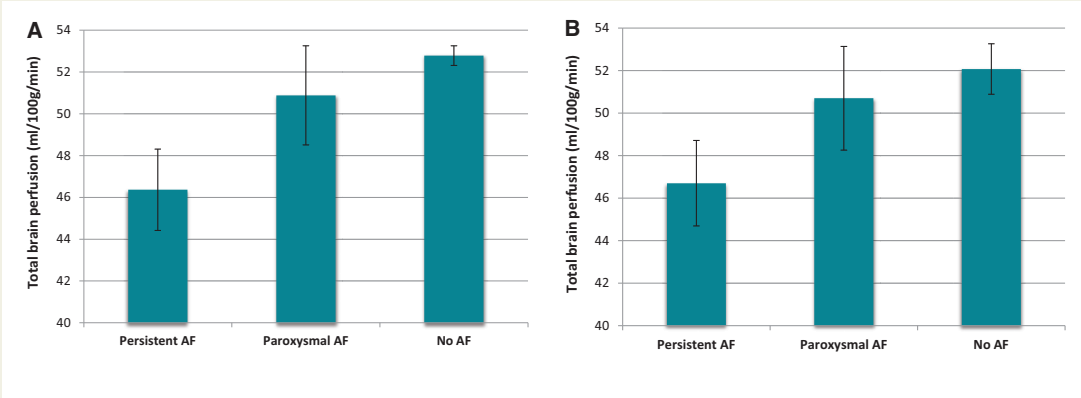

Figure 2 (*A*) Total brain perfusion in mL/100 g brain tissue/min in the three groups. Persistent AF: those with atrial fibrillation (AF) at the time of imaging; paroxysmal AF: those in sinus rhythm at imaging but with a previous history of AF; no AF: those in sinus rhythm and with no history of the 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.

Acknowledgements

The authors would like to express their gratitude to the participants of the AGES Reykjavik Study and the staff personal at Icelandic Heart Association.

Conflict of interest: none declared.

Funding

This work was supported by grants from the Science Fund of Landspitali – The National University Hospital of Iceland and The Helga Jonsdottir and Sigurlidi Kristjansson Memorial Fund. Landspitali-National University Hospital Science Fund and The Helga Jonsdottir and Sigurlidi Kristjansson Memorial Fund have also funded the AGES Reykjavik Study, in addition to National Institutes of Health contract N01-AG-1-2100, the National Institute of Aging Intramural Research Program, the Icelandic Heart Association, and Althingi, the Icelandic Parliament.

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.

Paper II

ESC European Society of Cardiology

Europace (2020) **22**, 530–537
doi:10.1093/europace/euz336

CLINICAL RESEARCH
Atrial fibrillation

Improved brain perfusion after electrical cardioversion of atrial fibrillation

Marianna Gardarsdottir[1], Sigurdur Sigurdsson[2], Thor Aspelund[2,3], Valdis Anna Gardarsdottir[4], Lars Forsberg[2], Vilmundur Gudnason[2,3], and David O. Arnar [3,4]*

[1]Department of Radiology, Landspitali—The National University Hospital of Iceland, Reykjavik, Iceland; [2]Icelandic Heart Association, Kopavogur, Iceland; [3]Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland; and [4]Department of Medicine, Landspitali—The National University Hospital of Iceland, 14C, Hringbraut, 101 Reykjavik, Iceland

Received 1 June 2019; editorial decision 10 November 2019; accepted 4 December 2019; online publish-ahead-of-print 20 December 2019

Aims Atrial fibrillation (AF) has been associated with reduced brain volume, cognitive impairment, and reduced cerebral blood flow. The causes of reduced cerebral blood flow in AF are unknown, but no reduction was seen in individuals without the arrhythmia in a previous study. The aim of this study was to test the hypothesis that brain perfusion, measured with magnetic resonance imaging (MRI), improves after cardioversion of AF to sinus rhythm (SR).

Methods and results All patients undergoing elective cardioversion at our institution were invited to participate. A total of 44 individuals were included. Magnetic resonance imaging studies were done before and after cardioversion with both brain perfusion and cerebral blood flow measurements. However, 17 did not complete the second MRI as they had a recurrence of AF during the observation period (recurrent AF group), leaving 17 in the SR group and 10 in the AF group to complete both measurements. Brain perfusion increased after cardioversion to SR by 4.9 mL/100 g/min in the whole brain ($P < 0.001$) and by 5.6 mL/100 g/min in grey matter ($P < 0.001$). Cerebral blood flow increased by 58.6 mL/min ($P < 0.05$). Both brain perfusion and cerebral blood flow remained unchanged when cardioversion was unsuccessful.

Conclusion In this study of individuals undergoing elective cardioversion for AF, restoration, and maintenance of SR for at least 10 weeks after was associated with an improvement of brain perfusion and cerebral blood flow measured by both arterial spin labelling and phase contrast MRI. In those individuals where cardioversion was unsuccessful, there was no change in perfusion or blood flow.

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

Introduction

Atrial fibrillation (AF) has become a serious public health problem and its prevalence is expected to triple in the next four decades.[1] Atrial fibrillation is a significant risk factor for cardioembolic stroke. Atrial fibrillation has furthermore been linked to cognitive decline and vascular dementia, independent of stroke.[2,3] The mechanisms behind the association of AF and a detriment in cognitive function are not clear despite multiple shared risk factors including hypertension, diabetes, heart failure, chronic kidney disease, and alcohol abuse.[4]

Atrial fibrillation has been associated with decreased brain volume as well as cognitive impairment suggesting a link between these.[5] There are many possible factors linking AF to decreased brain volume and dementia including altered neurohumoral regulation of the blood flow to the brain secondary to the arrhythmia, multiple microemboli causing small cerebral infarcts and decreased cerebral blood flow, in part due to beat-to-beat variation in stroke volume and lack of atrial contraction.

While cerebral blood flow in AF is not a particularly well-studied subject, there is nevertheless some recent clinical data that supports

* Corresponding author. Tel: +354 5431000; fax: +354 543 6467. *E-mail address:* davidar@landspitali.is

What's new?

- Cardioversion of atrial fibrillation (AF) to sinus rhythm resulted in improvement in cerebral blood flow and brain perfusion measured by phase contrast and arterial spin labelling magnetic resonance imaging of the brain.
- In those where cardioversion was unsuccessful no improvement in these parameters was seen.
- Decreased cerebral blood flow and brain perfusion could be a key mechanism in causing reduced brain volumes and cognitive decline seen with AF.
- These results might have important clinical implications but need to be further evaluated in large-scale clinical trials.

brain hypoperfusion and diminished cerebral blood flow in AF. In a large cohort of elderly individuals persistent AF was associated with both lower total cerebral blood flow and lower estimated brain perfusion measured by phase contrast magnetic resonance imaging (MRI) of the brain compared to those in sinus rhythm (SR).[6] While these results showing decreased cerebral blood flow and brain perfusion in AF with MRI were intriguing, there were some important limitations including the cross-sectional design of the study and indirect measurement of brain perfusion. The results also raise the important question of whether restoration of SR in those with AF could lead to improvement in or even restoration of normal cerebral blood flow.

In a recent large population study, lower cerebral perfusion was associated with brain volume loss, accelerated cognitive decline and a higher risk of dementia during a 7-year follow-up.[7] This same mechanism could contribute to the detriment of cognitive function seen in individuals with AF.[5,8]

The goal of this study was to test the hypothesis that blood flow to the brain is lowered in AF, resulting in decreased brain perfusion and cerebral blood flow, and that successful cardioversion to SR leads to improvement in these parameters. If this would be the case it would strengthen our previous observation as a kind of 'proof of concept'.

Methods

Individuals aged 18–75 years who were referred to the Landspitali—The National University Hospital in Reykjavik for elective direct-current cardioversion for AF were invited to participate in the study. Those with a pacemaker, an implantable cardioverter-defibrillator, other contraindications for MRI or severe claustrophobia were excluded. A study coordinator went through a safety questionnaire regarding MRI compatibility and collected baseline information. Informed written consent was obtained and the participant was advised not to use tobacco or caffeine at least 4 h before the MRI examination. When the date of the cardioversion was set the coordinator made an appointment for the first MRI study to be done prior to the cardioversion, preferably on the same day or the day before. On the day of the MRI, the patient underwent an electrocardiogram (ECG) to confirm that the patient was still in AF and a blood test including measurement of N-terminal pro brain natriuretic peptide (NT-proBNP). After the cardioversion, an appointment was made for the second MRI examination at least 10 weeks later. This timeframe was chosen to allow for the return of mechanical atrial systole, which takes a few weeks after restoration of electrical SR.

Approximately a week before the second MRI, the patient underwent a new ECG and was asked about symptoms of recurrent AF. If a patient who previously had been cardioverted to SR had a recurrence of AF on the ECG, they were excluded from further participation in the study as the time from cardioversion to recurrence was uncertain and the second MRI was cancelled. No 24-h Holter monitoring was performed. Those that achieved continued SR after a successful cardioversion, or continued in AF after unsuccessful cardioversion, that is maintained unchanged rhythm at the second MRI; went for the imaging procedure as planned. Those that went back into AF during the observation period were excluded from the study as it was not known when they had reverted to AF again, this could have happened anytime from a few hours after the cardioversion to some weeks later. The lack of knowledge on this would have made the results on this group very difficult to interpret.

Baseline data collected included information on age, sex, height and weight of the participant, as well as blood pressure and heart rate. Body mass index (BMI) was calculated from measured height and weight. Information on the individual's past medical history and cardiovascular risk factors was also collected, including information on the nature of AF (paroxysmal or persistent), length of AF episode, and history of previous cardioversion. Information on medication use included use of beta-blockers, anti-hypertensive medication, warfarin or novel oral anticoagulants (NOACs), aspirin or platelet inhibitors, diabetes medication, lipid-lowering medication, and digoxin was registered. Information was also obtained from medical records and results of echocardiography studies noted if done within 6 months prior to entering the study.

The study was approved by the Icelandic National Bioethics Committee, which acts as the Institutional Review Board for the Icelandic Heart Association and The National University Hospital (VSN-13-043) and by The Icelandic Data Protection Authority.

