Blood Flow and Cognition

C Miller Fisher Neuroscience Visionary Award Address
NECC Boston 2019

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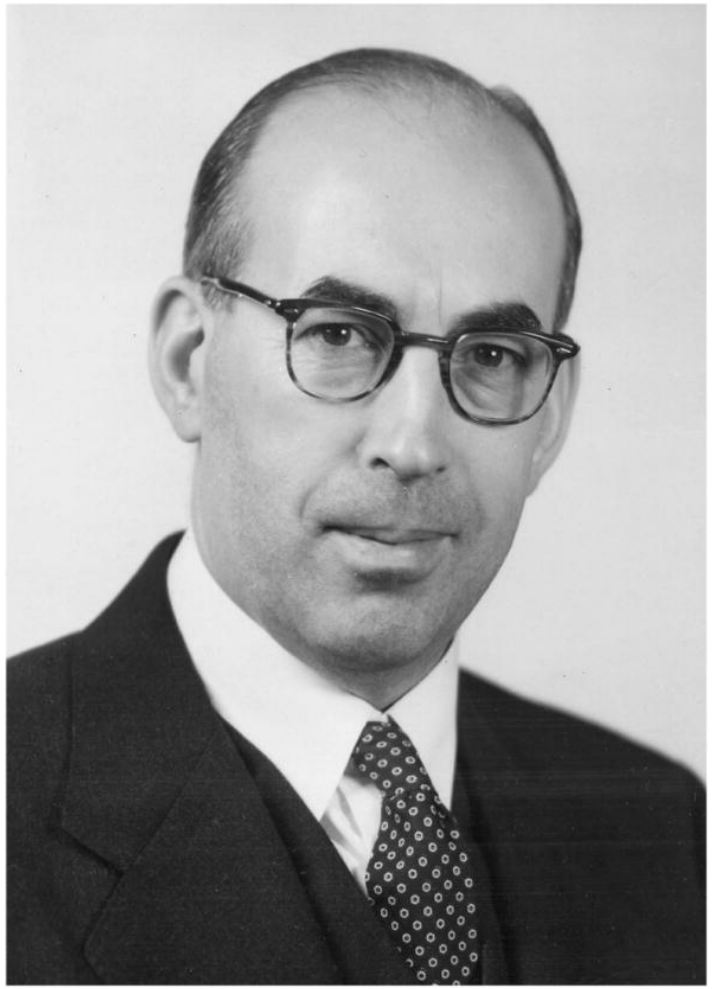
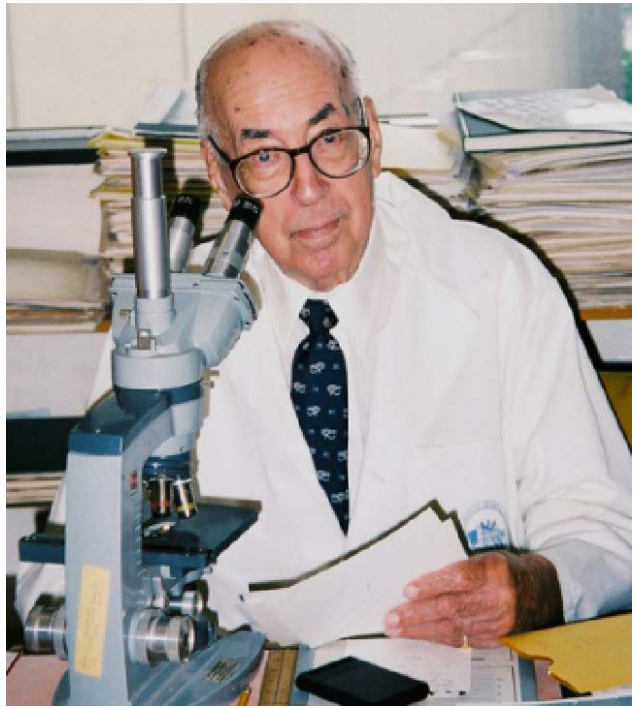
Disclosure Statement of Financial Interest

Affiliation/Financial Relationship	Company
1R01NS076277 (Blood Flow Cognition)	NIH/NINDS
1R01NS097876 (CREST-H)	NIH/NINDS
1U24 NS10723 (StrokeNet RCC)	NIH/NINDS
1U01 NS086872 (STrokeNet NCC)	NIH/NINDS
Royalty Income	Elsevier

C Miller Fisher
(1913-2012)





A Sample of Typical Titles

The Canadian Medical Association Journal

JULY, 1951 • VOL. 65, NO. 1

SENILE DEMENTIA—A NEW EXPLANATION OF ITS CAUSATION*

Miller Fisher, B.A., M.D., F.R.C.P.[C.]†
Montreal, Que.

