

Where does the blood actually go?

P2-04

Acute effects of cilostazol & isosorbide mononitrate on deep-tissue white-matter haemodynamics in wild-type mice

Albeshr Almasri★, Harry Trehwitt, Letitia McMullan, Kira Shaw, Catherine Hall

Brain Energy Lab, Sussex Neuroscience, School of Psychology, University of Sussex, Falmer, UK | UK Dementia Research Institute at UCL, London, UK | BHF–UK DRI Centre for Vascular Dementia Research at UCL, London, UK | ★ presenting author

KEY TAKEAWAY

With blood pressure unchanged, acute cilostazol + ISMN lower flux and oxygen use in deep tissue containing white matter while sparing cortex, evidence for regional redistribution

INTRODUCTION

RESULTS

FUTURE

Why is white matter so vulnerable?

Cerebral Small Vessel Disease (cSVD) is a leading cause of stroke and dementia. Damage concentrates in **white matter**: tracts fed by deep penetrating arterioles with little collateral supply.

The LACI trials suggest that cilostazol and isosorbide mononitrate are safe, tolerated, and may improve clinical outcomes in cSVD, but the acute haemodynamic mechanism remains unclear. We tested the simplest hypothesis: that they acutely boost white-matter flow.

LACI drugs used

CIL

Cilostazol

Vasodilator with antiplatelet activity; raises smooth-muscle cAMP.

ISMN

Isosorbide mononitrate

Organic nitrate releasing nitric oxide, a potent vasodilator.

FIG 1

Acute CIL+ISMN effects on cerebral microvascular haemodynamics

VC vs CIL+ISMN · WM: Young (solid) + Old (dashed) · GM: Young only

dt-WM

RBC Flux

Flux (norm.)

Young: Condition: 0.022 Time: Condition: 0.032 Old: Timepoint: 0.11 Condition: 0.012

BL 30m 1h 2h 4h 6h 24h

RBC Conc.

Conc. (norm.)

Young: Timepoint: 0.0072 Condition: 0.0072 Old: Timepoint: 0.21 Condition: 0.004

BL 30m 1h 2h 4h 6h 24h

CMRO₂

CMRO₂ (norm.)

Young: Timepoint: 0.0003 Condition: 0.016 Old: Timepoint: 0.0059 Condition: 0.0072

BL 30m 1h 2h 4h 6h 24h

GM

RBC Flux

Flux (norm.)

Timepoint: <0.016 Condition: 0.92

BL 30m 1h 2h 4h 6h 24h

RBC Conc.

Conc. (norm.)

Timepoint: 0.54 Condition: 0.003

BL 30m 1h 2h 4h 6h 24h

sO₂

sO₂ (norm.)

Timepoint: <0.001 Condition: 0.082

BL 30m 1h 2h 4h 6h 24h

The headline finding

Blood flow falls in the deep tissue containing white matter, while cortical grey matter is relatively preserved. With BP unchanged in our dataset, flux and oxygen consumption drop in dtWM as cortex holds steady, suggesting redistribution, not global vasodilation.

No change in BP → not a hypotensive effect in our dataset.

DIRECTION OF CHANGE VS. VEHICLE

Measure	dt-WM	Cortex	What it means
Flux (CBF)	↓↓	→	Strong drop at 4–6 h in dt-WM; cortex unaffected.
RBC speed	→	→	Speed barely changes anywhere.
RBC conc.	↓↓	↑	Fewer cells in dt-WM, more in cortex.
sO ₂	→	↑	Cortex trends higher late.
Total Hb	→	↓	Modest cortical Hb reduction.
CMRO ₂	↓	→	Lower O ₂ use in dt-WM, stronger in older mice.

Next

→ Two-photon imaging to localise **vascular level response**, from pial arteries through both ends of the capillary beds.

→ Test the same drugs in a **BCAS model** of chronic hypoperfusion.

→ Directly assess our working hypothesis of regional redistribution acutely via functional Ultrasound (fUS)

METHODS

MODEL

Wild-type C57BL/6J mice, male & female; young (4–5 mo) & middle-aged (~12 mo).

DESIGN

Within-subject crossover: every mouse receives **both conditions**, ≥ 6-day washout.

CONDITIONS

Vehicle (condensed milk) CIL + ISMN

Timeline

Baseline 10:45 AM 30m 1h 2h 4h 6h 11:00 AM

dt-WM

Deep tissue containing WM

Aspiration + 3D-printed cannula reaching deep white-matter tissue.

GM

Visual cortex

Coverslip over V1. Captures cortical grey-matter signals.

RECORDING

Laser Doppler (flux, RBC speed & conc.)

Hb spectroscopy (sO₂, total Hb) - derived CMRO₂

Linear mixed models, Dunnett's vs. vehicle. Blood pressure unchanged across conditions.

CONCLUSIONS

Flux and RBC concentration fall in dt-WM after CIL + ISMN.

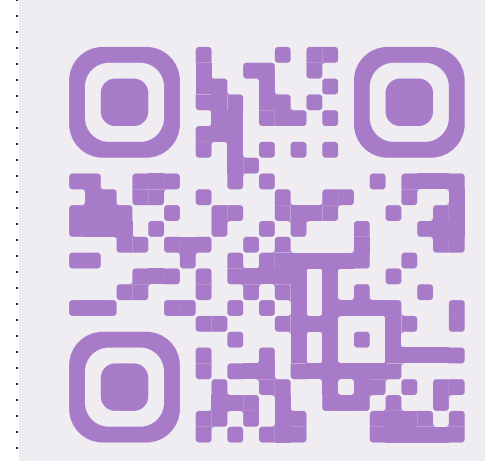
RBC speed and blood pressure remain stable, arguing against systemic hypotension.

Cortical grey matter is relatively preserved, with greater RBC movement and a trend to higher sO₂.

Older WM mice show the same direction of change, with a stronger reduction in estimated CMRO₂.

Together these challenge a simple "more blood to white matter" mechanism and instead suggest regional vascular–metabolic redistribution.

CONTACT



Albeshr Almasri

Presenting author

A.Almasri@sussex.ac.uk

US

UNIVERSITY OF SUSSEX

sussex

NEUROSCIENCE

MRC

Medical Research Council

UK Dementia Research Institute

UCL

ALZHEIMER'S ASSOCIATION

AAIC>26