All participants without a contraindication for MRI underwent a brain scan on a 1.5-T Signa Excite Twinspeed system (General Electric Medical Systems, Waukesha, WI, USA). The scan protocol included acquisition of pseudo-continuous arterial spin labelling (ASL) perfusion sequences for calculating brain perfusion with post-labelling delay of 1525 ms. Additionally, a phase contrast sequence for flow measurements in the cervical arteries was performed as well as anatomical imaging sequences of the whole brain for calculations of brain tissue volumes, including cerebrospinal fluid, grey matter, white matter, and white matter hyperintensities that were computed with a validated automatic image post-processing pipeline.[9,10] Total brain volume (TBV) was computed in millilitres (mL) as the sum of grey matter volume, white matter volume, and white matter hyperintensities volume. The intracranial volume was computed as the sum of TBV and cerebrospinal fluid volume. Brain volumes, in this study, were normalized to intracranial volume and presented as percentages of intracranial volume (TBV/ICV * 100).

Arterial spin labelling is a completely non-invasive method of measuring brain perfusion by using magnetically labelled arterial blood water as an endogenous tracer for quantification of cerebral blood flow in the capillary bed. Hence, this technique does not require an exogenous gadolinium-based tracer as in dynamic susceptibility contrast perfusion, as the blood itself acts as the freely diffusible tracer and the perfusion is measured directly. Inflowing hydrogen nuclei in the arterial blood water are magnetized and then imaged by first labelling the water molecules just proximal to the region of interest. After a certain time, transit time, the paramagnetic tracer flows into the plane to be imagined and interacts with tissue water. The inflow of inverted spins alters total tissue magnetization and consequently the tissue magnetization and image intensity, creating the tag image. The final product, the perfusion image, will reflect the amount of arterial blood delivered to each voxel within the slice within

the transit time, determining the delivery rate of oxygen and nutrients to the capillary bed.[10]

Total cerebral blood flow was measured for comparison with ASL using phase contrast MRI for flow measurement at the level of the skull base in both the internal carotid arteries and the basilar artery. The method of studying the blood flow by phase-contrast MRI is a reliable and highly reproducible method and 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.[11] More details on the acquisition and analysis of the images as well as calculation of perfusion and flow can be found elsewhere, previously described in detail by Sigurdsson *et al.*[10] The operators of the MRI system and the MR image analysts were blinded to all clinical information on the study participants.

Statistical analysis

Data were presented as mean (standard deviation) for continuous variables and as percentage for categorical variables. A *P*-value <0.05 was considered statistically significant. Characteristics between groups were compared using *t*-tests and χ^2 tests. 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. All analyses were performed using R version 3.5.3. Analysis of change in total cerebral blood flow by and between groups was performed using linear mixed models, using the lme4 package in R, with age and sex adjustment, as well as adjustment for brain volume. Analysis of brain perfusion was done similarly with adjustments but adjustment for brain volume was not necessary since the outcome is independent of brain volume due to its direct nature. Adjusted marginal means at each time-point and change between time-points was estimated using the emmeans package in R.

Analytical sample

In total, 142 individuals were initially contacted either with a letter or by telephone. Of those, 60 persons never replied or were not reached in time before their planned cardioversion. Fourteen individuals declined participation in the study, which left 68 individuals that accepted to take part in the study. Of those, 11 were excluded because of spontaneous return to SR before the cardioversion, 6 individuals were further excluded because of a pacemaker or an implanted cardioverter-defibrillator, 5 were excluded because of atrial flutter being the primary arrhythmia and one patient was excluded due to equipment malfunction (MRI machine malfunction at the day of the first examination). During the study period, one individual was further excluded because of a reclassification of the primary arrhythmia as atrial flutter rather than AF discovered while reviewing ECGs. That left 44 eligible and willing individuals to participate in the study.

Results

Of the 44 patients enrolled in the study, 35 (80%) were men and 9 women, mean age 64.4 years (*Table 1*). A total of 27 individuals (21 men) completed the study with two MRI examinations, 17 that were cardioverted to SR and remained in SR at the time of the second MRI examination (SR group) and 10 who continued to be in AF despite the cardioversion attempt (AF group). The remaining 17 participants had a recurrence of AF during the period from successful cardioversion to the second MRI examination and hence were excluded from further evaluation with a second MRI examination according to the study protocol (recurrent AF group). One of the 27 participants had missing blood flow measurement values due to a technical failure on the day of the second examination and therefore cerebral blood flow values measured with phase contrast MRI only exist for 9 individuals but perfusion values measured with ASL were available for all 10 individuals in the AF group.

With regards to baseline clinical characteristics, there was no significant difference between the three groups; SR group, AF group, and recurrent AF group in age, BMI, blood pressure, or heart rate at baseline (*Table 1*). Likewise, there was no significant difference between the groups with regards to history of coronary artery disease, valvular heart disease, heart failure, or hypertension. Pre-cardioversion heart rate on ECG was 80.5 ± 15.0 b.p.m. for the SR group, 83.1 ± 10.2 for the AF group, and 85.1 ± 14.8 for the recurrent AF ($P = 0.64$). There was no difference in pre-cardioversion and post-cardioversion heart rate on ECG for the AF group (83.1 ± 10.2 vs. 89.6 ± 13.7, $P = 0.13$) but a significant lowering was seen in the SR group (80.5 ± 15.0 vs. 58.1 ± 7.4, $P < 0.001$). Left ventricular ejection fraction measured by echocardiography as well as NT-proBNP values measured immediately before the cardioversion were also in the same ranges (*Table 2*). All patients were taking oral anticoagulants and the proportion of those taking NOACs was similar in all three groups (*Table 1*).

Baseline brain perfusion measured with ASL, both in the whole brain as well as in the grey matter of the brain and total cerebral blood flow measured with phase contrast MRI during the first MRI examination prior to the cardioversion in all 44 individuals enrolled into the study was not significantly different between the three outcome groups (*Table 2*). Furthermore, there was no difference in relative brain volume at baseline. On the other hand, brain perfusion measured by ASL was significantly higher after cardioversion in the SR group when compared with the AF group, both with regards to whole brain perfusion as well as grey matter perfusion ($P < 0.05$) (*Table 3*, *Figure 1*). The change in ASL perfusion in the SR group was significant for both whole brain, 4.9 mL/min ($P < 0.001$), and grey matter perfusion, 5.6 mL/min ($P < 0.001$), as opposed to the AF group, were no significant change was detected, −1.6 mL/min ($P = 0.36$) and −1.9 mL/min ($P = 0.34$), respectively (*Table 3*, *Figures 2* and *3*).

There was also no significant difference between the groups in total cerebral blood flow measured with phase contrast MRI during the first examination (*Table 2*). Total cerebral blood flow furthermore increased between the pre- and post-cardioversion MRI examinations in the SR group by 58.6 mL ($P < 0.05$) but remained unchanged in the AF group, −20.8 mL ($P = 0.52$) (*Table 2*, *Figures 1* and *2*).

There was no significant difference in interval from the first to the second MRI examination between the SR group and the AF group (20.7 weeks and 24.5 weeks, respectively, $P = 0.52$).

Discussion

In this prospective study of individuals undergoing elective cardioversion for AF, restoration, and maintenance of SR for at least 10 weeks after was associated with an improvement of brain perfusion and cerebral blood flow measured by both ASL and phase contrast MRI. In those individuals where cardioversion was unsuccessful, there was no change in perfusion or blood flow.

Brain perfusion in AF has not been particularly well-studied. Some studies have indicated that cerebral blood flow is lowered during AF

Table 1 Patient characteristics

	Male ($n = 35$)	Female ($n = 9$)	*P*-value	SR group ($n = 17$)	AF group ($n = 10$)	Recurrent AF group 3 ($n = 17$)	*P*-value all groups
Age (years) (at entry into study)	64.1 (8.3)	65.8 (8.5)	0.59	62.6 (9.8)	65.9 (6.3)	65.3 (7.6)	0.53
Height (cm)	181.2 (6.4)	165.0 (5.5)	<0.001	177.2 (10.2)	175.9 (7.9)	179.8 (8.6)	0.53
Weight (kg)	95.4 (14.7)	87.0 (16.2)	0.14	94.4 (19.5)	95.3 (10.6)	92.1 (13.2)	0.86
Body mass index (kg/m^2)	29.0 (3.4)	31.8 (5.1)	0.05	29.8 (4.6)	30.8 (2.3)	28.5 (3.8)	0.33
Systolic blood pressure (mmHg)	134.2 (17.5)	128.8 (16.5)	0.41	132.3 (16.8)	134.0 (15.7)	133.3 (19.3)	0.97
Diastolic blood pressure (mmHg)	86.7 (12.7)	83.3 (12.8)	0.48	82.9 (11.9)	85.6 (7.0)	89.2 (15.3)	0.37
Heart rate (at baseline) (b.p.m.)	77.3 (12.0)	83.9 (11.9)	0.15	77.6 (14.5)	80.2 (12.4)	78.8 (9.8)	0.87
Ever smoker, former, or current	25 (71.4)	7 (77.8)	1.0	10 (58.8)	10 (100.0)	12 (70.6)	0.07
Smoking (never)	10 (28.6)	2 (22.2)	0.69	7 (41.2)	0 (0.0)	5 (29.4)	<0.01
Hypertension (reported, history of)	21 (60.0)	7 (77.8)	0.55	13 (76.5)	6 (60.0)	9 (52.9)	0.35
Lipid disorder (reported, history of)	11 (31.4)	2 (22.2)	0.90	3 (17.6)	6 (60.0)	4 (23.5)	0.052
Coronary heart disease (reported)	10 (28.6)	1 (11.1)	0.52	2 (11.8)	5 (50.5)	4 (23.5)	0.09
PCI with or without stent insertion, CABG (reported, history of)	4 (11.4)	1 (11.1)	1.0	1 (5.9)	3 (30.0)	1 (5.9)	0.11
Valve disease, history of or reported at echo or other cardiac disease	14 (40.0)	5 (55.59	0.75	8 (47.1)	4 (40.0)	7 (41.2)	0.78
Other cardiac surgery or intervention	1 (2.9)	1 (11.1)	0.87	1 (5.9)	0 (0.0)	1 (5.9)	0.74
Reduced cardiac contractility, history of or reported at echo (EF < 55%), clinical HF	12 (34.3)	6 (66.7)	0.17	4 (23.5)	5 (50.0)	9 (52.9)	0.18
Other cardiac disease, history of	2 (5.7)	0 (0.0)	1.0	0 (0.0)	0 (0.0)	2 (11.8)	0.19
Stroke (cerebral infarct or embolus)	1 (2.9)	1 (11.1)	0.87	2 (11.8)	0 (0.0)	0 (0.0)	0.19
Anti-hypertensive medication (including beta-blockers)	28 (80.0)	9 (100.0)	0.34	14 (82.4)	9 (90.0)	14 (82.4)	0.85
Beta-blocker use	22 (62.9)	9 (100.0)	0.08	13 (76.5)	8 (80.0)	10 (58.8)	0.40
Warfarin use	8 (22.9)	4 (44.4)	0.38	5 (29.4)	4 (40.0)	3 (17.6)	0.44
Thrombin/Xa inhibitor use	25 (71.4)	5 (55.6)	0.61	12 (70.6)	5 (50.5)	13 (76.5)	0.35
Aspirin and anti-platelet medication use	6 (17.2)	0 (0.0)	0.41	0 (0.0)	4 (40.0)	2 (11.8)	<0.05
Lipid lowering medication	10 (28.6)	1 (11.1)	0.52	1 (5.9)	7 (70.0)	3 (17.6)	<0.01
Diabetes medication	1 (2.9)	1 (11.1)	0.87	1 (5.9)	0 (0.0)	1 (5.9)	0.74
Digoxin	4 (11.4)	3 (33.3)	0.28	4 (23.5)	1 (10.0)	2 (11.8)	0.54
Class III anti-arrhythmic use	3 (8.6)	4 (44.4)	<0.05	4 (23.5)	0 (0.0)	3 (17.6)	0.26

