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Effect of ageing on the cerebral hemodynamics in the marmoset monkey

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INTRODUCTION

Age results in a deterioration of cardiovascular functionality, leading to an increased risk of cerebrovascular diseases, whose links with alteration/loss of cerebral activity and cognitive abilities deserve intensive exploration. Nonhuman primates, being closer to humans than the commonly used rodent species, are precious models for developing studies on human health and diseases. Thus we analyzed **blood flow dynamics in intracranial arteries and venous sinuses** of **young (4 years old) and old (9 years old) adult, male and female, marmoset monkeys *Callithrix jacchus***. This species is particularly invaluable with a lifespan around 10 years.

Methods

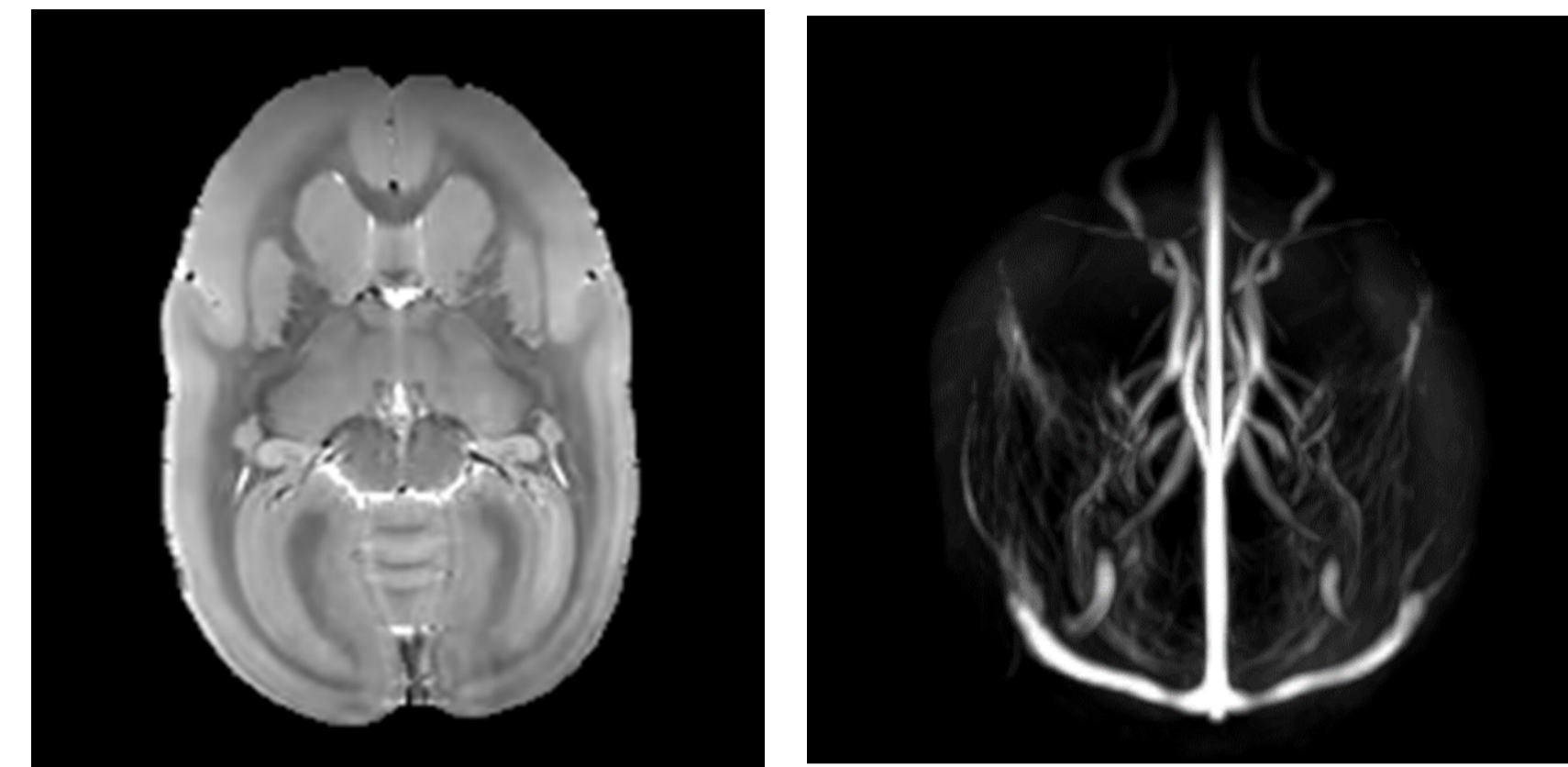
MRI scans were performed using a 7-T MRI scanner (Brukerbiospec), (emitting coil = Φ 72 mm, receiving surface coil = Φ 30 mm). Each study took ~90 min/marmoset to acquire successively **T2w, Time Of Flight (TOF) and Phase Contrast Angiography (PCA)** images. The TOF images were used to position the two PCA scanning planes perpendicular to flow direction in the arterial vessels and the venous sinuses.

