

## Linking the heart–eye–brain axis: Ocular and cerebral blood flow changes after catheter ablation in atrial fibrillation

Q2 Q1

Q6

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Q3

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Cerebral hypoperfusion during atrial fibrillation (AF) has emerged as a key contributor to impaired brain health and can be improved by restoration of sinus rhythm (SR).<sup>1</sup> However, use of conventional tools for examining cerebral blood flow (CBF), such as single photon emission computed tomography (SPECT), is limited in routine practice. Ocular blood flow (OBF), which can be non-invasively evaluated using laser speckle flowgraphy (LSFG), is increased by SR restoration in patients with persistent AF (PeAF)<sup>2</sup> and has been proposed as a potential surrogate for CBF.<sup>3</sup> Therefore, we aimed to investigate whether SR restoration from AF improved not only OBF but also CBF, and if so, whether CBF changes correlated with OBF changes through direct comparisons of LSFG and SPECT measurements.

We prospectively enrolled 12 patients with PeAF and 12 patients with paroxysmal AF (Paf) (mean age,  $67.8 \pm 7.2$  years; 25% women) who underwent catheter ablation (CA) between April 2023 and July 2024. None of the participants included in this study were reported in any previous studies. Follow-up was completed by January 2025. The study protocol was approved by the Institutional Review Board of Tohoku University. During CA, pulmonary vein isolation was achieved in all patients using either radiofrequency or cryoballoon ablation. All participants received anticoagulation therapy at least 1 month before and 3 months after the procedure. Measurements of both OBF<sup>2</sup> and global CBF<sup>4</sup> were performed within 2 days before and 6 months after CA. LSFG for OBF measurement uses a fundus camera equipped

with an 830-nm diode laser and a charge-coupled device camera, to capture a speckle contrast pattern generated by laser light scattered by moving blood cells in the ocular fundus. The mean blur rate (MBR), an index of retinal blood flow velocity, was calculated from this speckle pattern.<sup>4</sup> CBF image acquisition was performed using <sup>99m</sup>Tc-ethyl cysteinate dimer SPECT with a dual-head gamma camera system (NM/CT870 DR, GE Healthcare). Global CBF was quantified using the Patlak plot method.<sup>5</sup>

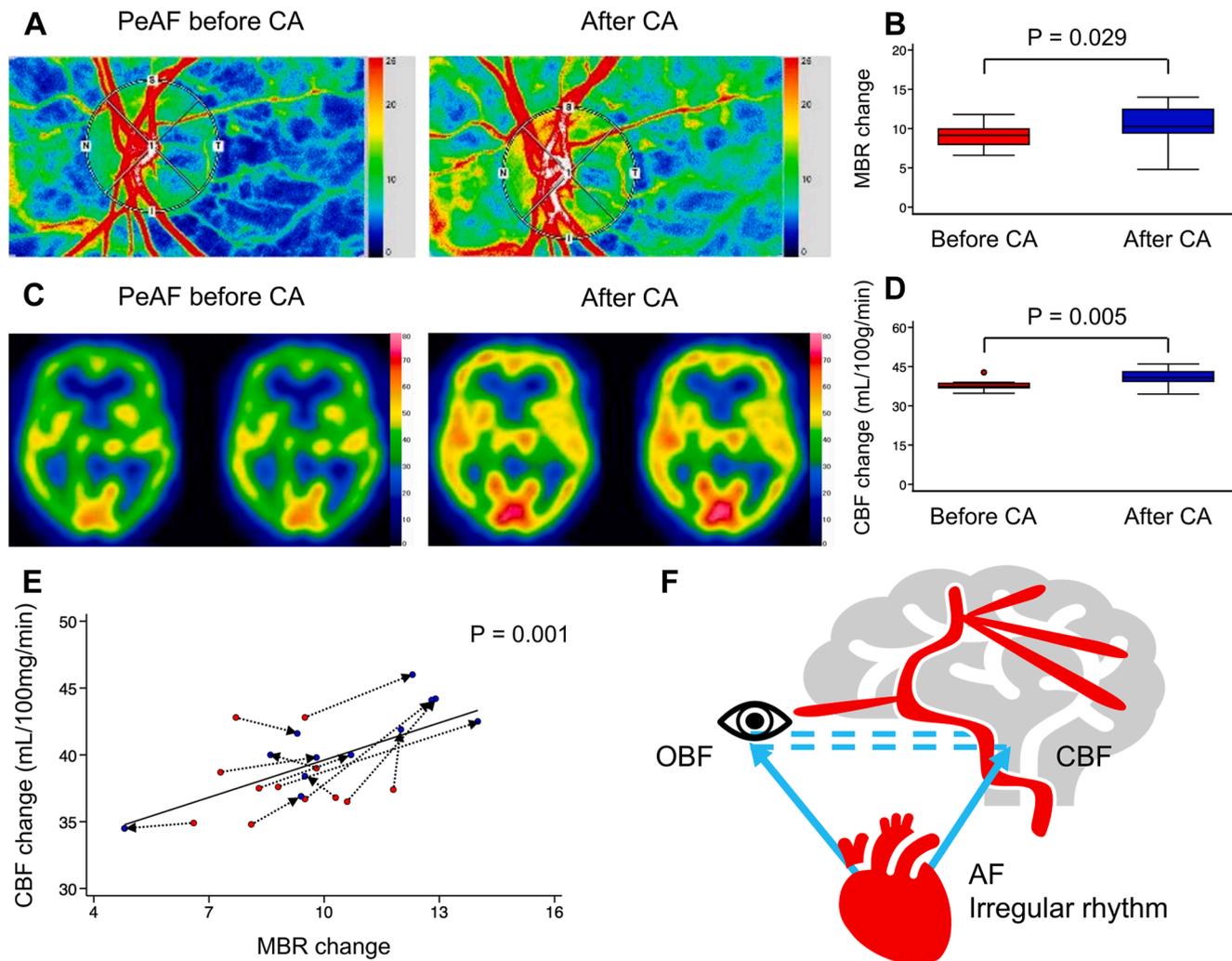
All statistical analyses were conducted using Stata software version 18 (StataCorp). Because no prior studies have evaluated changes in MBR following CA, sample size estimation was based on differences in global CBF between 6 patients with Paf and 6 with PeAF before CA. A between-group difference of 3.9 mL/min per 100 g indicated that 12 patients per group would provide 80% power at a 2-sided significance level of 0.05. Changes in MBR and global CBF before and after CA were compared using paired t test in PeAF and Paf groups separately. Multivariable linear regression analyses were then conducted to evaluate between-group differences in MBR and global CBF changes. Stepwise variable selection was applied with a threshold of  $P < .10$  to identify adjustment variables that were different between the 2 groups at baseline, including heart rate, estimated glomerular filtration rate, left atrial diameter and brain natriuretic peptide level. The association between changes in MBR and CBF was assessed using a repeated-measure linear mixed-effects model in PeAF and Paf groups