DEMENTIA in the older age groups is now responsible for approximately one-third of all first admissions to mental hospitals, this high incidence, no doubt, reflecting the well-known relative increase in the number of older people in the general population. For each patient whose condition requires care in a mental hospital there must be several others who can be looked after at home as they become submerged to a greater or lesser degree in what Kinnear Wilson has called "the sea of mindlessness". The magnitude of the practical problem posed by this illness or group of illnesses needs no further emphasis. However, there is an equally important aspect which too often is neglected; I refer to the fact that here "Nature" is performing the most varied experiments, providing us with unique information concerning the organic substrate of a vast array of symptoms including defective memory, depression, hallucinations, delusions, paranoia, delirium, insomnia and anxiety. This rich mine of psychiatric data lies for the most part, unworked.

Many disease entities, including neurosyphilis, alcoholism, cranial trauma, Huntington's chorea, pernicious anæmia, tuberous sclerosis, multiple sclerosis, vitamin deficiency, hydrocephalus and drug addiction can be associated with dementia in older persons, but these are not under discussion in this paper. When cases of dementia with the above diagnoses have been excluded, there still remains the vast majority which are labelled arteriosclerotic dementia, senile dementia, presbyophrenia, Alzheimer's disease or Pick's disease. The clinical and pathological criteria for each of these diagnoses have remained nebulous and confusing in spite of many excellent studies.

Mental deterioration following upon strokes, whether due to hæmorrhage, thrombosis or embolism, is usually classified as arteriosclerotic, without attempting any further distinction. When all cases with a history of stroke are separated out there is still left a large number in which deterioration has been slowly progressive and unmarked by a definite cerebrovascular accident. In this group, diagnosis is most difficult. If the dementia appears around the age of 50, Alzheimer's or Pick's disease is diagnosed although neither has specific clinical or pathological features. At a later age the diagnosis rests between cerebral arteriosclerosis and so-called senile dementia. Clinical distinctions between these two have been made on many occasions, but there are so many exceptions and so much overlapping, that it is problematical if any definite difference really exists.

From a pathological point of view the differential diagnosis may be just as difficult. Apart from the occurrence of convolutional atrophy, senile plaques or neurofibrillar changes in both, there is usually some cerebral arteriosclerosis in all cases with resultant difficulty in deciding how much of the entire picture is due to the arteriosclerosis and how much to such vague and unknown factors as abiotrophy. When vessel changes are minimal, senile dementia is diagnosed. When they are severe, arteriosclerotic dementia is favoured, while in the presence of moderate changes in the vessels, the dementia is suspected of being "mixed".

A recent pathological study of a case of severe senile dementia has uncovered a previously unsuspected lesion. At post-mortem examination virtually complete occlusion of the cervical portion of both internal carotid arteries was found, the intracranial cerebral vessels themselves being almost free of arteriosclerosis. The basilar artery and other collateral channels must have carried the entire blood supply to the brain. Had the carotid vessels not been examined, the dementia

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were unusually large.

The carotid arteries in the neck were examined in detail (Fig. 1). On the left side, the region of the bulb or sinus was completely occluded, three-fifths of the lumen being occupied by an eccentric yellow mass, the remaining two-fifths showing a firm white tissue in which a minute hole may have been present. The left internal carotid artery above the carotid bulb was firmly distended with dark red clot which extended upwards and was probably continuous with the clot found in the cerebral portion of the left internal carotid artery. The wall of the internal carotid artery above the bulb was normal.

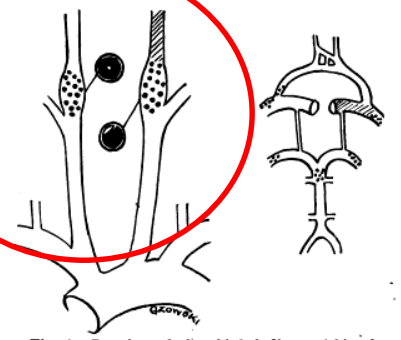


Fig. 1.—Drawing of the chief findings within the carotid arteries. The stippled areas represent atherosclerosis, the hatched area represents fresh blood clot. The Circle of Willis is drawn to scale. The black circular areas are cross-section views of the artery.

