Stroke-related visual impairment; is there an association with atrial fibrillation?

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Word count: 1415

Number of tables: 1

Number of figures: 1

Cover title: Stroke-related vision impairment and AF

Contributor statement: FR and GL planned this study. LH, CH, CC, BS and NG gathered data for the study. FR drafted this paper. All authors reviewed the final paper.

Transparency statement: The lead author confirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Declarations of interest: Claire Howard is funded by a National Institute for Health Research (NIHR) clinical doctoral fellowship award outside the submitted work. Lauren Hepworth is funded by a Stroke Association post-doctoral fellowship award outside the submitted work. Gregory Lip reports consultancy and speaker fees from Bayer, Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronik, Boehringer Ingelheim, Microlife, Roche and Dauuchi-Sankyo outside the submitted work.

Data sharing statement: Data is available from the lead author on reasonable request.

Funding: Fiona Rowe is funded by a National Institute for Health Research (NIHR) Career Development Fellowship award (NIHR-CDF-2012-05-126) for this research project. This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Keywords: Stroke, Visual impairment, Atrial fibrillation, Blood pressure, Visual acuity, Visual field, Eye movements, Visual perception

Abstract

Background/Objectives: Stroke-related visual impairment and atrial fibrillation are both common following stroke. This study explores whether presence of visual impairment following stroke is associated with presence of atrial fibrillation (AF).

Subjects/Methods: The Impact of Visual Impairment after Stroke (IVIS) study is a multi-centre, acute stroke unit, prospective epidemiology study. Standardised visual assessments included visual acuity, reading, visual fields, eye movements and visual perception. AF and blood pressure (BP) were measured on admission. Further data capture included stroke type, age, gender, stroke severity. Analysis included descriptive statistics, independent samples analysis and multivariate analysis for comparison of AF and visual impairment against covariates.

Results: 1500 stroke admissions were recruited of which 1204 stroke survivors had visual assessment. New onset stroke-related visual impairment (n=703) was significantly associated with older age and stoke severity. AF and BP data were available for 889 stroke survivors. AF was present on admission for 258 stroke

survivors and significantly associated with older age, stroke severity and discharge destination. A significant association was found for presence of AF and presence of visual impairment. However, stroke severity was a contributing factor for this association. High systolic BP (>140mmHg) was present in 62% and high diastolic BP (>90mmHg) in 29%, but not associated with presence of visual impairment.

Conclusions: AF and visual impairment, independently, occur commonly in stroke. Although our results show an association between AF and visual impairment, this appears to be independently influenced by stroke severity. AF was not associated with type of visual impairment or extent of visual recovery. It remains unknown if AF causes more severe visual impairment.

Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia globally with a rising prevalence and incidence worldwide [1]. AF is a major cause of ischaemic stroke and transient ischaemic attack, and these are associated with higher rates of mortality and morbidity, including disability and longer hospital stays [2,3].

Visual impairment due to stroke is common, with a reported prevalence in about two thirds of stroke survivors and incidence of new onset visual impairment in about 60% [4,5]. New onset visual impairment can involve both afferent and efferent pathways, individually or in combination, including central vision impairment, visual field loss, eye movement disorders and visual perceptual and neglect disorders [4,5]. Whilst stroke with AF is reported as more common in the elderly and in females [6], as is stroke-related visual impairment [5], there is a lack of information about the association of AF with visual impairment within the stroke population.

The purpose of this exploratory study was to analyse the presence and association of AF and visual impairment within a prospective stroke epidemiology cohort.

Materials and methods

Details of the Impact of Visual Impairment after Stroke (IVIS) study has been published previously [5]. Ethical approval was obtained from the Health Regulatory Authority (North West – Haydock Research Ethics Committee reference 14/NW/0166) and the study was undertaken in accordance with the Tenets of Helsinki.

Every stroke survivor with ability to undertake a visual assessment had assessment of visual acuity, reading, ocular alignment and movements, visual fields, visual attention and visual perception. Presence or absence of atrial fibrillation at the time of hospital admission plus blood pressure measurements were also recorded. High blood pressure was defined as 140/90 mmHg or greater.