The marmoset was placed in a thermostated cradle in a prone position under oxygen ventilation with Isoflurane (1.5 to 2.5%). Cardiac and respiratory frequencies were monitored. Blood flow velocity acquisition (PCA) was synchronized with ECG signal.

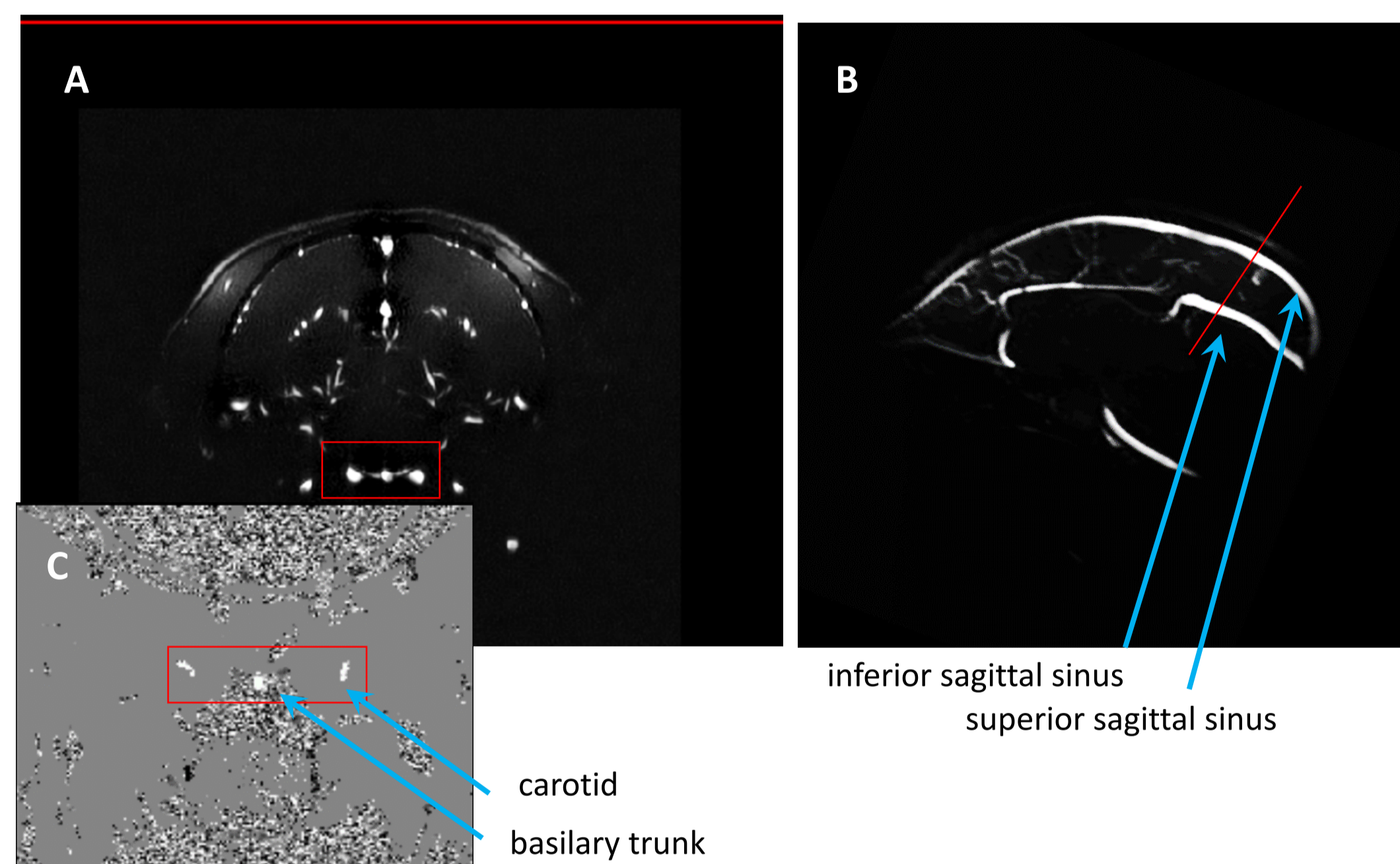


The marmosets originated from the CerCo marmoset colony (Toulouse). All experiments were carried out according to