The right internal carotid artery in the region of the bulb was almost occluded by a symmetrical yellowish layer, at one edge of which a thin lumen 0.5 mm. in diameter was seen. Above the bulb the artery was normal. Both common carotid arteries were large and patent, including their origin from the innominate artery and aorta respectively. The mouths of the external carotid arteries were slightly narrowed by atherosclerotic deposits, but not to an important degree.

Summary.—This patient after having progressive senile dementia for several years, finally died due to a recent thrombosis of the left internal carotid artery. Both internal carotid arteries showed old atherosclerotic occlusion strictly localized to the carotid sinus. It is postulated that chronic cerebral ischæmia due to blockage of the carotid arteries caused the progressive cerebral deterioration. Attacks of unconsciousness or fainting, which are not uncommon in elderly dements, occurred on two occasions. The absence of pulses at the ankles should prove to be characteristic. Both posterior communicating arteries were small, so that blood must have passed through small collateral channels to reach the territory of the internal carotid arteries. The presence of a coarse tremor of the hands coupled with slowness of gait is a common part of the picture in senile dementia.

The following two cases are examples of senile dementia in which carotid disease is strongly suggested on clinical grounds.

CASE 2

Male, aged 74. Patient was admitted in July, 1948, at the age of 71. From his family it was learned that for a few years he had been a "difficult character", hard to please, impatient, restless and irritable. He would tear his clothes for no reason and was careless about throwing matches away after lighting his pipe. The neighbours were frightened of him and the family sometimes thought he was insane.

The patient himself complained of weakness of the arms, stiffness of all limbs, and a mild tremor of the right hand. Walking was difficult and sometimes on the street attacks of uncontrollable running came on in which he would stop only when he bumped into some object. He also complained of right-sided headache, a burning feeling in both feet and dyspnœa on exertion.

On examination he was well developed, well nourished and of good colour. The face bore a fixed expression. There was difficulty in gazing upwards and possibly bilateral ptosis. The patient moved about slowly with tiny steps. There was rigidity of all limbs. The tendon reflexes were sluggish but equal and the plantar response was downwards. Vibration sense was normal. The blood pressure was 190/90, and there was normal sinus cardiac rhythm. The blood Kahn was negative.

In hospital he was unhappy, restless, depressed and said he would go crazy if kept in. In July, 1948, hyoscine was prescribed because of the rigidity of the limbs, but the patient became excited, and for several days had hallucinations, delusions and constantly talked nonsense. This reaction subsided but he continued to have bouts of unusual behaviour. In January, 1949, he said he had heard his wife speaking to him, that he was detained from leaving the hospital by rifle-carrying guards and also claimed that his wife spent the night washing paint off houses in a nearby village. In the following months he was frequently disorientated in time and place, particularly at night when he would become indignant at imaginary wrongs and use abusive language.

By mid-1950 his face was expressionless and he had a characteristic stooped posture and shuffling short-step gait. All movements were slow and deliberate. The limbs displayed "lead-pipe" rigidity.

Examination in February, 1951, showed little change. He walked slowly with shuffling, six inch steps, the toes turned in, and the body stooped. The voice was monotonous. All limbs showed rigidity, the right more than the left. The pupils were equal and reacted to light. There was no facial weakness. The tendon reflexes were normal and the plantar responses downwards. Vibration was appreciated at the mid tarsus.