Descriptive statistics were used to report types of visual problems with diagnoses such as hemianopia, gaze palsy, strabismus and visual agnosia. Results of visual acuity assessments were captured as numerical data. Independent samples analysis with chi square and Kruskal-Wallis tests were used for evaluation of stroke onset, gender, type of stroke and age. An independent t test was used for parametric comparisons between groups and Mann Whitney test for non-parametric comparisons between groups. Significant variables were entered into a multi-variable analysis. A backward selection procedure was used to construct the multivariable model to determine if AF presence/absence was an independent predictor of new

onset visual impairment. Variables were entered and retained in the model with $p<0.05$.

Results

IVIS cohort

Overall, 1500 stroke admissions were recruited over 15 months (1st July 2014 - 30th September 2015). Mean age at time of stroke was 73.27 years (SD 13.67) with 48.1% female and 51.9% male. Stroke type was infarction in 87.5% and haemorrhage in 12.5%, right-sided in 46.3%, left-sided in 47.9% and bilateral stroke in 5.5%. Thrombolysis (rt-PA) was undertaken in 9.6% (n=144). Stroke severity measured by Barthel score was a mean of 9.75 (SD 7.76). Ethnicity included white British (94.2%), white Irish (0.9%), other white (1.5%), Indian (0.6%), Pakistani (0.5%) and Chinese (0.5%).

Of 1500 stroke admissions, 296 (19.7%) did not have vision assessments: 116 died and 180 were unable to undergo assessment, predominantly because of the severity of their stroke. The remaining 1204 stroke survivors formed the study cohort for the present analysis: 337 (27.9%) had normal eye examinations, while 867 (72.0%) were found to have vision problems during assessment: 164 were attributed to prior ocular history. New onset stroke-related visual problems were found in 703 stroke survivors; 354 with impaired central vision in one or both eyes, 473 with eye movement disorders, 298 with visual field loss, 315 with visual neglect and 57 with visual perceptual disorders.

Stroke survivors with new onset visual impairment were older in age (p=0.0001) with more severe strokes (p=0.0001) than those with prior un-related, or no, visual

impairment. There was no significant difference for gender (p=0.365), stroke type (p=0.083) or if thrombolysis intervention had been received (p=0.092).

Atrial fibrillation and blood pressure data

Data on presence/absence of AF and blood pressure was available for 889 patients. AF was detected during an admission in 29% (n=258). Mean systolic and diastolic blood pressure was 150.09 (SD 29.26) and 80.88 (SD16.96) respectively. High systolic blood pressure (≥140mmHg) was present in 62.1% and high diastolic (≥ 90mmHg) in 29.0% (figure 1).

Presence of AF on stroke admission was significantly different for stroke severity (lower Barthel score, p=0.006) and age at stroke onset (older, p=0.0001); see table 1. Presence of AF was also significant for discharge destination, with less stroke survivors with AF being discharged to independent living (p=0.0001), with a greater number dying before vision assessment was possible (p=0.002) and with presence of new onset visual impairment regardless of type of visual impairment (p=0.0001).

There was no significance for presence/absence of AF in relation to stroke type (p=0.924), Index of Multiple deprivation (IMD, p=0.865), ethnicity (p=0.157), systolic blood pressure (p=0.369), diastolic blood pressure (p=0.692) or whether those with visual impairment had recovery of their visual problem, regardless of type (p=0.733).

Four baseline factors (age, stroke severity, discharge and death prior to assessment) were evaluated to see if AF presence/absence was an independent predictor of new onset visual impairment. Statistical analysis, using a backward selection multi-variable logistic regression, showed that only severity of stroke (Barthel score) was

independently associated with both presence of AF and new onset visual impairment, p=0.0001.

Discussion

AF is associated with more severe and disabling strokes and visual impairment is more prevalent in severe strokes. We hypothesised that visual impairment would be worse in AF versus non-AF strokes. In the absence of previous studies addressing this hypothesis, we sought to explore the IVIS study data. Although both AF and the occurrence of visual impairment are associated with more severe strokes and older age, we found no significant difference for type of visual impairment and AF, with equal proportions of different visual impairment categories and diagnoses within visual category. Second, there was no significant difference for having one or multiple visual impairments or for recovery rates, inferring that having AF does not cause more visual impairment or impede recovery of vision.