Data are shown as mean (standard deviation) for continuous variables and % for categorical variables.
AF, atrial fibrillation; AF group: those that were not converted into sinus rhythm; CABG, coronary artery bypass graft; EF, ejection fraction; HF, heart failure; PCI, percutaneous coronary intervention; recurrent AF: those that were successfully converted into sinus rhythm but had recurrent atrial fibrillation at follow-up; SR, sinus rhythm; SR group: those successfully converted to sinus rhythm.

Table 2 Brain perfusion and cerebral blood flow at baseline

Baseline value	SR group ($n = 17$)	AF group ($n = 10$)	Recurrent AF group ($n = 17$)	*P*-value
ASL whole brain	36.6 (8.2)	34.0 (7.9)	36.1 (8.6)	0.73
ASL grey matter	40.2 (9.6)	37.2 (9.4)	39.8 (10.3)	0.72
Total CBF[a]	557.4 (109.9)	588.8 (144.2)	528.2 (110.5)	0.45
Relative BV	71.4 (4.6)	69.9 (2.3)	69.1 (3.7)	0.32
EF	57.6 (8.1)	57.6 (9.1)	55.5 (8.6)	0.83
BNP	1172.6 (950.1)	437.3 (236.6)	927.3 (584.2)	0.06

Data are age and sex adjusted and shown as mean (standard deviation). For ASL whole brain and grey matter the units were mL/min but for total CBF mL. BNP units were pg/mL. Relative BV and EF are expressed as %.
AF, atrial fibrillation; AF group, those that were not converted into sinus rhythm; ASL, arterial spin labelling; BNP, brain natriuretic peptide; BP, brain perfusion; BV, brain volume; CBF, cerebral blood flow; EF, ejection fraction; recurrent AF, those that were successfully converted into sinus rhythm but had recurrent atrial fibrillation at follow-up; SR, sinus rhythm; SR group, those successfully converted to sinus rhythm.
[a]Adjusted for brain volume.

Table 3 Perfusion and cerebral blood flow values at MRI visit 1 and visit 2

Perfusion and cerebral blood flow		First visit	Second visit	Change	*P*-value[a]
ASL whole brain	SR group (*n* = 17)	36.3 (1.9)	41.2 (1.9)	4.9 (1.3)	<0.001
	AF group (*n* = 10)	34.4 (2.6)	32.8 (2.6)	−1.6 (1.7)	0.36
ASL grey matter	SR group (*n* = 17)	39.9 (2.3)	45.5 (2.3)	5.6 (1.4)	<0.001
	AF group (*n* = 10)	37.8 (2.9)	35.9 (3.0)	−1.9 (2.0)	0.34
Total cerebral blood flow[b]	SR group (*n* = 17)	555.2 (29.2)	613.8 (29.5)[c]	58.6 (24.1)	<0.05
	AF group (*n* = 10)	586.8 (38.2)	566.0 (39.9)[c]	−20.8 (32.0)	0.52

Data are age and sex adjusted and shown as estimated marginal means (standard errors) using Kenward–Roger Degrees of Freedom Approximation. For ASL whole brain and grey matter the units were mL/min but for total cerebral blood flow mL.
AF, atrial fibrillation; AF group, those that were not converted into sinus rhythm; ASL, arterial spin labelling; MRI, magnetic resonance imaging; recurrent AF, those that were successfully converted into sinus rhythm but had atrial fibrillation at follow-up; SR, sinus rhythm; SR group, those successfully converted to sinus rhythm.
[a]Change between visits.
[b]Adjusted for brain volume.
[c]*N* = 9.

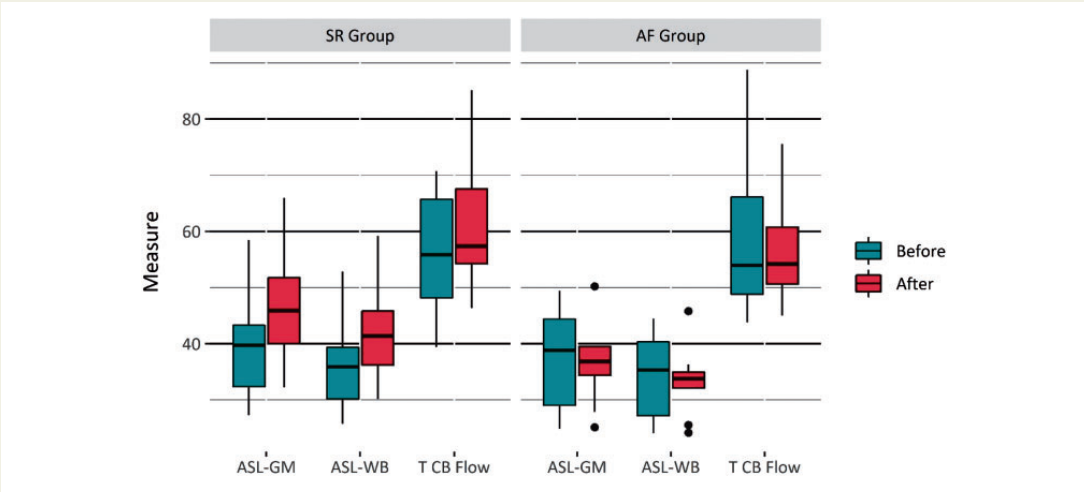

Figure 1 Box whisker plot of brain perfusion by ASL MRI in the grey matter of the brain and the whole brain and by phase contrast MRI of the total cerebral blood flow in the SR group and the AF group before and after cardioversion. The right column for each parameter in both groups shown the increment in perfusion and blood flow after a successful cardioversion or no change after an unsuccessful cardoversion. Total cerebral blood flow measurements were scaled by a factor of 10. AF, atrial fibrillation; ASL, arterial spin labelling; MRI, magnetic resonance imaging; SR, sinus rhythm; T CB Flow, total cerebral blood flow.

and that brain oxygenation and cerebral blood flow may be improved after restoration of SR.[12–16] Those studies used indirect methods for measurement of cerebral blood flow and some investigated regional perfusion only. Additionally, not all studies compared perfusion in AF to perfusion in SR or included patients undergoing cardioversion of AF.

In our study, we used the relatively novel method of ASL for measuring brain perfusion. ASL is an accurate, non-invasive method for directly measuring perfusion in the capillary bed of the whole brain in a reliable and safe manner. At the same time, ASL makes it possible to extract information on both regional and tissue level during the same session.[10,17] In a previous cohort study of ours we have shown that the presence of AF was associated with lower cerebral blood flow and estimated brain perfusion than in those in SR.[6] Decreased brain perfusion and cerebral blood flow could be contributing factors to reduced brain volume and subsequent cognitive impairment, although the pathophysiologic mechanisms linking AF to cognitive impairment are most likely complex and multifactorial. Cognitive function has been recently been shown to improve after AF ablation.[18] The results of our investigation on cerebral blood flow in AF however show that reduced brain perfusion does occur with this arrhythmia and that it may be reversible with return to SR, suggesting that hypoperfusion could play a role. Other possible mechanisms that might link AF with decreased brain volume include cerebral microemboli from the heart, systemic inflammation, cerebral microbleeds, and possibly even genetic factors.[3,19,20]

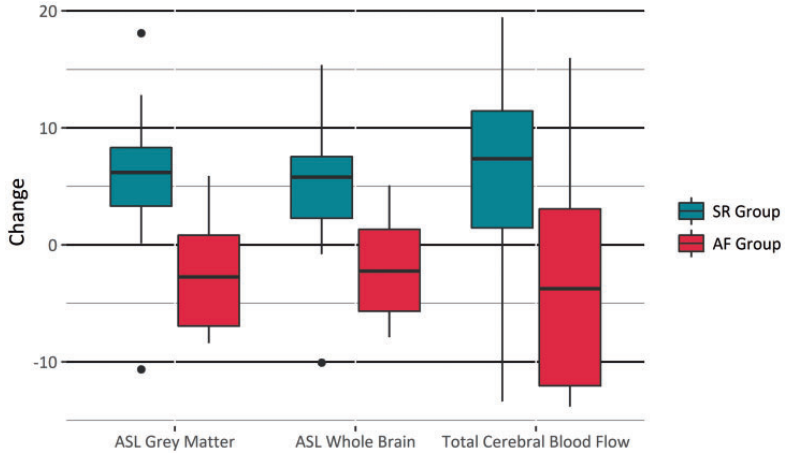

Figure 2 Box whisker plot showing the change in brain perfusion by ASL MRI in the grey matter of the brain and the whole brain and by phase contrast MRI of the total cerebral blood flow in the SR group and the AF group after cardioversion. The upper columns show a positive change in perfusion and cerebral blood flow in the SR group after a successful cardioversion, whereas the lower columns show no change in the AF group after an unsuccessful cardioversion. Total cerebral blood flow measurements were scaled by a factor of 10. AF, atrial fibrillation; ASL, arterial spin labelling; MRI, magnetic resonance imaging; SR, sinus rhythm.