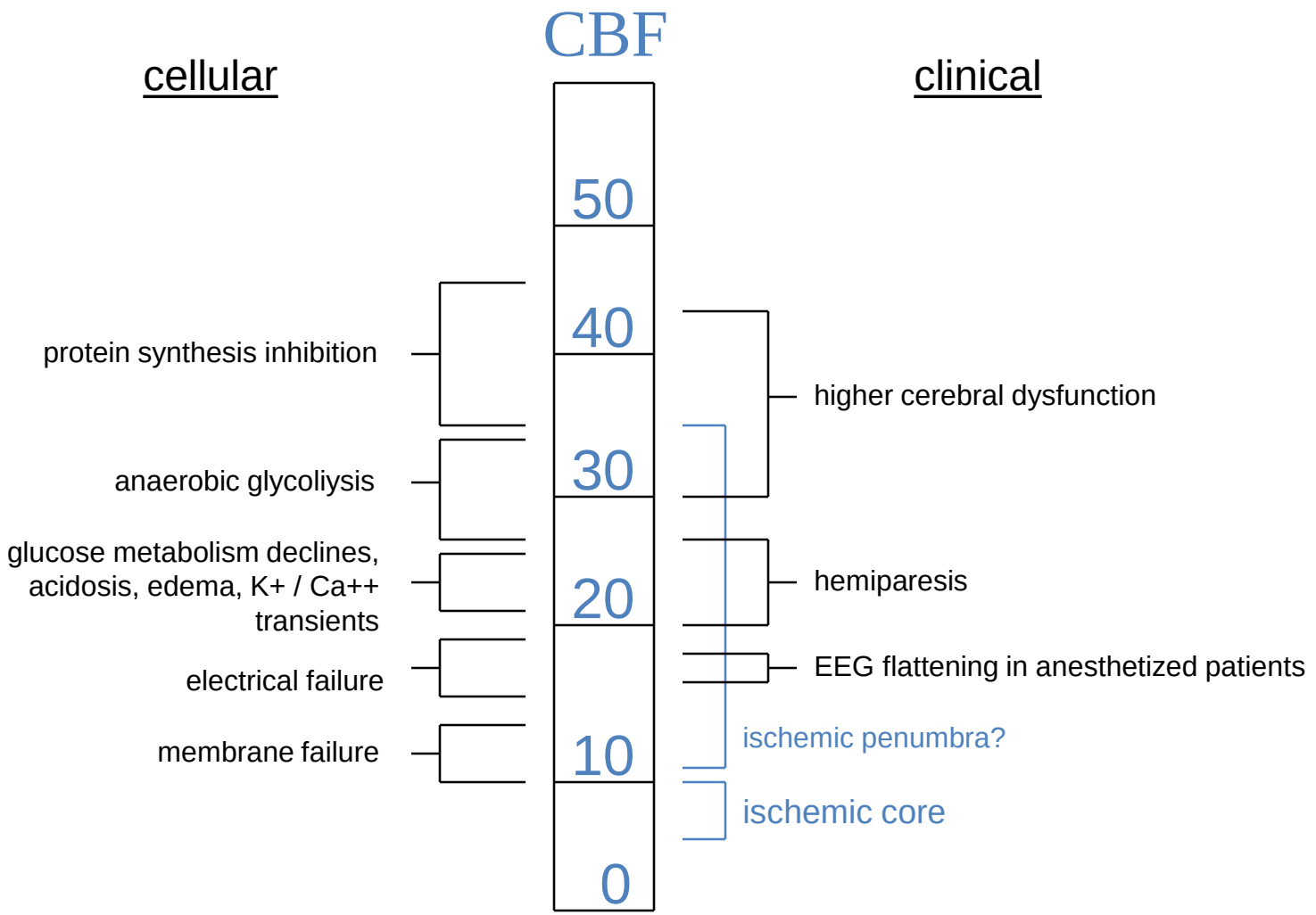
He thought he had been in hospital about a year and wanted to get out and "get active again". He did not know his age but knew where he was.

Pulsation in the left internal carotid was absent, while in the right it was much reduced but probably present. Pulsation was absent in both posterior tibial and dorsalis pedis arteries. The blood pressure was 180/100. There was a loud basal cardiac murmur maximum beneath the mid-clavicle on the right side. A striking pulsation within