Our exploratory study does not infer visual impairment is more severe with or without AF. Overall in the IVIS study, stroke survivors with new onset visual impairment were older and had more severe strokes [5]. Those in the IVIS study with AF at presentation also had more severe stroke and were older. Indeed, stroke with AF is reported as more common in the elderly and in females and associated with poorer outcomes [6]. However, *severity* of visual impairment was not reported in the IVIS study so the question of whether AF might cause a worse extent of visual impairment cannot be answered by this exploratory analysis.

The presence of AF has been reported in association with visual impairment but specifically in relation to ocular vasculature and related eye conditions. For example,

AF is associated with retinal ischaemic monocular blindness [7], retinal vein occlusion [8] and with an increased risk of normal-tension glaucoma [9]. The association with normal tension glaucoma remains controversial. However, not only does cardiogenic embolism related to AF present as an ischaemic stroke or systemic thromboembolism, another presentation to the ophthalmologist would be as a retinal artery occlusion. These patients are high risk for incident cardiovascular events [10]. The presence of retinal artery (or venous) occlusion in AF patients confers a high risk for subsequent ischaemic stroke [11]. Patients presenting with retinal artery (or venous) occlusion are also at higher risk for new onset AF [12].

The significant association of retinal vessel occlusion with AF, with an increased risk factor of AF for retinal artery and vein occlusions is suggested to represent an increase in age-related vascular changes and cardiovascular disease [13,14]. AF generates cardiac emboli which can cause retinal artery blockage. However, the mechanistic association for retinal vein occlusion remains unclear and is likely multifactorial [13]. Retinal vein occlusion shares risk factors with stroke and AF detection in retinal vein occlusion may, therefore, be of importance in acknowledging the association between both conditions rather than a causal relationship [8,12].

A clinical recommendation that may be suggested by these results is for any stroke survivor or patient with transient ischaemic attack who has AF should have a thorough eye examination.

Limitations

This was an ancillary analysis to the IVIS study which concentrated on documentation of visual impairment in stroke survivors. Importantly, *severity* of visual impairment was not reported in the IVIS study, and associations with other forms of

visual impairment such as strabismus and ocular motility disorders, neurological visual field loss such as homonymous hemianopia, visual inattention and visual perceptual deficits such as agnosia, alexia and hallucinations, has not been explored. Paroxysmal AF data was not collected. Further prospective studies with detailed visual assessments of AF-related stroke are needed.

Conclusions

Both AF and visual impairment, independently, are common in stroke. Whilst there does not appear to be an increased occurrence of visual impairment in strokes with versus without atrial fibrillation, it is as yet unknown whether stroke survivors with atrial fibrillation develop more severe visual impairment. Future research is required to test the hypothesis whether visual impairment is worse in AF-related stroke compared to non-AF related stroke.