Wolters *et al.*[7] showed in a recent population-based study that lower cerebral perfusion measured by phase contrast MRI was linked to accelerated cognitive decline and higher risk of developing dementia, supporting this association, but interestingly this rather large study of almost 5000 individuals did not report whether individuals had AF or not. The mechanism of decreased perfusion in AF could be a combination of reduced stroke volume due to variability in R-R intervals, resultant changes in atrial filling and ventricular loading and simultaneous loss of atrial contractility. It is also conceivable that AF with a rapid ventricular response might additionally result in even lower brain perfusion. In this study, the rate control both before and after cardioversion was adequate and therefore unlikely that heart rate played a major role in the changes seen in brain perfusion.

Cardiovascular risk factors were similar between those in the SR group and the AF group, suggesting that they did not play a significant role in influencing the difference in measured perfusion of the brain and cerebral blood flow. Atherosclerosis may, along with age and autoregulation, affect the threshold for perfusion, but there was no difference either in age or presence of coronary artery disease between the groups in the present study. Whether older brains are more susceptible to the effect of reduced blood flow and perfusion is not known, but Bunch *et al.*[8,21] actually found more reduction of regional cerebral blood flow in younger age groups with AF compared to normal subjects and higher risk of Alzheimer disease in the younger age groups. However, it stands to reason that superimposed atherosclerosis would further compromise the cerebral circulation, possibly showing a consequent decline with advancing age.

In this study, restoration of SR resulted in improvement of perfusion as opposed to individuals remaining in AF after unsuccessful cardioversion. These results may have important clinical implications. The difference in both perfusion and blood flow after successful cardioversion was almost 15% measured by ASL and phase contrast MRI in the whole brain and grey matter. No changes in brain volumes were detected pre- and post-cardioversion, although it should be emphasized that the study cohort was younger than in previous studies showing an effect of AF on brain volume.[5,6,9,22] Also, the time between the pre- and post-cardioversion MRI examination was only a few weeks. Therefore, we did not include cognitive testing nor did we actually expect this to be affected in such a short observation period. The main focus was on changes in blood flow with SR in comparison to AF.

Whether all patients demonstrate these changes in perfusion is not clear and larger studies would be needed to further investigate this important effect of AF on brain perfusion and cerebral blood flow, preferably with brain volume and cognition considered in addition to perfusion as endpoints. Whether maintenance of SR can then delay onset of brain atrophy or cognitive decline also needs to be explored further although the results of this study are clearly intriguing.

Limitations

The sample in this study was rather small and hence yields low power in statistical calculations. This was especially apparent in calculations for total cerebral blood flow, due to high variability in measured values, even though there is high correlation with ASL.[10] The initial goal was to include a higher number of patients in this study but as indicated in the Methods section 17 patients dropped out as they went back in to AF during the period between the cardioversion and second MRI. Given the results of our much larger recent study ($n = 2291$) showing that patients in AF have lower total cerebral blood flow and brain perfusion than those in SR, we were very

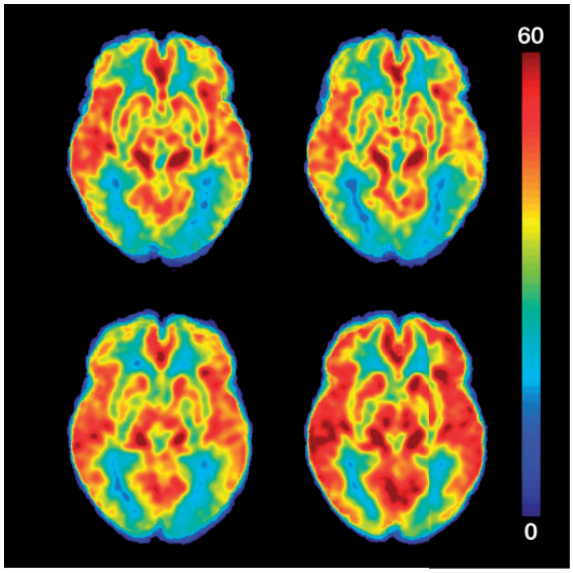

Figure 3 Average brain perfusion of the whole brain before and after cardioversion measured by ASL MRI. Upper panel shows average baseline brain perfusion of the AF group (left) and no detectable change (right) after an unsuccessful cardioversion. Lower panel shows baseline brain perfusion in the SR group (right) and a visible improvement of perfusion with restoration of sinus rhythm after a successful cardioversion (left). The perfusion is most prominent in the cortex of the brain where perfusion is naturally more apparent. The scale on the right shows colour coded perfusion, with the lowest value (0 mL/100 g/min) being blue and the highest (60 mL/100 g/min) being red. AF, atrial fibrillation; ASL, arterial spin labelling; MRI, magnetic resonance imaging; SR, sinus rhythm.

interested to evaluate if this phenomenon in AF patients could be reversed by cardioversion to SR. Despite the small sample, the results do suggest that cerebral blood flow and brain perfusion improve after restoration of SR which in our opinion is an important observation. An important strength of this study is the use of ASL for measurement of brain perfusion and the study design with individual observations both before and after cardioversion.

It can be difficult to ascertain whether individuals might have a brief recurrence of AF or not after cardioversion or even pulmonary vein ablation. Perhaps a Holter monitor for 24 h would have been of help but nevertheless an AF free Holter monitor would not have excluded a potential paroxysmal recurrence at another point in time during the observation period. Ideally, an implantable loop recorder might have been best for this purpose. In this study, however, clinical follow-up with an ECG and brief interval history was chosen.

Conclusion

Restoration of SR in individuals with AF resulted in improvement of cerebral blood flow. It has previously been suggested that subjects with AF may have decreased cerebral blood flow, diminished brain volume, and impaired cognitive function. These results imply that decreased cerebral blood flow might be one of the mechanisms of cognitive decline in individuals with AF. The fact that this is reversed with cardioversion to SR offers a proof of concept in kind and may have important clinical implications, but requires further investigation, preferably in a larger cohort and with longer follow-up.

Acknowledgements

The authors would like to express their sincere gratitude to the participants of the study.

Conflict of interest: none declared.

Funding

This work was supported by the Science Fund of Landspitali—The National University Hospital of Iceland and The Helga Jonsdottir and Sigurlidi Kristjansson Memorial Fund. Landspitali—National University Hospital Science Fund and The Helga Jonsdottir and Sigurlidi Kristjansson Memorial Fund have also funded the AGES Reykjavik Study, in addition to National Institutes of Health contract N01-AG-1-2100, the National Institute of Aging Intramural Research Program, the Icelandic Heart Association, and Althingi, the Icelandic Parliament.

References

1. Lane DA, Skjøth F, Lip GYH, Larsen TB, Kotecha D. Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. *J Am Heart Assoc* 2017;**6** pii: e005155.

2. 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.
3. Dietzel J, Haeusler KG, Endres M. Does atrial fibrillation cause cognitive decline and dementia? *Europace* 2018;**20**:408–19.
4. Kalantarian S, Ruskin JN. Atrial fibrillation and cognitive decline: phenomenon or epiphenomenon? *Cardiol Clin* 2016;**34**:279–85.
5. 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.
6. Gardarsdottir M, Sigurdsson S, Aspelund T, Rokita H, Launer LJ, Gudnason V *et al*. Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. *Europace* 2018;**20**:1252–8.
7. Wolters FJ, Zonneveld HI, Hofman A, van der Lugt A, Koudstaal PJ, Vernooij MW *et al*. Cerebral perfusion and the risk of dementia: a population-based study. *Circulation* 2017;**136**:719–28.
8. 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.
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. 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.
12. Petersen P, Kastrup J, Videbæk R, Boysen G. Cerebral blood flow before and after cardioversion of atrial fibrillation. *J Cereb Blood Flow Metab* 1989;**9**:422–5.
13. 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.
14. 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.
15. Wutzler A, Nee J, Boldt L-H, Kuhnle Y, Graser S, Schroder T *et al*. Improvement of cerebral oxygen saturation after successful electrical cardioversion of atrial fibrillation. *Europace* 2014;**16**:189–94.
16. 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.
17. Haller S, Zaharchuk G, Thomas DL, Lovblad KO, Barkhof F, Golay X. Arterial spin labeling perfusion of the brain: emerging clinical applications. *Radiology* 2016;**281**:337–56.
18. Kirchhof P, Haeusler KG, Blank B, De Bono J, Callans D, Elvan A *et al*. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. *Eur Heart J* 2018;**39**:2942–55.
19. Rivard L, Khairy P. Mechanisms, clinical significance, and prevention of cognitive impairment in patients with atrial fibrillation. *Can J Cardiol* 2017;**33**:1556–64.
20. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. *Lancet Neurol* 2012;**11**:272–82.
21. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS *et al*. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol* 2011;**22**:839–45.
22. 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.

Paper III

Aortic stiffness and brain perfusion in a population-based study.

Marianna Gardarsdottir[1, 2], Sigurdur Sigurdsson[3], Lars Forsberg[3, 4], Gary F Mitchell[5], Lenore J. Launer[6], Thor Aspelund[2, 3], Vilmundur Gudnason[2, 3], David O Arnar[1, 2].

[1]Landspitali University Hospital, Reykjavik, Iceland, [2]University of Iceland, Reykjavik, Iceland, [3]The Icelandic Heart Association, Kopavogur, Iceland, [4]Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden, [5]Cardiovascular Engineering, Inc., Needham, Massachusetts, USA, [6]National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA.

Corresponding author: David O. Arnar. Landspitali–University, 14F Hringbraut, 101 Reykjavik, Iceland. Phone: +354 543-1000, fax: +354 543-6467. Email: davidar@landspitali.is.

Abstract

Aortic stiffness, a marker of vascular aging that increases with cumulative exposure to vascular risk factors, has been associated with cerebral hypoperfusion and structural brain changes. However, the relationships between aortic stiffness, aging, and markers of brain health remain incompletely characterized in population-based cohorts without overt cognitive impairment.

In a population-based sample of randomly selected descendants from a large community study (mean age 62 years, range 55–81 years), aortic stiffness was assessed using carotid–femoral pulse wave velocity measured by applanation tonometry. Brain perfusion and structural brain measures were assessed using magnetic resonance imaging, and cognitive performance was evaluated using standardized neuropsychological tests. Participants were stratified by median CFPWV (8.6 m/s).

