REDUCED LEFT ATRIAL ROTATIONAL FLOW IS INDEPENDENTLY ASSOCIATED WITH THE RISK OF EMBOLIC BRAIN INFARCTS

Marco Spartera*, Antonio Stracquadanio, Guilherme Pessoa-Amorim, George Hanston, Sara Mazziucco, Victoria Young, Adam Von Ende, Aaron T Hess, Vanessa M Ferreira, James Kennedy, Stefan Neubauer, Barbara Casadei*, Rohan S Wijesuriendra*. From the Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford (MS, GPA, AS, VMF, ATH, SN, RSW, BC), the University of Oxford Centre for Clinical Magnetic Resonance Research (MS, GPA, AS, RSW, ATH, VMF, SN), the Wolfson Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neuroscience (SM), Oxford University Hospital NHS Foundation Trust (MS, GH, SM, VY, AS, GPA, VMF, JK, SN, RSW, BC), and CTSU Nuffield Department of Population Health, University of Oxford (AVE, GPA). *Joint senior authors

10.1136/heartjnl-2022-BCS.229

Introduction Atrial fibrillation (AF) is a major risk factor for ischaemic stroke. Low blood flow velocities within the fibrillating left atrium (LA) are thought to predispose to activation of the coagulation cascade (1) and local thrombus formation (2), with consequent higher risk of cardioembolic stroke (1,3-5). Nevertheless, up to 20-25% of embolic strokes occur in the absence of AF or any other identifiable cause (6,7).

4D Flow cardiac magnetic resonance (CMR) studies have also shown that normal LA blood flow is typically vortical (8,9) and such feature, in addition to high flow velocity, may play an important role in preventing thrombus formation by shear-mediated inhibition of platelet adhesion (10,11).

Despite this body of evidence, it remains unclear whether altered LA 4D flow characteristics are independently associated...
with cardioembolic stroke. Here, we evaluated the relationship between LA flow velocity and vorticity and large non-cortical or cortical brain infarcts (LNCCIs) which are likely to be embolic in origin (3,12,13), in patients with or without AF and either a previous history of ischaemic stroke or an increased clinical risk of stroke (i.e. CHA2DS2VASc score ≥1).

Methods
Study Design
A total of 134 patients with either a previous history of ischaemic stroke or no history of stroke but a CHA2DS2VASc score ≥1 were recruited into the study and underwent a heart and brain magnetic resonance imaging (MRI) cross sectionally.

MRI protocol
CMR scans were performed at 3T. For assessment of LA flow characteristics, all patients underwent ECG-gated time-resolved 3D phase-contrast CMR with 3-directional velocity encoding imaging (‘4D-Flow’) as previously described (14) using our post-processing tool (available at https://doi.org/10.5287/bodleian:ey4ovzdbB). Briefly, data analysis included 3D segmentation of LA volume, and determination of LA velocities and LA vorticity (Figure 1). Brain MRI protocol included analysis of detection of brain infarcts, defined as either large non-cortical and/or cortical infarcts (i.e. LNCCI).

Results
A total of 134 individuals were included in the final analysis. Of these, a total of 67 (50%) had a diagnosis of AF and 58 (43%) were in AF at the time of the scan. Among the 67 (50%) participants in SR without a past history of AF, a new diagnosis of asymptomatic AF in 1 patient.

Brain and cardiac magnetic resonance imaging
On brain MRI, 39 participants (29%) displayed at least one embolic brain infarct (i.e. LNCCI), 20 (15%) had at least one small non-cortical infarct (i.e. non-embo logic infarcts), and 75 (56%) had no brain infarct. Baseline characteristics are reported in Table 1.

Predictors of embolic brain infarcts
After adjusting for rhythm at the time of the scan, each SD reduction in LA vorticity was associated with an approximately 2-fold higher risk of prevalent LNCCI [OR (95% CI) = 2.19 (1.20-4.01) per SD, P = 0.011]. Conversely, no significant association with LNCCIs was found for LA peak flow velocity with cardioembolic stroke. Here, we evaluated the relationship between LA flow velocity and vorticity and large non-cortical or cortical brain infarcts (LNCCIs) which are likely to be embolic in origin (3,12,13), in patients with or without AF and either a previous history of ischaemic stroke or an increased clinical risk of stroke (i.e. CHA2DS2VASc score ≥1).