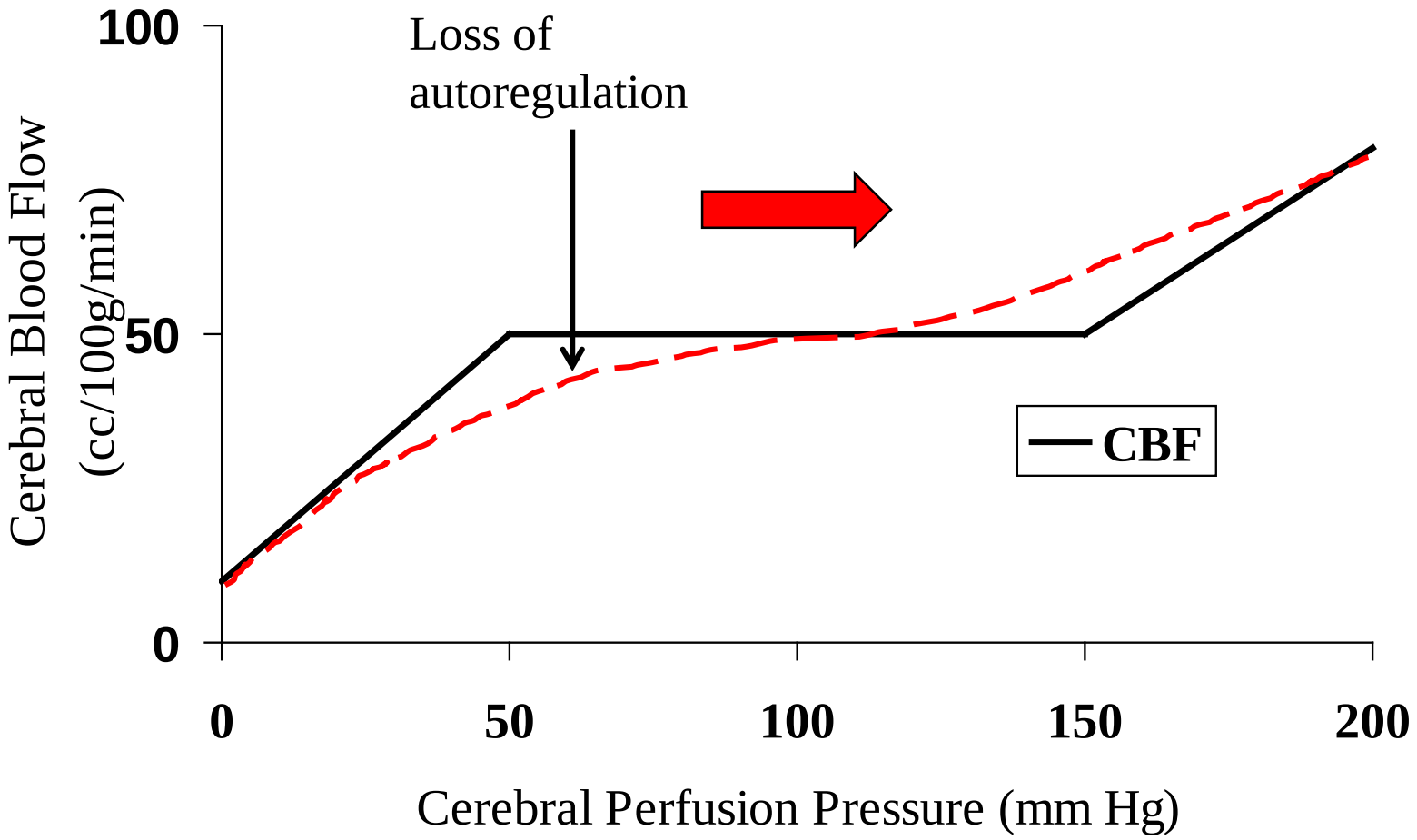
Impact of Hemodynamics on Brain Function

1. Hyperacute setting: flow thresholds for cognition
2. Acute stroke management: “pressure dependent exam”
3. Chronic hypoperfusion: Cognitive impairment… recovery?