the National Committee for Ethical Reflection on Animal Testing (authorization n°: 05215.03 delivered by MESRI).

Methods



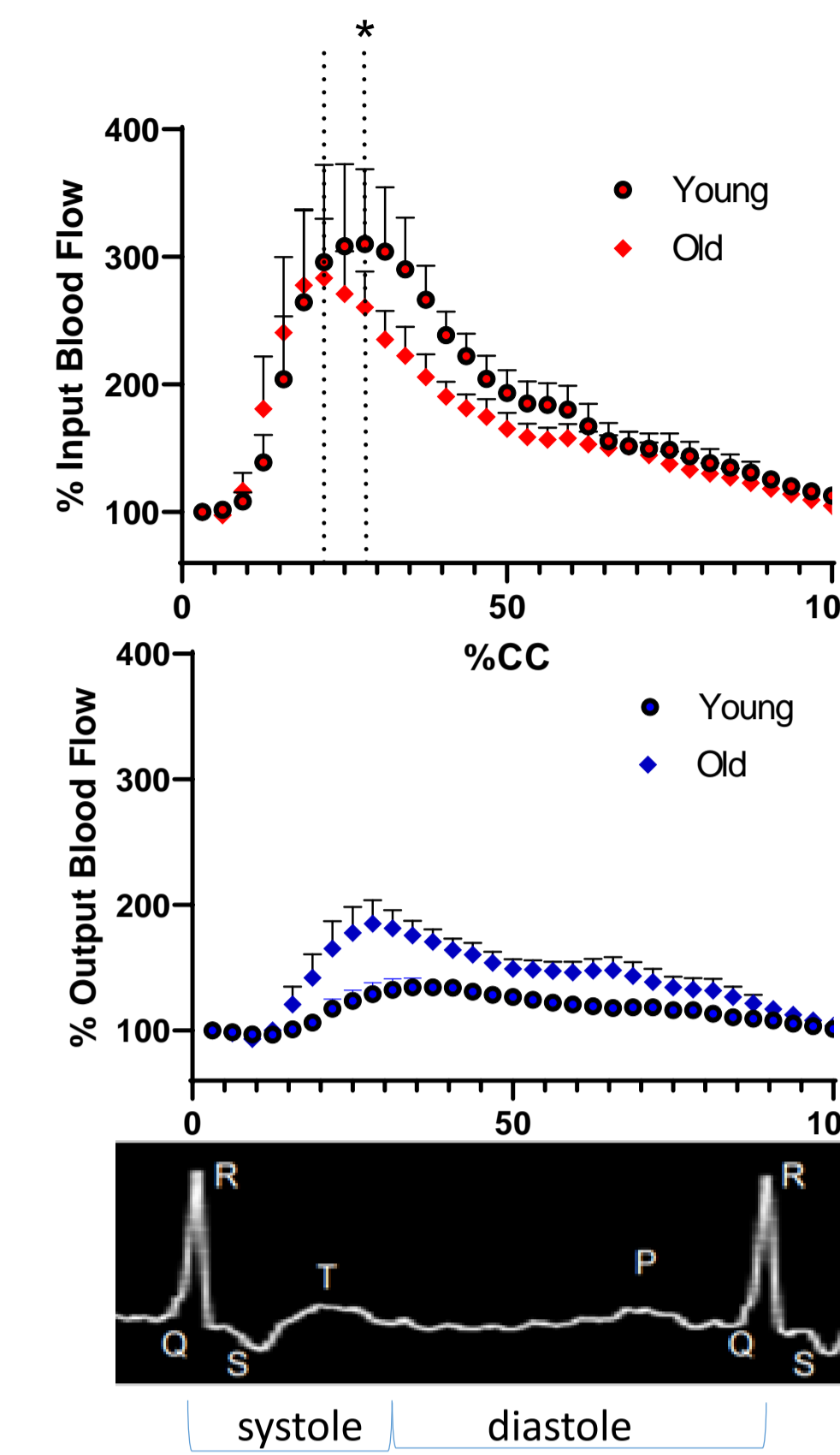
T2 and TOF images of a marmoset brain. Horizontal plane. T2: TR/TE: 6859/36 ms, FOV: 48x48mm, Matrix: 240x240, voxel size: 0.2x0.2x0.3 mm³. TOF: TR/TE: 11/3 ms, flip angle=80°, FOV: 48x48mm, Matrix: 320x320, voxel size = 0.15x0.15x0.3 mm³.