References

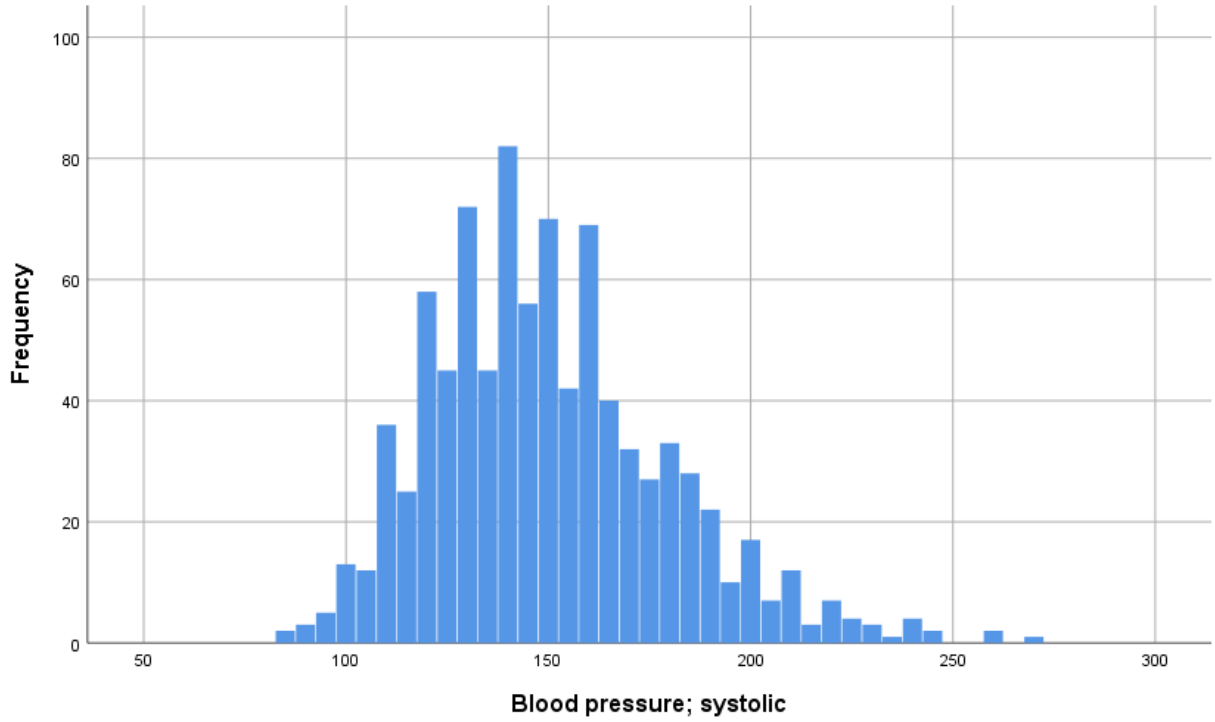
1. Zulkifly H, Lip GYH, Lane DA. Epidemiology of atrial fibrillation. *Int J Clin Pract*. 2018 Mar;72(3):e13070
2. Pistoia F, Sacco S, Tiseo C, et al. The Epidemiology of Atrial Fibrillation and Stroke. *Cardiol Clin*. 2016 May;34(2):255-68
3. Hahne K, Mönnig G, Samol A. Atrial fibrillation and silent stroke: links, risks, and challenges. *Vasc Health Risk Manag.* 2016 Mar 7;12:65-74

4. Hepworth LR, Rowe FJ, Walker MF, et al Post-stroke visual impairment: A systematic literature review of types and recovery of visual conditions. *Ophth Res*. 2016;5 DOI: 10.9734/OR/2016/21767
5. Rowe FJ, Hepworth LR, Howard C, et al. High incidence and prevalence of visual problems after acute stroke: An epidemiology study with implications for service delivery. *PLoS One.* 2019 Mar 6;14(3):e0213035
6. Goel D, Gupta R, Keshri T, Rana S. Prevalence of atrial fibrillation in acute ischemic stroke patients: A hospital-based study from India. *Brain Circ.* 2020 Feb 18;6(1):19-25
7. Zarkali A, Cheng SF, Dados A, et al. Atrial Fibrillation: An Underestimated Cause of Ischemic Monocular Visual Loss? *J Stroke Cerebrovasc Dis.* 2019 Jun;28(6):1495-1499
8. Rim TH, Oh J, Lee CS, et al. Evaluation of the Association Between Retinal Vein Occlusion and the Risk of Atrial Fibrillation Development: A 12-Year, Retrospective Nationwide Cohort Study. *Sci Rep.* 2016 Nov 7;6:34708
9. Zaleska-Żmijewska A, Janiszewski M, Wawrzyniak ZM, et al. Is atrial fibrillation a risk factor for normal-tension glaucoma? *Medicine (Baltimore).* 2017 Oct;96(43):e8347
10. Woo SC, Lip GY, Lip PL. Associations of retinal artery occlusion and retinal vein occlusion to mortality, stroke, and myocardial infarction: a systematic review. *Eye (Lond).* 2016 Aug;30(8):1031-8
11. Christiansen CB, Lip GY, Lamberts M, et al. Retinal vein and artery occlusions: a risk factor for stroke in atrial fibrillation. *J Thromb Haemost*. 2013 Aug;11(8):1485-92

12. Christiansen CB, Torp-Pedersen C, Olesen JB, et al. Risk of incident atrial fibrillation in patients presenting with retinal artery or vein occlusion: a nationwide cohort study. *BMC Cardiovasc Disord*. 2018 May 10;18(1):91
13. Kewcharoen J, Tom ES, Wiboonchutikula C, et al. Prevalence of Atrial Fibrillation in Patients with Retinal Vessel Occlusion and Its Association: A Systematic Review and Meta-Analysis, Current Eye Research. 2019; 44:12, 1337-1344
14. Callizo J, Feltgen N, Ammermann A, et al. Atrial fibrillation in retinal vascular occlusion disease and non-arteritic anterior ischemic optic neuropathy. PLoS One. 2017 Aug 3;12(8):e0181766. doi: 10.1371/journal.pone.0181766