Cerebral ischemic thresholds

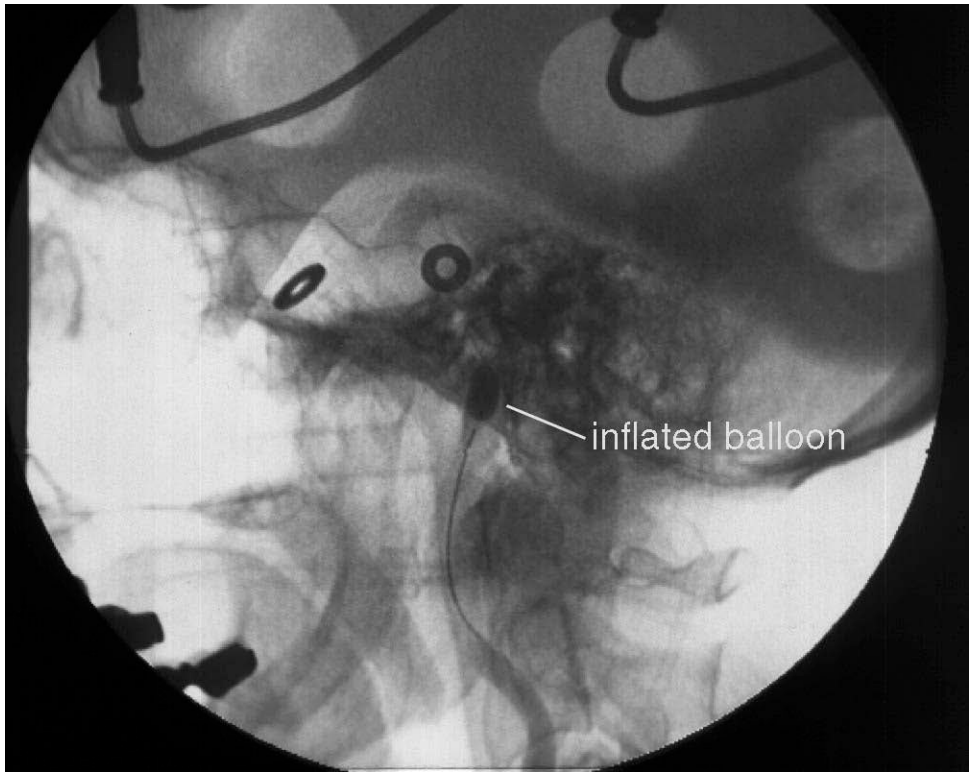


Cerebral Hemodynamics - Autoregulation

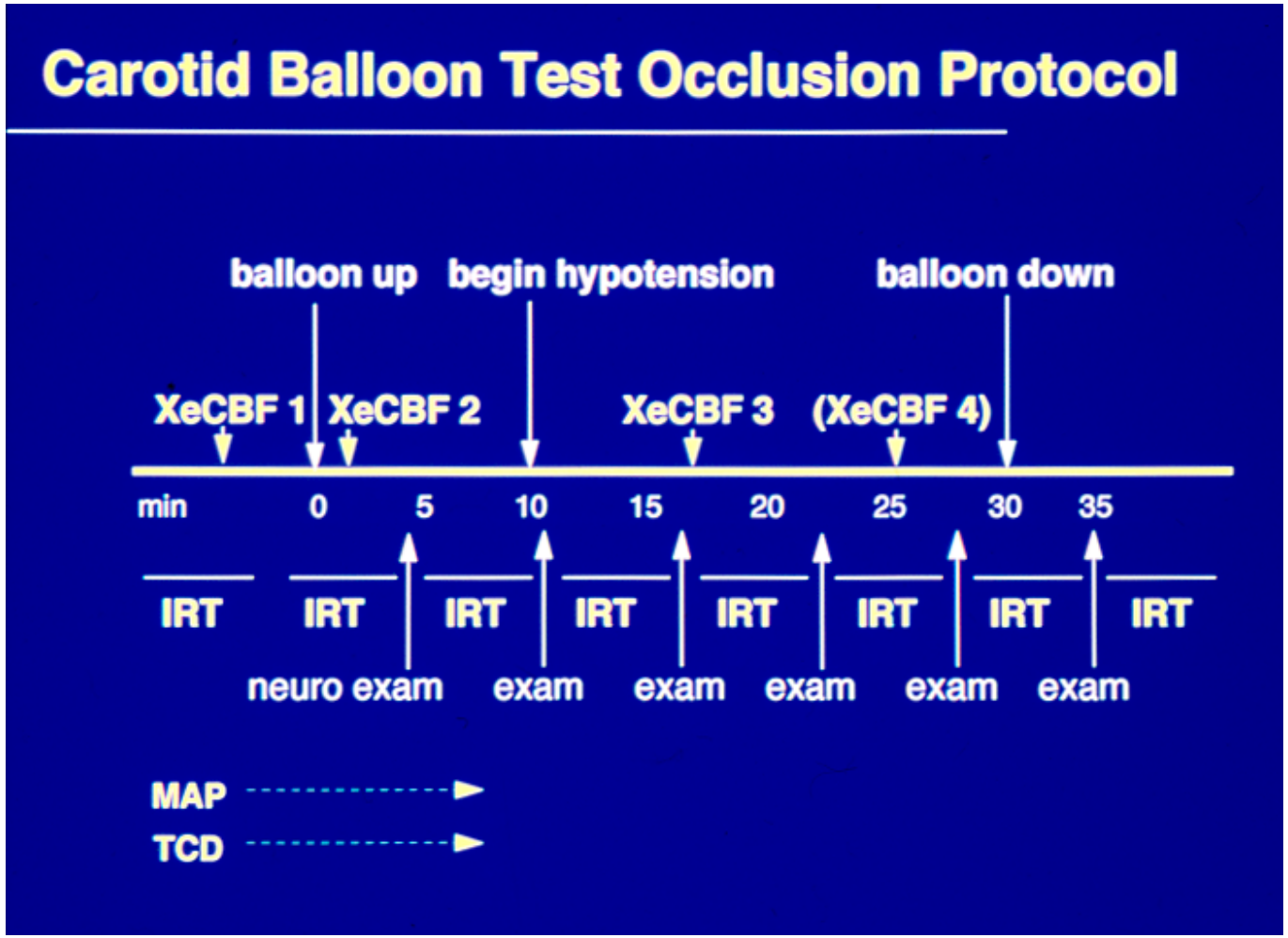