Participants with higher aortic stiffness were older, had higher heart rate and blood pressure, and more frequently used antihypertensive medication. Total brain perfusion, grey matter perfusion, and white matter perfusion were significantly lower in individuals with higher aortic stiffness. Relative brain volume was lower, and white matter hyperintensity volume higher in unadjusted analyses, whereas cognitive performance did not differ between groups. In multivariable models, increased aortic stiffness was independently associated with lower total brain perfusion, whereas chronological age was independently associated with lower brain volumes and greater WMH burden.

These findings suggest that aortic stiffening and chronological aging may represent related but distinct contributors to brain health, with aortic stiffness primarily associated with alterations in brain perfusion in this relatively young population-based sample. The association between aortic stiffness and cerebral perfusion, but not structural brain measures, is consistent with the concept that alterations in cerebral hemodynamics may represent an early manifestation of vascular aging preceding detectable structural brain injury. These observations highlight vascular aging as an early hemodynamic link between cardiovascular and brain health and underscore a potential window for vascular risk factor management to preserve cerebrovascular function across the lifespan.

Key words

Aortic stiffness, brain perfusion, arterial stiffness, brain volume, cognitive impairment.

Introduction

Aortic stiffness, or large artery stiffening, has been increasingly recognized as a contributor to cerebral small vessel disease and cognitive decline, suggesting that reduced aortic compliance may promote microvascular dysfunction and brain tissue injury (1–3). In the cardiometabolic disease paradigm, vascular risk factors promote structural and functional changes in the aorta, leading to increased arterial stiffness and adverse cardiovascular outcomes (4,5). Although age and mean arterial pressure are dominant cross-sectional correlates of carotid–femoral pulse wave velocity (CFPWV), arterial stiffening is increasingly recognized not only as a consequence but also as a contributor to cardiometabolic disease (5–7). As the aorta stiffens, its buffering capacity declines, increasing transmission of pulsatile energy to distal microvascular beds, including the cerebral circulation (8,9). Because the brain receives a large proportion of cardiac output and operates under low vascular resistance, the cerebral circulation is particularly vulnerable to the hemodynamic load that can contribute to changes in brain perfusion and subsequent structural brain injury and cognitive impairment (10–16). Aortic stiffness reflects vascular aging and serves as an integrative marker of cumulative hemodynamic stress (17,18). It can be measured noninvasively using applanation tonometry as CFPWV and has previously been associated with lower global and regional brain perfusion (10,19). However, the relationships between aging, aortic stiffness, and brain health remain incompletely characterized in population-based cohorts. Therefore, this study examined the associations of age and aortic stiffness with brain perfusion, brain structure, and cognitive function in a population-based sample.

Materials and methods

The effect of aortic stiffness and age on brain perfusion, brain structure and function was studied in a sample from the OffGen study. The OffGen study was designed to investigate neurologic, cardiovascular, sensory, lifestyle and medical history differences among offspring of AGES-Reykjavik Study participants. The AGES-Reykjavik Study is a large population-based study of descendants of the Reykjavik Study; a total population study performed in Iceland in 1967-1994 (20,21). The OffGen cohort (n = 956) was recruited in 2011-2015, with a mean age of 62 years (range 55-81 years) at recruitment. The study involved selective analysis of subclinical disease and traits such as brain morphology and function based on genetics and other profiles in parents. Here, we report the findings from 269 OffGen participants randomly selected from the cohort who underwent pulse wave velocity (PWV) assessment using applanation tonometry, brain perfusion quantification and analysis of brain structure with magnetic resonance imaging (MRI) as well as assessment of cognitive performance using standardized neuropsychological tests.

Assessment of aortic stiffness with applanation tonometry as CFPWV is an accurate and validated method and considered the reference standard for non-invasive evaluation of aortic stiffness,

measuring the travel time of the arterial pulse wave (3,6,22). CFPWV is a useful measure of vascular aging and atherosclerotic risk and serves as a valuable risk stratification tool for preventive intervention (1,3,23–25). Tonometric CFPWV provides an accurate direct and physiologically grounded assessment of aortic stiffness, whereas oscillometric estimates of pulse wave velocity (PWV), another method of assessing aortic stiffness, are largely driven by age and systolic blood pressure, and show limited independent agreement with measured CFPWV after accounting for these factors ((26,27).

The hemodynamic acquisition and analysis protocol of CFPWV, a measure of aortic wall stiffness, has been described in detail before (28). In brief, following 15–20 minutes of supine posture, auscultatory brachial blood pressure was assessed using a computer-controlled device automatically inflating the cuff to a user preset maximum pressure and then precisely controlled deflation at 2 mmHg/second. This device digitized and recorded mean and oscillometric cuff pressure, electrocardiogram (1000 Hz) and a cuff microphone channel (12 kHz) throughout the inflation and deflation sequence so that all blood pressure measurements could be over-read by the core lab (Cardiovascular Engineering, Inc.). Applanation tonometry with electrocardiogram for measurement of regional pulse wave velocity (PWV) was obtained from the brachial, radial, femoral, and carotid arteries using a custom transducer (Cardiovascular Engineering, Inc.). Body surface measurements from suprasternal notch to pulse recording sites were obtained by using a fiberglass tape measure for carotid, brachial, and radial sites and a caliper for the femoral site. The time delay of the pulse wave between the sites was measured, then divided by the distance (surface distance between carotid and femoral) as previously described by Mithcell et al. (29).

Arterial spin labeling (ASL) MRI is a non-invasive method of measuring brain perfusion by using magnetically labelled arterial blood water as an endogenous tracer for quantification of brain perfusion in the capillary bed. Inflowing hydrogen nuclei in the arterial blood water are magnetized, and the water molecules first labeled just proximally to the area to be imaged and then imaged for direct quantification of total or regional brain perfusion in the capillary bed (Figure 1). The perfusion image reflects the amount of arterial blood delivered to each voxel, measured in units of milliliters of blood flow per gram of tissue per unit (mL/g/min) determining the delivery rate of oxygen and nutrients to the capillary bed (30,31). ASL provides both high temporal and spatial resolution for measurement of perfusion and is both reliable and easily repeatable for multiple measurements (31–34).

All participants without contraindication for MRI underwent a brain scan on a 1.5-T Signa Excite Twinspeed system (General Electric Medical Systems, Waukesha, WI, USA). The perfusion scan protocol included acquisition of 3-dimensional pseudo-continuous ASL (pCASL) perfusion sequences for calculation of brain perfusion with post-labelling delay of 1525 ms (30,35). Quantitative ASL perfusion maps were calculated for the total brain, total grey matter (GM), and total white matter

(WM) using a validated automated image post-processing pipeline (30,35). Additionally, anatomical imaging sequences of the whole brain were made for calculations of brain tissue volumes; cerebrospinal fluid, GM, WM as well as WM hyperintensities (WMH) that were segmented with a validated automatic image post-processing pipeline (35,36). Total brain volume (TBV) was computed in milliliters (mL) as the sum of GM volume, WM volume, and WMH volume. The intracranial volume (ICV) was computed as the sum of TBV and cerebrospinal fluid volume (CSF) volume. Brain volumes in this study were normalized to intracranial volume and presented as percentages of intracranial volume. The anatomical imaging scan protocol included a T1-weighted 3-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. Details on the MRI acquisition and flow measurement have previously been described elsewhere in the AGES-Reykjavik brain MRI image acquisition protocol (35). The operators of the MRI system and the MR image analysts were blinded to all clinical information on the study participants. For cognitive testing, the Mini-Mental State Examination and the Digit Symbol Substitution Test were administered to all participants. 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).

This study was a cross-sectional observational analysis. For characteristics comparison, participants were divided into two groups (lower and higher aortic stiffness) based on the median CFPWV (8.6 m/s). For regression models, the negative inverse transformation of CFPWV (niCFPWV) was used to normalize the right-skewed distribution due to non-linear age- and pressure-related aortic stiffening and to reduce heteroskedasticity of CFPWV (niCFPWV= -1000/CFPWV) (37). Analysis of brain perfusion and relative brain volume was performed using generalized linear models with age and sex adjustment, as well as adjustment for heart rate, mean arterial pressure (MAP), use of antihypertensive medication and cognitive measures. The assumption of a normal distribution of the residuals from the continuous perfusion measures was verified by inspecting qq-plots of residuals from the regression models. All analyses were performed using R Statistical Software version 4.4.2. Data were presented as mean (standard deviation) for continuous variables and as % for categorical variables. A p-value <0.05 was considered statistically significant.

The study was approved by the National Bioethics Committee in Iceland, which acts as the Institutional Review Board for the Icelandic Heart Association and the National University Hospital (VSN 11-047), as well as the Icelandic Data Protection Authority. Informed written consent was obtained from all participants. Language improvement was assisted by ChatGPT (OpenAI; GPT-5.3), accessed in November 2025. No AI tools were used for data analysis or generation of results. The authors take full responsibility for the content.

Results

The sample consisted of 269 men and women aged 58 to 76 years (mean age 62 years). In unadjusted analyses, individuals with higher CFPWV were older, had higher heart rate and blood pressure, including higher mean arterial pressure (MAP), and were more likely to use antihypertensive medication (Table 1). They also had significantly lower brain perfusion in the total brain, the GM, and the WM (Table 1, Figures 2 and 3). Relative total brain and GM volume were lower and WMH volume higher in individuals with higher aortic stiffness, whereas cognitive performance did not differ between groups (Table 1). Across increasing quintiles of niCFPWV, median total brain perfusion progressively decreased, with the highest perfusion values observed in the lowest quintile and lower values in higher quintiles (Figure 4). In multivariable regression analyses, increased aortic stiffness remained independently associated with lower total brain perfusion after adjustment for age, sex, MAP, heart rate, and antihypertensive medication (Table 2). In contrast, aortic stiffness was not independently associated with relative total brain, GM, WM, or WMH volume. Older age was not independently associated with total brain perfusion but was independently associated with lower relative total brain, GM, and WM volume and higher WMH volume (Table 2). MAP was not significantly associated with total brain perfusion, but higher heart rate was associated with higher total brain perfusion and lower relative GM volume (Table 2).