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**Figure 1**

Comparisons of changes in ocular and cerebral blood flow before and after catheter ablation. Representative laser speckle flowgraphy (LSFG) (A) and cerebral blood flow (CBF) images (B) before and after catheter ablation (CA) in persistent atrial fibrillation (PeAF). Box plot showing changes in mean blur rate (MBR) (C) and global CBF (D) before and after CA in PeAF patients (N = 12). Linear mixed-effects model showing a significant positive correlation between changes in MBR and global CBF in patients with PeAF (E, red and blue dots represent the values before and after CA). A graphical abstract of a heart-eye-brain axis in atrial fibrillation (AF) (F).

separately. A 2-tailed  $P$ -value  $< 0.05$  was considered statistically significant.

At baseline, the PeAF group (during AF rhythm) exhibited significantly higher heart rate ( $82.4 \pm 20.4$  vs.  $62.8 \pm 20.2$  bpm,  $P = .027$ ), estimated glomerular filtration rate ( $73.4 \pm 15.1$  vs.  $58.9 \pm 12.3$  mL/min per  $1.73 \text{ m}^2$ ,  $P = .017$ ), left atrial diameter ( $36.8 \pm 12.6$  vs.  $45.3 \pm 4.9$  mm,  $P < .001$ ), and brain natriuretic peptide levels ( $147.0 \pm 105.4$  vs.  $28.2 \pm 17.4$  pg/mL,  $P = .001$ ) than the Paf group. No other baseline characteristics differed between the 2 groups. After CA, all patients remained in SR. In the PeAF group, both OBF and global CBF increased significantly compared with baseline (MBR:  $9.0 \pm 1.5$  to  $10.5 \pm 2.5$ ,  $P = .029$ , Figure 1A and 1C; global CBF:  $38.0 \pm 2.6$  to  $40.8 \pm 3.3$  mL/100g per min,  $P = .005$ , Figure 1B and 1D). Changes in ocular or cerebral perfusion were not observed in the Paf group (MBR:  $10.1 \pm 2.3$  to  $9.5 \pm 1.8$ ,  $P = .282$ ; global CBF:  $43.3 \pm 4.4$  to  $42.3 \pm 6.0$  mL/100g per min,  $P = .346$ ). In the multivariable regression analysis, the PeAF group demonstrated greater changes in

both MBR (estimate 2.06, 95% CI 3.68, 0.44) and global CBF (estimate 3.98, 95% CI 6.84, 1.12 mL/100g per min) compared with the Paf group. Linear mixed-effects modeling revealed a significant positive correlation between changes in MBR and CBF in the PeAF group ( $P < .001$ , Figure 1E). The correlation was not found in the Paf group ( $P > .05$ ).

In this study, SR restoration from AF rhythm was associated with significant increases in MBR and global CBF, with a positive correlation observed between these changes. These findings suggest that rhythm control therapy may enhance both ocular and cerebral perfusion. Anatomically, the ocular circulation originates from the ophthalmic artery, a direct branch of the internal carotid artery, which also supplies the cerebral circulation.<sup>3</sup> Accordingly, alterations in OBF may reflect changes in cerebral perfusion.

LSFG offers several advantages, including simplicity, short examination time, noninvasiveness, and cost-effectiveness, making it well-suited for repeated assessments and potential preventive screening.<sup>4</sup> Although further validation is required,

LSFG may represent a practical surrogate modality for assessing cerebral circulation in patients with AF undergoing CA. Despite limitations related to the small sample size and relatively short follow-up period, these results support a mechanistic link between cardiac rhythm regulation and cerebral perfusion within the heart–eye–brain axis (Figure 1F).

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