TOF: Coronal (A) and sagittal (B) planes. One intracranial section across the inferior part of the Willis polygon was chosen to measure blood velocity simultaneously in both the left and right internal carotids and the basilar trunk (C). Position for signal acquisition of blood velocity in sinuses was chosen on a sagittal section

PCA: TR/TE: 15/4.2 ms, flip angle=20°, FOV: 30x24mm, Matrix: 200x160, voxel size: 0.15x0.15x1 mm³, VENC: 50cm/s (arteries), 20cm/s (sinuses). Images were acquired according to prospective cardiac gating (15-22 frames as a function of heart rate) and covered in average 75% of the cardiac cycle. The cardiac frequency averaged 170 bpm.

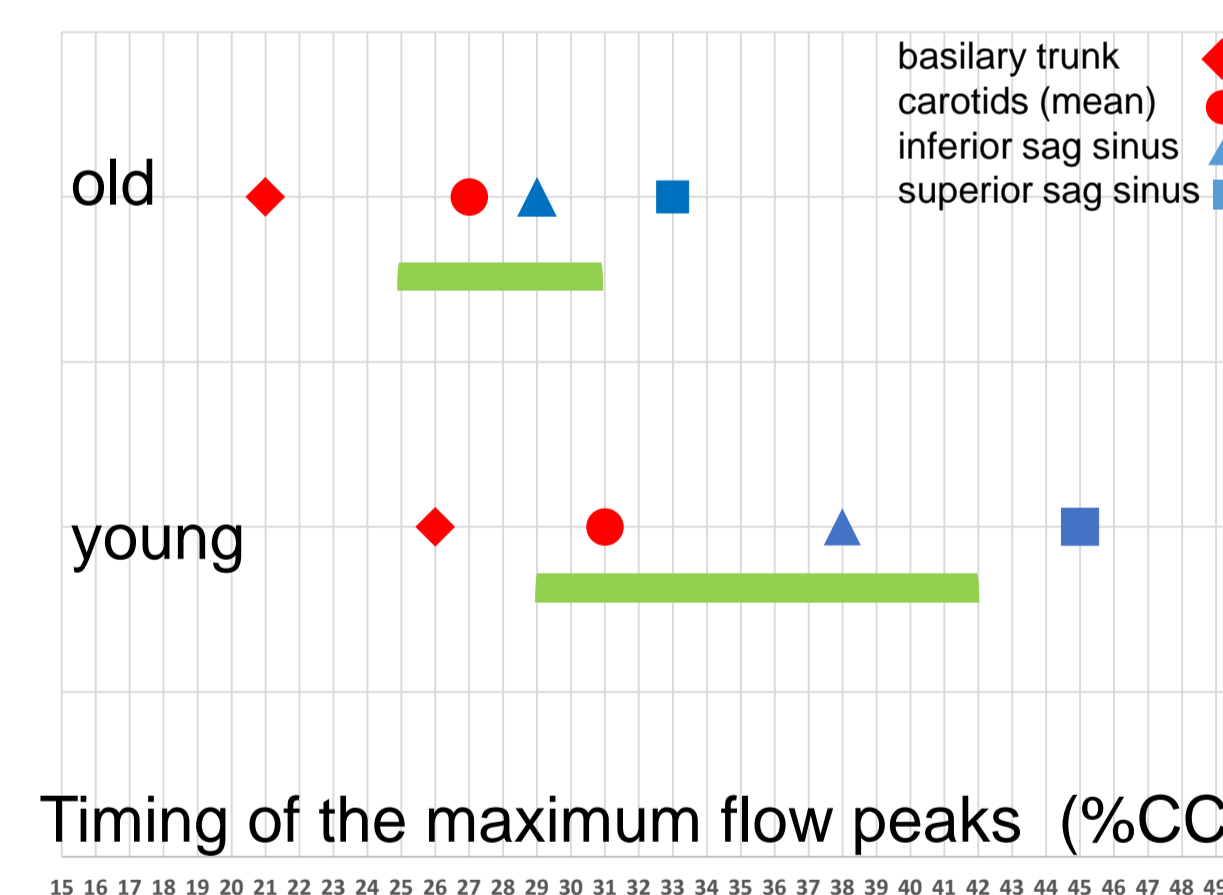
Data acquisition : Bruker ParaVision 6.0.1 software.
Data analyses : Data were analyzed using an in-house processing method with an optimised region growing algorithm for blood speed segmentation, which automatically extracts the region of interest at each level over the segments of the cardiac cycle. Velocity was averaged for each ROI and blood flow was calculated (vessel area x mean velocity). Data were extrapolated to cover the whole cardiac cycle (CC), and interpolated to obtain similar segmentation of the CC for all marmosets (32 steps of 3.13 % CC).



Basiliary and carotid arteries contribution

We evaluated that the **carotid system provides 57.2 ± 8,5% of the blood (μl/mn) dispatched to the brain**, with an equal contribution of the two internal carotids (49% and 51%, (right and left respectively (n=14)). In humans, the carotid system appears more prominent (75 to 78% of the blood supply).

The **blood flow peak recorded in the basiliary trunk precedes those of the carotids in the old marmosets (n=7)**. This difference is not significant in the young marmosets (n=7)