Discussion

The main finding of this study is that increased aortic stiffness, quantified by CFPWV, was independently associated with lower total brain perfusion in a population-based sample after adjustment for age, sex, heart rate, MAP, and antihypertensive medication use. Total brain perfusion demonstrated a stepwise decrease across increasing quintiles of niCFPWV, and despite overlapping interquartile ranges, the central tendency progressively shifted toward lower perfusion with increasing arterial stiffness. These findings are consistent with the concept that declining buffering capacity of the proximal aorta in aortic stiffness and advancing age may alter cerebral hemodynamics by increasing transmission of pulsatile energy to the high-flow, low-resistance cerebral microvasculature (38,39). Chronic exposure to excessive pulsatility may promote vascular damage through vascular remodeling, impaired cerebrovascular reactivity, and increased vascular resistance, ultimately leading to reduced brain perfusion (9,14,18). Intact resistance vessel reactivity is essential for cerebral autoregulation and an adequate hyperemic response that, if impaired, may predispose the brain to transient hypotensive ischemia and hypertensive injury (11).

Relative total brain volume and GM volume were smaller in individuals with higher aortic stiffness in unadjusted analyses; however, these associations with structural brain measurements were attenuated after multivariable adjustment. Similarly, WMH volume was greater in participants with higher aortic stiffness in the unadjusted model, reflecting increased small vessel disease burden, but this association

was also attenuated after adjustment. This may reflect the relatively small WMH burden in this comparatively younger population-based sample. Other studies have reported associations between increased aortic stiffness and higher WMH volume, as well as between aortic stiffness and brain atrophy, another marker of small vessel disease, suggesting that aortic stiffening may accelerate age-related brain changes across the adult lifespan (14,40). Loss of GM volume as observed in our study may represent a downstream consequence of chronic microvascular injury and hypoperfusion (11,41). Hemodynamic changes may therefore precede structural brain injury and may become more apparent in older populations with longer exposure to vascular risk factors.

In this study, chronological age was a strong independent determinant of lower relative total brain and GM volume, as well as higher WMH volume. Aortic stiffness represents a vascular manifestation of biological aging and may capture cumulative hemodynamic stress not fully reflected by chronological age alone. In contrast, aortic stiffness was associated with alterations in brain perfusion rather than structural brain measures after multivariable adjustment. This pattern suggests that the hemodynamic effects of vascular aging may be more readily detectable in dynamic measures such as brain perfusion, whereas structural brain changes may reflect cumulative biological aging processes. In this relatively young sample, the effects of vascular aging on brain volume and atrophy may therefore not yet be readily apparent.

No significant differences in cognitive performance were observed between individuals with lower and higher aortic stiffness, which may reflect the relatively young age and preserved cognitive function of this sample. In a larger community-based study of older individuals, including parents of the Offspring cohort, Mitchell et al. reported associations between increased aortic stiffness, brain tissue damage and cognitive impairment (3). Microvascular damage and subsequent vascular remodeling may represent a mechanistic link between increased aortic stiffness, WMH burden, brain atrophy, and cognitive impairment (3).

In our study, increased aortic stiffness was associated with lower total brain perfusion independent of potential confounders such as MAP. In contrast, higher heart rate was positively associated with total brain perfusion, likely reflecting acute hemodynamic influences on brain perfusion rather than cumulative vascular changes. Because perfusion is a dynamic physiological measure sensitive to pulse wave transmission, it may be affected earlier than structural brain measures such as brain volume, which may reflect the stronger association between aortic stiffness and perfusion compared with structural brain changes observed in this study.

Chronic microvascular damage and cerebral hypoperfusion associated with increased aortic stiffness share common upstream determinants with other age-related cardiovascular conditions, highlighting aortic stiffness as a marker of vascular aging and cumulative vascular risk exposure. The predictive value of individual cardiovascular risk factors may diminish with advancing age because of selective

survival and increasing comorbidity, whereas aortic stiffness reflects the cumulative impact of lifelong vascular exposures (42–45). Because aortic stiffening often precedes the development of hypertension, assessment of CFPWV may provide complementary information about cerebrovascular risk beyond traditional cardiovascular risk factors (23,46,47). Consistent with this concept, the prevalence of increased aortic stiffness rises markedly with age and contributes substantially to cardiovascular and cerebrovascular disease burden (5).

The transmission of pulsatile energy to the cerebral circulation is influenced by impedance mismatch between the compliant aorta and stiffer branch arteries. In healthy young individuals, this impedance mismatch promotes wave reflection that limits transmission of pulsatile energy to the microcirculation. With advancing vascular aging, progressive impedance matching reduces wave reflection and allows greater transmission of pulsatile energy into distal vascular beds, including the cerebral microcirculation (6,48). This mechanism may partly explain the association between increased aortic stiffness and reduced brain perfusion observed in the present study.

Importantly, arterial stiffness is influenced by modifiable factors, including lifestyle behaviors and vascular risk factor control, and may be partially attenuated by antihypertensive therapies that reduce pulse pressure (14,49). Aortic stiffness may therefore provide complementary information about vascular health beyond chronological age or hypertension alone. The graded reduction in brain perfusion across stiffness quintiles observed in this study supports the hypothesis that increased arterial stiffness contributes to altered cerebral hemodynamics. Measurement of CFPWV may thus have value for cardiovascular risk stratification and prevention, although, whether reductions in arterial stiffness translate into prevention of age-related cognitive impairment remains uncertain (17,39,50).

Conclusion

In conclusion, increased aortic stiffness was independently associated with lower total brain perfusion in this population-based sample, supporting the concept that vascular aging may influence cerebral hemodynamics. In contrast, structural brain changes were more strongly associated with chronological age than with aortic stiffness in this relatively young sample. These findings suggest that alterations in brain perfusion may represent an early hemodynamic manifestation of vascular aging that precedes detectable structural brain injury. Because arterial stiffness reflects the cumulative impact of lifelong vascular exposure and remains influenced by modifiable risk factors, its assessment may provide valuable insight into cerebrovascular health and the long-term consequences of vascular aging. These observations underscore the potential importance of preventive measures and vascular risk factor management to preserve brain perfusion and maintain brain health across the adult lifespan.

Acknowledgements

We thank the participants in the study and the radiographers in The Icelandic Heart Association; Bryndis Oskarsdottir, Grimheidur Johannsdottir, Gyda Karlsdottir and Gudlaug Bjornsdottir.

Declaration of interest statement

Gary F. Mitchell is the owner of Cardiovascular Engineering, Inc., a company that designs and manufactures devices that measure arterial stiffness. The company uses these devices in studies that evaluate the effects of diseases and interventions on vascular stiffness. G.F.M. also serves as a consultant to and receives grants and honoraria from Novartis, Merck, Bayer, Servier, Philips, and deCODE genetics and is a co-inventor on pending patent applications that disclose methods for estimating carotid-femoral pulse wave velocity and additional measures of vascular age by using convolutional neural networks.

References

1. Sethi S, Rivera O, Oliveros R, Chilton R. Aortic stiffness: pathophysiology, clinical implications, and approach to treatment. Integr Blood Press Control. 2014;7:29–34. doi:10.2147/IBPC.S59535 PubMed Central PMCID: PMC4046515.

2. Mitchell GF, Powell JT. Arteriosclerosis: A Primer for “In Focus” Reviews on Arterial Stiffness. Arterioscler Thromb Vasc Biol. 2020 May;40(5):1025–7. doi:10.1161/ATVBAHA.120.314208

3. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. Brain. 2011 Nov;134(Pt 11):3398–407. doi:10.1093/brain/awr253 PubMed Central PMCID: PMC3212721.

4. Lacolley P, Regnault V, Laurent S. Mechanisms of Arterial Stiffening: From Mechanotransduction to Epigenetics. Arterioscler Thromb Vasc Biol. 2020 May;40(5):1055–62. doi:10.1161/ATVBAHA.119.313129

5. Hamel-Sellman DJ, Prescott BR, Korzinski TJ, Xanthakis V, Cooper LL, Hamburg NM, et al. Relations of Artificial Intelligence Vascular Age With Cardiometabolic Disease Progression: The Framingham Heart Study. J Am Heart Assoc. 2025 Dec 16;14(24):e044872. doi:10.1161/JAHA.125.044872

6. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004 Jun;43(6):1239–45. doi:10.1161/01.HYP.0000128420.01881.aa

7. The Reference Values for Arterial Stiffness’ Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: ‘establishing normal and reference values.’ Eur Heart J. 2010 Oct 1;31(19):2338–50. doi:10.1093/eurheartj/ehq165

8. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension. 2015 Sep;66(3):698–722. doi:10.1161/HYP.0000000000000033

9. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol 1985. 2008 Nov;105(5):1652–60. doi:10.1152/japplphysiol.90549.2008 PubMed Central PMCID: PMC2584844.

10. Li X, Xing J, Hui Y, Shi H, Li R, Zhang S, et al. Hippocampal volume mediates the association of arterial stiffness with cognitive impairment in adult population. J Hypertens. 2024 Sep 1;42(9):1566–72. doi:10.1097/HJH.0000000000003760 PubMed Central PMCID: PMC11296271.

11. Mitchell GF. Aortic Stiffness and Cerebral Blood Flow. Am J Hypertens. 2011 Oct 1;24(10):1056–1056. doi:10.1038/ajh.2011.112

12. Henskens LHG, Kroon AA, Van Oostenbrugge RJ, Gronenschild EHBM, Fuss-Lejeune MMJJ, Hofman PAM, et al. Increased Aortic Pulse Wave Velocity Is Associated With Silent Cerebral Small-Vessel Disease in Hypertensive Patients. Hypertension. 2008 Dec;52(6):1120–6. doi:10.1161/HYPERTENSIONAHA.108.119024

13. Tsao CW, Seshadri S, Beiser AS, Westwood AJ, Decarli C, Au R, et al. Relations of arterial stiffness and endothelial function to brain aging in the community. Neurology. 2013 Sep 10;81(11):984–91. doi:10.1212/WNL.0b013e3182a43e1c PubMed Central PMCID: PMC3888200.

14. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E. Arterial stiffness, the brain and cognition: A systematic review. Ageing Res Rev. 2014 May;15:16–27. doi:10.1016/j.arr.2014.02.002

15. Pase MP, Beiser A, Himali JJ, Tsao C, Satizabal CL, Vasan RS, et al. Aortic Stiffness and the Risk of Incident Mild Cognitive Impairment and Dementia. Stroke. 2016 Sep;47(9):2256–61. doi:10.1161/STROKEAHA.116.013508 PubMed Central PMCID: PMC4995162.

16. Cui C, Sekikawa A, Kuller LH, Lopez OL, Newman AB, Kuipers AL, et al. Aortic Stiffness is Associated with Increased Risk of Incident Dementia in Older Adults. J Alzheimers Dis. 2018;66(1):297–306. doi:10.3233/JAD-180449 PubMed Central PMCID: PMC6313252.