Hypoperfusion affects Brain Function in hyperacute ischemia

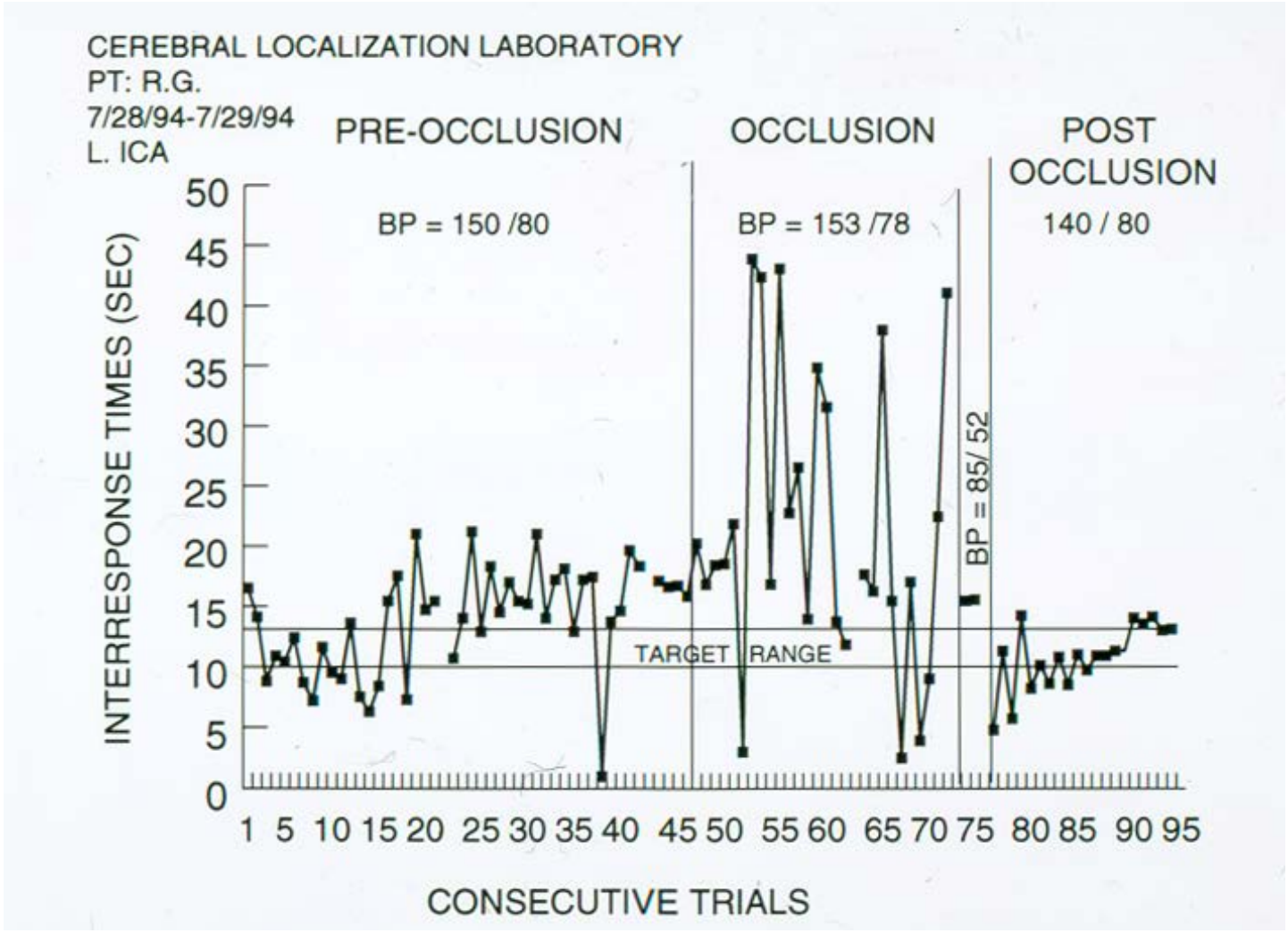
Hemodynamic effects in acute setting: ICA Balloon Test Occlusion