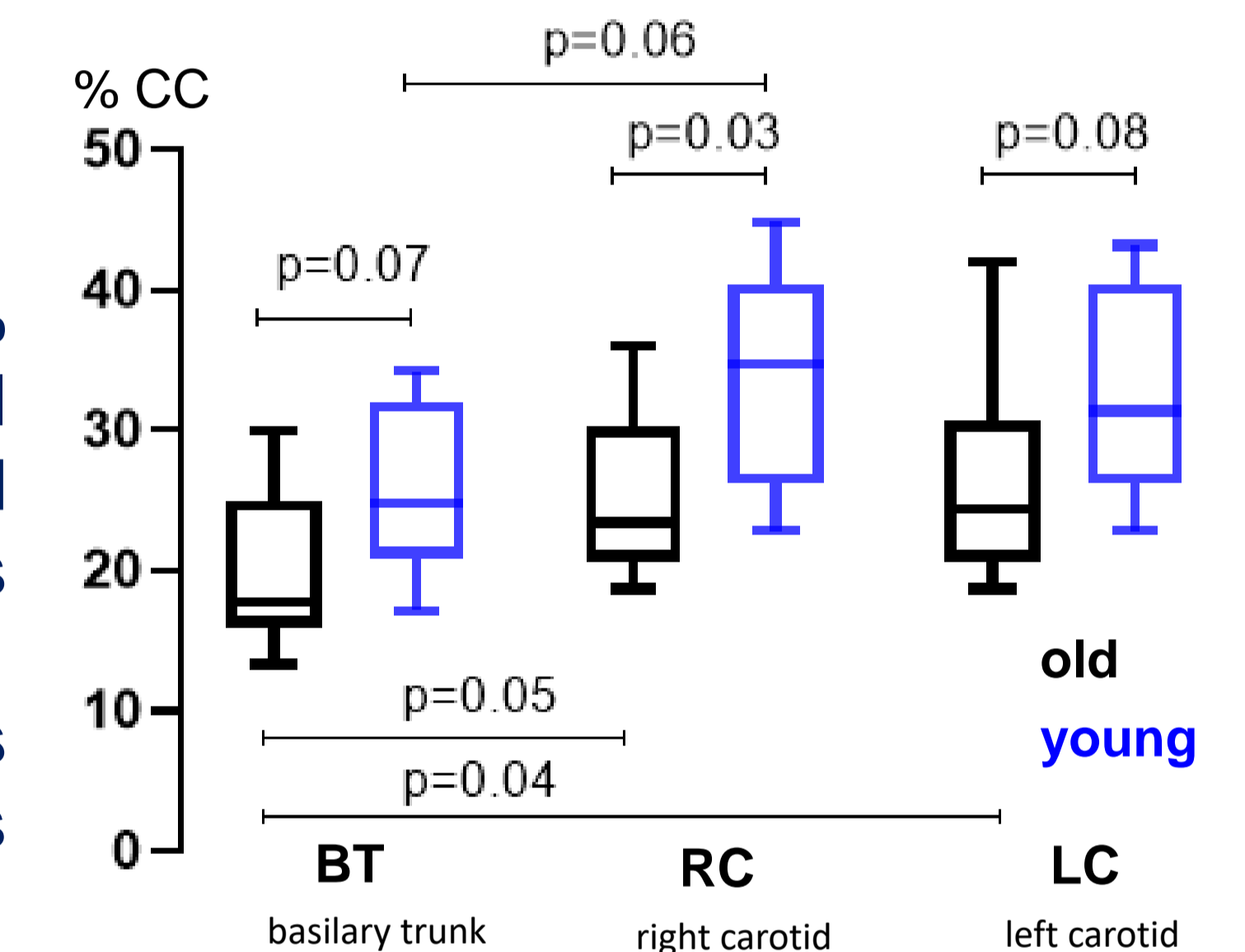


RESULTS

Arterial flow and venous flow timecourses

When normalizing flow values to the first one (P wave of the cardiac cycle), **arterial blood flow rapidly increases and peaks** when 20-30% of the cardiac cycle (CC) is reached, which occurs **significantly earlier in old (21.8% CC, n=7) than in young marmosets (28.1% CC, n=7) (p<0,05)**. Arterial blood flow cumulated from both carotids and basiliary trunk reaches higher relative increase in young (320%) than in old marmosets (291%).

Venous flow timecourse is rather steady in young marmosets but tends to show a peak shortly after the arterial peak in old marmosets (28% CC, versus 38% in young adult marmosets).



Arterial-venous time lapse

The **time interval (in terms of CC) between arterial (red) and venous (blue) maximal blood flow peaks** appears smaller in old (n=7) than in young marmosets (n=7). The green rectangle symbolises the time interval between the mean maximal arterial and the mean maximal venous flow peaks (young: 29-42 %CC, old: 25-31%CC). This would suggest a faster blood transit inside the brain tissue in old than in young marmosets.

CONCLUSIONS

This cross sectional study originally shows that intracranial blood flow parameters differ in several ways between young and old adult marmosets :
-the arterial blood flow peaks earlier in old monkeys, suggesting age-related changes in the vessel structural properties (vessel wall rigidity).
-the kinetics of blood flow input-output in the brain tissue is different in old monkeys. Both brain vessels and tissue mechanical characteristics may be altered by age (compliance).

A longitudinal study, on a larger population, is necessary to formalize the temporal evolution of these changes and to test whether some parameters could be used to detect signs of early/pathological ageing. The marmoset model can easily be used to couple non invasive imaging and behavioral studies all along the marmoset life, at a high and adjustable frequency. Such a screening would help to define the timing of normal/pathological changes in the cerebrovascular system of the ageing primate.