Figure 1. Blood pressure measurements on admission

A, Systolic



B, Diastolic

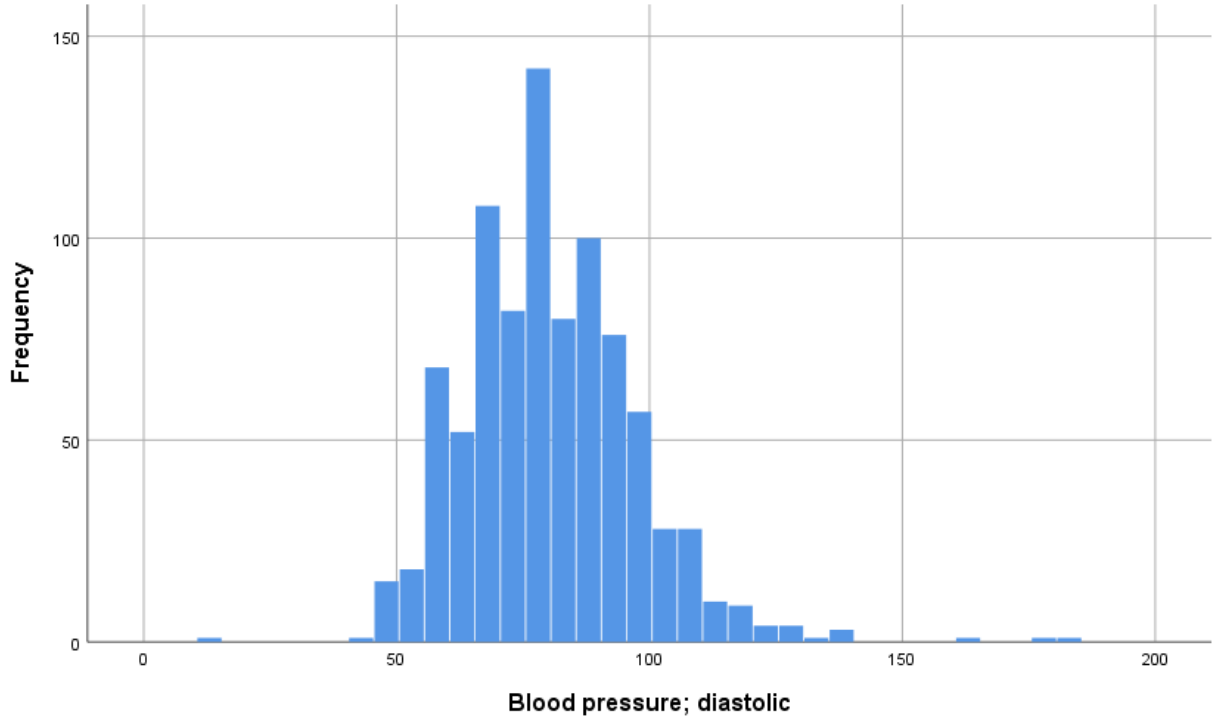


Table 1. Associations for atrial fibrillation

[mean (SD)]	Atrial fibrillation		
	Present	Absent	Significance, p value
Barthel score	7.87 (7.20)	10.57 (7.85)	0.006
Age at stroke	79.72 (9.91)	70.58 (13.94)	0.0001
Systolic blood pressure	150.28 (30.48)	149.95 (28.75)	0.369
Diastolic blood pressure	82.03 (17.22)	80.40 (16.85)	0.692
Visual impairment			0.0001
Visual acuity; near, distance			0.783, 0.115
Ocular alignment; near, distance			0.869, 0.702
Ocular motility			0.130
Visual field			0.343
Visual inattention			0.727
Visual perception			0.137
Single vs multiple visual impairment type			0.807
Recovery of visual impairment			0.733
Visual acuity			0.079
Ocular alignment			0.431
Ocular motility			0.113
Visual field			0.083
Visual inattention			0.787
Visual perception			0.907