17. Li A, Yan J, Zhao Y, Yu Z, Tian S, Khan AH, et al. Vascular Aging: Assessment and Intervention. Clin Interv Aging. 2023 Aug;Volume 18:1373–95. doi:10.2147/CIA.S423373

18. Jefferson AL, Cambronero FE, Liu D, Moore EE, Neal JE, Terry JG, et al. Higher Aortic Stiffness Is Related to Lower Cerebral Blood Flow and Preserved Cerebrovascular Reactivity in Older Adults. Circulation. 2018 Oct 30;138(18):1951–62. doi:10.1161/CIRCULATIONAHA.118.032410

19. Tarumi T, Shah F, Tanaka H, Haley AP. Association Between Central Elastic Artery Stiffness and Cerebral Perfusion in Deep Subcortical Gray and White Matter. Am J Hypertens. 2011 Oct 1;24(10):1108–13. doi:10.1038/ajh.2011.101

20. 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 May;165(9):1076–87. doi:10.1093/aje/kwk115 PubMed Central PMCID: PMC2723948.

21. Bjornsson OG. Stages I-III, 1967-1969, 1970-1971 and 1974-1976. Participants, Invitation, Response etc. The Icelandic Heart Association; Reykjavik: 1979. Report ABC XVIII. Health Survey in the Reykjavik Area-Men. Davidsson D, Olafsson H, Olafsson O, Sigfusson N, Thorsteinsson T, editors. 1979.

22. Climie RE, Gallo A, Picone DS, Di Lascio N, van Sloten TT, Guala A, et al. Measuring the Interaction Between the Macro- and Micro-Vasculature. Front Cardiovasc Med. 2019;6:169. doi:10.3389/fcvm.2019.00169 PubMed Central PMCID: PMC6882776.

23. Angoff R, Mosarla RC, Tsao CW. Aortic Stiffness: Epidemiology, Risk Factors, and Relevant Biomarkers. Front Cardiovasc Med. 2021;8:709396. doi:10.3389/fcvm.2021.709396 PubMed Central PMCID: PMC8606645.

24. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006 Nov;27(21):2588–605. doi:10.1093/eurheartj/ehl254

25. Nelson MR, Stepanek J, Cevette M, Covalciuc M, Hurst RT, Tajik AJ. Noninvasive Measurement of Central Vascular Pressures With Arterial Tonometry: Clinical Revival of the Pulse Pressure Waveform? Mayo Clin Proc. 2010 May;85(5):460–72. doi:10.4065/mcp.2009.0336

26. Del Giorno R, Troiani C, Gabutti S, Stefanelli K, Gabutti L. Comparing oscillometric and tonometric methods to assess pulse wave velocity: a population-based study. Ann Med. 2021 Jan;53(1):1–16. doi:10.1080/07853890.2020.1794538

27. Schwartz JE, Feig PU, Izzo JL. Pulse Wave Velocities Derived From Cuff Ambulatory Pulse Wave Analysis: Effects of Age and Systolic Blood Pressure. Hypertension. 2019 Jul;74(1):111–6. doi:10.1161/HYPERTENSIONAHA.119.12756

28. Mitchell GF, Lacourcière Y, Ouellet JP, Izzo JL, Neutel J, Kerwin LJ, et al. Determinants of Elevated Pulse Pressure in Middle-Aged and Older Subjects With Uncomplicated Systolic Hypertension: The Role of Proximal Aortic Diameter and the Aortic Pressure-Flow Relationship. Circulation. 2003 Sep 30;108(13):1592–8. doi:10.1161/01.CIR.0000093435.04334.1F

29. Mitchell GF, Izzo JL, Lacourciere Y, Ouellet JP, Neutel J, Qian C, et al. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. Circulation. 2002 Jun 25;105(25):2955–61. doi:10.1161/01.cir.0000020500.77568.3c

30. 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(12):e0144743. doi:10.1371/journal.pone.0144743 PubMed Central PMCID: PMC4687637.

31. Calamante F, Thomas DL, Pell GS, Wiersma J, Turner R. Measuring cerebral blood flow using magnetic resonance imaging techniques. J Cereb Blood Flow Metab. 1999 Jul;19(7):701–35. doi:10.1097/00004647-199907000-00001

32. John A. Detre. Arterial Spin Labeled Perfusion MRI. 2008. MAGNETOM Flash2008(1):6–9.

33. Wintermark M, Sesay M, Barbier E, Borbely K, Dillon WP, Eastwood JD, et al. Comparative overview of brain perfusion imaging techniques. Stroke. 2005 Sep;36(9):e83-99. doi:10.1161/01.STR.0000177884.72657.8b

34. Jahng GH, Song E, Zhu XP, Matson GB, Weiner MW, Schuff N. Human brain: reliability and reproducibility of pulsed arterial spin-labeling perfusion MR imaging. Radiology. 2005 Mar;234(3):909–16. doi:10.1148/radiol.2343031499 PubMed Central PMCID: PMC1851681.

35. 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 Feb;59(4):3862–70. doi:10.1016/j.neuroimage.2011.11.024 PubMed Central PMCID: PMC4712156.

36. Zijdenbos AP, Forghani R, Evans AC. Automatic “pipeline” analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. IEEE Trans Med Imaging. 2002 Oct;21(10):1280–91. doi:10.1109/TMI.2002.806283

37. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Cheng S, et al. Relations of Central Hemodynamics and Aortic Stiffness with Left Ventricular Structure and Function: The Framingham Heart Study. J Am Heart Assoc. 2016 Mar 9;5(3):e002693. doi:10.1161/JAHA.115.002693

38. Vasan RS, Pan S, Xanthakis V, Beiser A, Larson MG, Seshadri S, et al. Arterial Stiffness and Long-Term Risk of Health Outcomes: The Framingham Heart Study. Hypertension. 2022

May;79(5):1045–56. doi:10.1161/HYPERTENSIONAHA.121.18776 PubMed Central PMCID: PMC9009137.

39. O'Rourke MF, Safar ME. Relationship Between Aortic Stiffening and Microvascular Disease in Brain and Kidney: Cause and Logic of Therapy. Hypertension. 2005 Jul;46(1):200–4. doi:10.1161/01.HYP.0000168052.00426.65

40. Won J, Tomoto T, Shan K, Tarumi T, Zhang R. Associations of Central Arterial Stiffness With Brain White Matter Integrity and Gray Matter Volume in MRI Across the Adult Lifespan. J Magn Reson Imaging. 2025 Jul;62(1):215–29. doi:10.1002/jmri.29713

41. Tarumi T, Ayaz Khan M, Liu J, Tseng BY, Parker R, Riley J, et al. Cerebral hemodynamics in normal aging: central artery stiffness, wave reflection, and pressure pulsatility. J Cereb Blood Flow Metab. 2014 Jun;34(6):971–8. doi:10.1038/jcbfm.2014.44 PubMed Central PMCID: PMC4050241.

42. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006 Feb 7;113(5):657–63. doi:10.1161/CIRCULATIONAHA.105.555235

43. Glynn RJ, Field TS, Rosner B, Hebert PR, Taylor JO, Hennekens CH. Evidence for a positive linear relation between blood pressure and mortality in elderly people. Lancet. 1995 Apr 1;345(8953):825–9. doi:10.1016/s0140-6736(95)92964-9

44. Kannel WB, D'Agostino RB, Silbershatz H. Blood pressure and cardiovascular morbidity and mortality rates in the elderly. Am Heart J. 1997 Oct;134(4):758–63. doi:10.1016/s0002-8703(97)70061-9

45. Webb AJS, Werring DJ. New Insights Into Cerebrovascular Pathophysiology and Hypertension. Stroke. 2022 Apr;53(4):1054–64. doi:10.1161/STROKEAHA.121.035850

46. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA. 2012 Sep 5;308(9):875–81. doi:10.1001/2012.jama.10503 PubMed Central PMCID: PMC3594687.

47. Herzog MJ, Müller P, Lechner K, Stiebler M, Arndt P, Kunz M, et al. Arterial stiffness and vascular aging: mechanisms, prevention, and therapy. Signal Transduct Target Ther. 2025 Sep 1;10(1):282. doi:10.1038/s41392-025-02346-0

48. Mitchell GF, Gudnason V, Launer LJ, Aspelund T, Harris TB. Hemodynamics of increased pulse pressure in older women in the community-based Age, Gene/Environment Susceptibility-Reykjavik Study. Hypertension. 2008 Apr;51(4):1123–8. doi:10.1161/HYPERTENSIONAHA.107.108175 PubMed Central PMCID: PMC11106724.

49. Mitchell GF, Guo CY, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. Circulation. 2007 May 22;115(20):2628–36. doi:10.1161/CIRCULATIONAHA.106.667733

50. Ait-Oufella H, Collin C, Bozec E, Laloux B, Ong KT, Dufouil C, et al. Long-term reduction in aortic stiffness: a 5.3-year follow-up in routine clinical practice. J Hypertens. 2010 Nov;28(11):2336–41. doi:10.1097/HJH.0b013e32833da2b2

Table 1. Subject characteristics comparison between subjects with lower and higher CFPWV split by median CFPWV (8.6 m/s).

Characteristics stratified by median CFPWV (8.6 m/s)	Lower CFPWV group 1 (<8.6 m/s) n=134	Higher CFPWV group 2 (>8.6 m/s) n=135	P-value
Age (years)	61.9 (3.7)	63.7 (4.2)	<0.001
Sex (% men)	58	47	>0.05
Systolic BP (mm Hg)	118.5 (12.9)	130.0 (14.3)	<0.001
Diastolic BP (mm Hg)	61.2 (8.4)	65.2 (8.7)	<0.001
Mean arterial pressure (mm Hg)	83.0 (9.4)	90.2 10.4)	<0.001
Heart rate (bpm)	59.8 (8.2)	66.1 (9.7)	<0.001
Anti-hypertension medication use	41	59	<0.05
Total brain perfusion (mL/100g/min)	51.0 (9.3)	46.7 (9.9)	<0.001
Grey matter perfusion (mL/100g/min)	57.0 (10.7)	52.0 (11.3)	<0.001
White matter perfusion (mL/100g/min) unit	42.6 (7.7)	39.4 (7.9)	<0.001
Relative total brain volume (%)	81.8 (2.5)	80.9 (2.7)	<0.01
Relative grey matter volume (%)	49.3 (1.8)	48.7 (1.9)	<0.05
Relative white matter volume (%)	32.5 (1.6)	32.2 (1.6)	>0.05
WMH volume* (%)	0.39	1.01	<0.05
MMSE score	28.2 (1.6)	28.3 (1.6)	>0.05
DSST score	48.4 (10.5)	47.0 (11.0)	>0.05

CFPWV: carotid-femoral pulse wave velocity, BP: systolic blood pressure, WMH: white matter hyperintensities, MMSE: mini mental-state examination, DSST: digit symbol substitution test. Values are shown as mean (*median) (standard deviation) for continuous variables and % for categorical variables.