Methods
Study Design
A total of 134 patients with either a previous history of ischaemic stroke or no history of stroke but a CHA2DS2VASc score ≥1 were recruited into the study and underwent a heart and brain magnetic resonance imaging (MRI) cross sectionally.

MRI protocol
CMR scans were performed at 3T. For assessment of LA flow characteristics, all patients underwent ECG-gated time-resolved 3D phase-contrast CMR with 3-directional velocity encoding imaging (‘4D-Flow’) as previously described (14) using our post-processing tool (available at https://doi.org/10.5287/bodleian:ey4ovzdbB). Briefly, data analysis included 3D segmentation of LA volume, and determination of LA velocities and LA vorticity (Figure 1). Brain MRI protocol included analysis of detection of brain infarcts, defined as either large non-cortical and/or cortical infarcts (i.e. LNCCI).

Results
A total of 134 individuals were included in the final analysis. Of these, a total of 67 (50%) had a diagnosis of AF and 58 (43%) were in AF at the time of the scan. Among the 67 (50%) participants in SR without a past history of AF, a new diagnosis of asymptomatic AF in 1 patient.

Brain and cardiac magnetic resonance imaging
On brain MRI, 39 participants (29%) displayed at least one embolic brain infarct (i.e. LNCCI), 20 (15%) had at least one small non-cortical infarct (i.e. non-embolic) without LNCCI, and 75 (56%) had no brain infarct. Baseline characteristics are reported in Table 1.

Predictors of embolic brain infarcts
After adjusting for rhythm at the time of the scan, each SD reduction in LA vorticity was associated with an approximately 2-fold higher risk of prevalent LNCCI [OR (95% CI) = 2.19 (1.20-4.01) per SD, P = 0.011]. Conversely, no significant association with LNCCIs was found for LA peak flow velocity with cardioembolic stroke. Here, we evaluated the relationship between LA flow velocity and vorticity and large non-cortical or cortical brain infarcts (LNCCIs) which are likely to be embolic in origin (3,12,13), in patients with or without AF and either a previous history of ischaemic stroke or an increased clinical risk of stroke (i.e. CHA2DS2VASc score ≥1).

Methods
Study Design
A total of 134 patients with either a previous history of ischaemic stroke or no history of stroke but a CHA2DS2VASc score ≥1 were recruited into the study and underwent a heart and brain magnetic resonance imaging (MRI) cross sectionally.

MRI protocol
CMR scans were performed at 3T. For assessment of LA flow characteristics, all patients underwent ECG-gated time-resolved 3D phase-contrast CMR with 3-directional velocity encoding imaging (‘4D-Flow’) as previously described (14) using our post-processing tool (available at https://doi.org/10.5287/bodleian:ey4ovzdbB). Briefly, data analysis included 3D segmentation of LA volume, and determination of LA velocities and LA vorticity (Figure 1). Brain MRI protocol included analysis of detection of brain infarcts, defined as either large non-cortical and/or cortical infarcts (i.e. LNCCI). Such association is maintained after adjustment for clinical, haemodynamic, and CMR structural and functional parameters.

Abstract E Figure 2 Relationship between left atrial (LA) vorticity and embolic brain infarcts
Reduced LA blood flow vorticity is independently associated with prevalent brain infarcts of likely embolic origin, defined as large non-cortical and cortical infarcts (LNCCIs). Such association is maintained after adjustment for clinical, haemodynamic, and CMR structural and functional parameters.