Table 2. Multivariable associations of aortic stiffness with total brain perfusion and relative total brain volume, adjusted for age, sex, heart rate, mean arterial pressure and antihypertensive medication use.

Total brain perfusion	**Variable**	**β**	**Standard error**	**P-value**
	Age	-0.22	0.15	>0.05
	Sex	5.10	1.15	<0.001
	HR	0.17	0.07	<0.05
	MAP	-0.03	0.06	>0.05
	HTN med	-1.84	1.28	>0.05
	niCFPWV	-0.08	0.03	<0.01
Relative total brain volume	**Variable**	**β**	**Standard error**	**P-value**
	Age	-0.26	0.04	<0.001
	Sex	1.41	0.30	<0.001
	HR	-0.03	0.02	>0.05
	MAP	-0.01	0.02	>0.05
	HTN med	-0.20	0.31	>0.05
	niCFPWV	0.003	0.01	>0.05
Relative grey matter volume	**Variable**			
	Age	-0.19	0.03	<0.001
	Sex	1.17	0.21	<0.001

	HR	-0.04	0.01	<0.05
	MAP	0.004	0.01	>0.05
	HTN med	-0.37	0.21	>0.05
	niCFPWV	0.0001	0.01	>0.05
Relative white matter volume	**Variable**			
	Age	-0.07	0.03	<0.01
	Sex	0.25	0.21	>0.05
	HR	-0.002	0.01	>0.05
	MAP	-0.009	0.01	>0.05
	HTN med	0.18	0.21	>0.05
	niCFPWV	0.002	0.01	>0.05
WMH volume	**Variable**			
	Age	0.31	0.07	<0.001
	Sex	0.07	0.55	>0.05
	HR	-0.02	0.03	>0.05
	MAP	-0.01	0.03	>0.05
	HTN med	0.22	0.56	>0.05
	niCFPWV	0.02	0.01	>0.05

CFPWV: carotid-femoral pulse wave velocity, HR: heart rate, MAP: mean arterial pressure, HTN med: antihypertensive medication, niCFPWV: negative inverse carotid-femoral pulse wave velocity, WMH: white matter hyperintensities.

Figure 1. ASL planning with labeling plane at the upper cervical spine (orange) perpendicular to the carotid and basilar artery and image volume (green). PCASL: pseudo-continuous ASL.

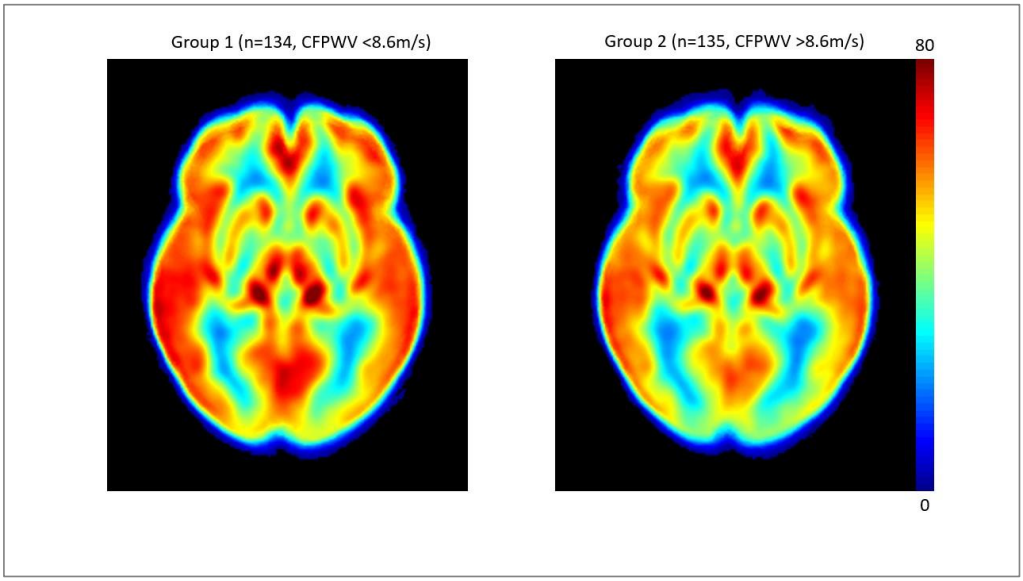

Figure 2. Average brain perfusion map split by median CFPWV (8.6 m/s) measured by ASL MRI. On the left the group with lower cfPWV (<8.6 m/s) is pictured, and on the right the group with higher cfPWV(>8.6 m/s) is pictured. The perfusion is most prominent in the cortex of the brain, where perfusion is naturally most apparent. The scale on the right shows color coded perfusion, with the lowest value (0 mL/100g/min) being blue and the highest (60 mL/100g/min) being red. CFPWV; carotid-femoral pulse wave velocity, ASL; arterial spin labeling; MRI; magnetic resonance imaging.

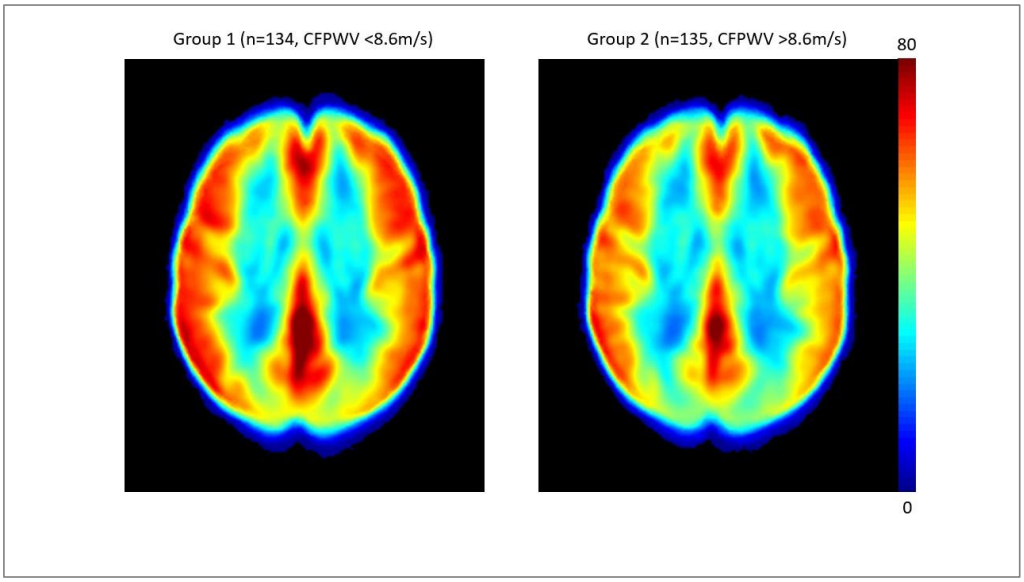

Figure 3. Sample MRI from group 1 and group 2. Average brain perfusion map split by median CFPWV (8.6 m/s) measured by ASL MRI. On the left the group with lower CFPWV (<8.6 m/s) is pictured, and on the right the group with higher CFPWV (>8.6 m/s) is pictured. The perfusion is most prominent in the cortex of the brain, where perfusion is naturally most apparent. The scale on the right shows color coded perfusion, with the lowest value (0 mL/100g/min) being blue and the highest (60 mL/100g/min) being red. CFPWV; carotid-femoral pulse wave velocity, ASL; arterial spin labeling; MRI; magnetic resonance imaging.

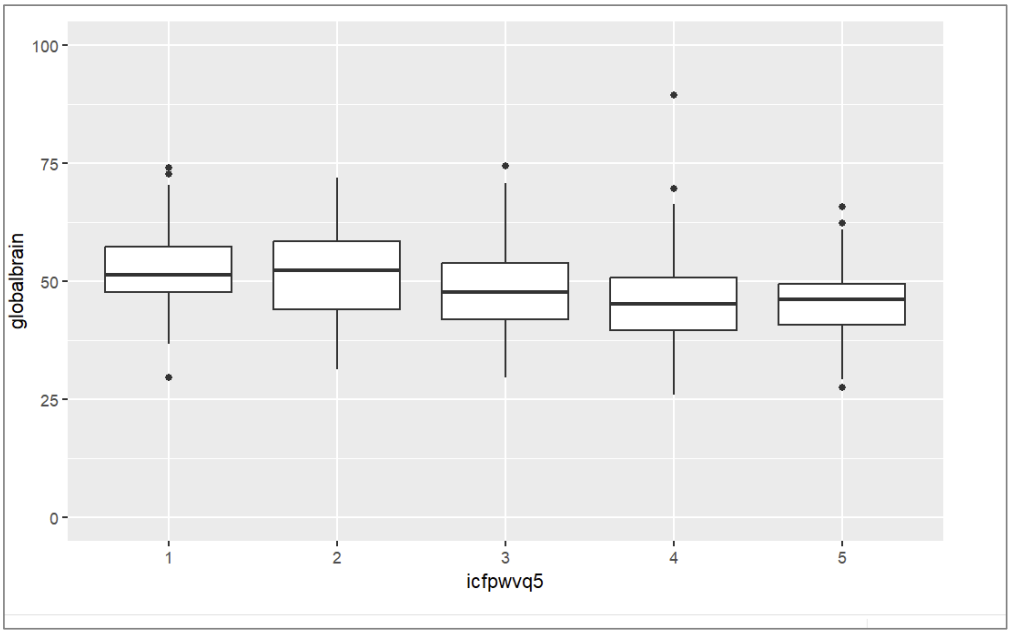

Figure 4. Global brain perfusion across quintiles of negative inverse carotid femoral pulse wave velocity (niCFPWV). globalbrain: total brain perfusion, icfpwvq5: aortic stiffness as negative inverse carotid-femoral pulse wave velocity across increasing quartiles of negative inverse carotid-femoral pulse wave velocity.