Abstract E Figure 3 Percentage of embolic and lacunar brain infarcts for each tertile of LA vorticity
Percentage of patients with MRI-detected likely-embolic brain infarcts (i.e. large non-cortical and cortical infarcts, LNCCIs; panel A) or non-embolic infarcts (i.e. small non-cortical infarcts; panel B), stratified by LA vorticity tertiles.
After further adjusting for age, history/evidence of AF, and CHA2DS2-VASc score (Figure 2), LA vorticity remained significantly associated with LNCCIs [OR (95% CI) = 2.10 (1.12-3.92) per SD, P=0.021]. The observed age-, CHA2DS2-VASc-, and rhythm-adjusted association between LA vorticity and LNCCIs remained significant after further adjusting for multiple covariate specifications (Figure 2, all P<0.05). In keeping with these results, LNCCIs were significantly more prevalent in those patients displaying the lowest level of LA vorticity than in the middle and highest levels of LA vorticity (P = 0.001; Figure 3). In keeping with these results, LNCCIs were significantly more prevalent in those patients displaying the lowest level of LA vorticity than in the middle and highest levels of LA vorticity (P = 0.001; Figure 3).

Discussion

The main finding of this cardiovascular and brain MRI study is that reduced LA blood flow vorticity is significantly and specifically associated with large, likely-embolic, brain infarcts (i.e., LNCCI) (15), independently of AF, age, clinical stroke risk, and LA and LV volumes and function. LNCCI are typically associated with worse neurological symptoms (15), cognitive decline (3), and a cardiac or vascular embolic source (7) compared with smaller non-cortical lesions, which are more likely to be of vascular origin. The fact that up to 20-25% of LNCCI remain of undetermined cause after a conventional full diagnostic evaluation suggests that some pathophysiological mechanisms of embolic stroke are currently poorly characterized (6,7). Our finding of an independent association between lower LA flow vorticity (by 4D Flow CMR) and LNCCI, but not with smaller non-cortical or lacunar infarcts, suggests that low LA flow vorticity may constitute a previously unrecognised risk factor for cardioembolic stroke, which may be used to identify patients that would benefit from tailored anti-thrombotic treatment for embolic stroke prevention. These could include both low-risk patients with AF (i.e., CHA2DS2-VASc 0-1) and patients in SR without any prior history of AF.

In conclusion, reduced rotational LA blood flow is associated with embolic (but not lacunar) brain infarcts, independently of age, cardiac rhythm, stroke risk factors, and cardiac structure or function. Our study provides a clear rationale for investigating whether LA vorticity can identify individuals in SR or low-risk individuals with AF who would benefit from oral anticoagulation therapy for the prevention of cardioembolic stroke.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>LNCCI (N = 39)</th>
<th>Non-LNCCI (N = 95)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years old</td>
<td>71 ± 9</td>
<td>69 ± 8</td>
<td>0.291</td>
</tr>
<tr>
<td>Male</td>
<td>24 (61)</td>
<td>55 (58)</td>
<td>0.697</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>26.9 ± 5</td>
<td>28.4 ± 5.5</td>
<td>0.131</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (74)</td>
<td>73 (77)</td>
<td>0.759</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>6 (15)</td>
<td>12 (13)</td>
<td>0.671</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>31 (79)</td>
<td>13 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>12 (31)</td>
<td>19 (20)</td>
<td>0.179</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>6 (15)</td>
<td>14 (15)</td>
<td>0.924</td>
</tr>
<tr>
<td>CHA2DS2-VASc Score*</td>
<td>3 (2 – 4)</td>
<td>3 (2 – 4)</td>
<td>0.190</td>
</tr>
<tr>
<td>Rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus Rhythm (without AF diagnosis)</td>
<td>20 (51)</td>
<td>46 (48)</td>
<td>0.763</td>
</tr>
<tr>
<td>AF (persistent/permanent)</td>
<td>15 (39)</td>
<td>43 (45)</td>
<td>0.470</td>
</tr>
<tr>
<td>AF (paroxysmal)</td>
<td>3 (8)</td>
<td>6 (6)</td>
<td>0.772</td>
</tr>
<tr>
<td>AF (silent)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0.291</td>
</tr>
<tr>
<td>Recent AF onset (≤12 months)</td>
<td>8 (21)</td>
<td>17 (18)</td>
<td>0.724</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or median (Q1-Q3) for continuous variables and as N (%) for categorical variables. Statistically significant P values (<0.05) are marked in bold. LNCCI, Large non-cortical or cortical infarcts; BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack; LA, Left Atrium; LV, Left Ventricle; ECG, electrocardiogram; AF, atrial fibrillation. *calculated without considering the stroke event on admission.