CBF and clinical monitoring during BTO

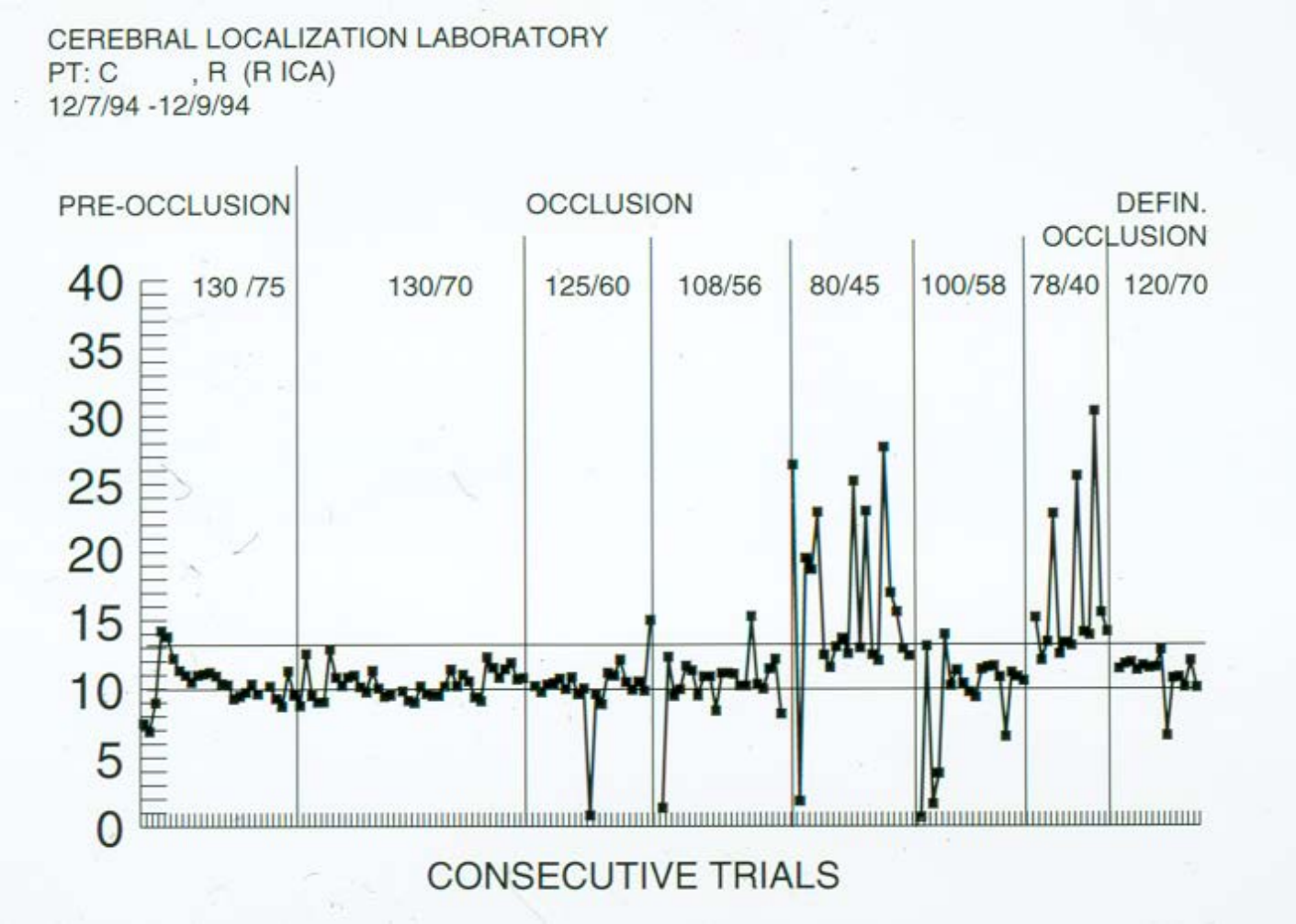


Pt RG: failed balloon test occlusion



Lazar RM, Marshall RS et al , JNNP 1996;60(5):559-63

Pt RC: Pressure –dependent BTO



Lazar RM, Marshall RS et al , JNNP 1996;60(5):559-63

Hypoperfusion Effects in Acute Stroke

Induced hypertension supports cognitive function in acute stroke

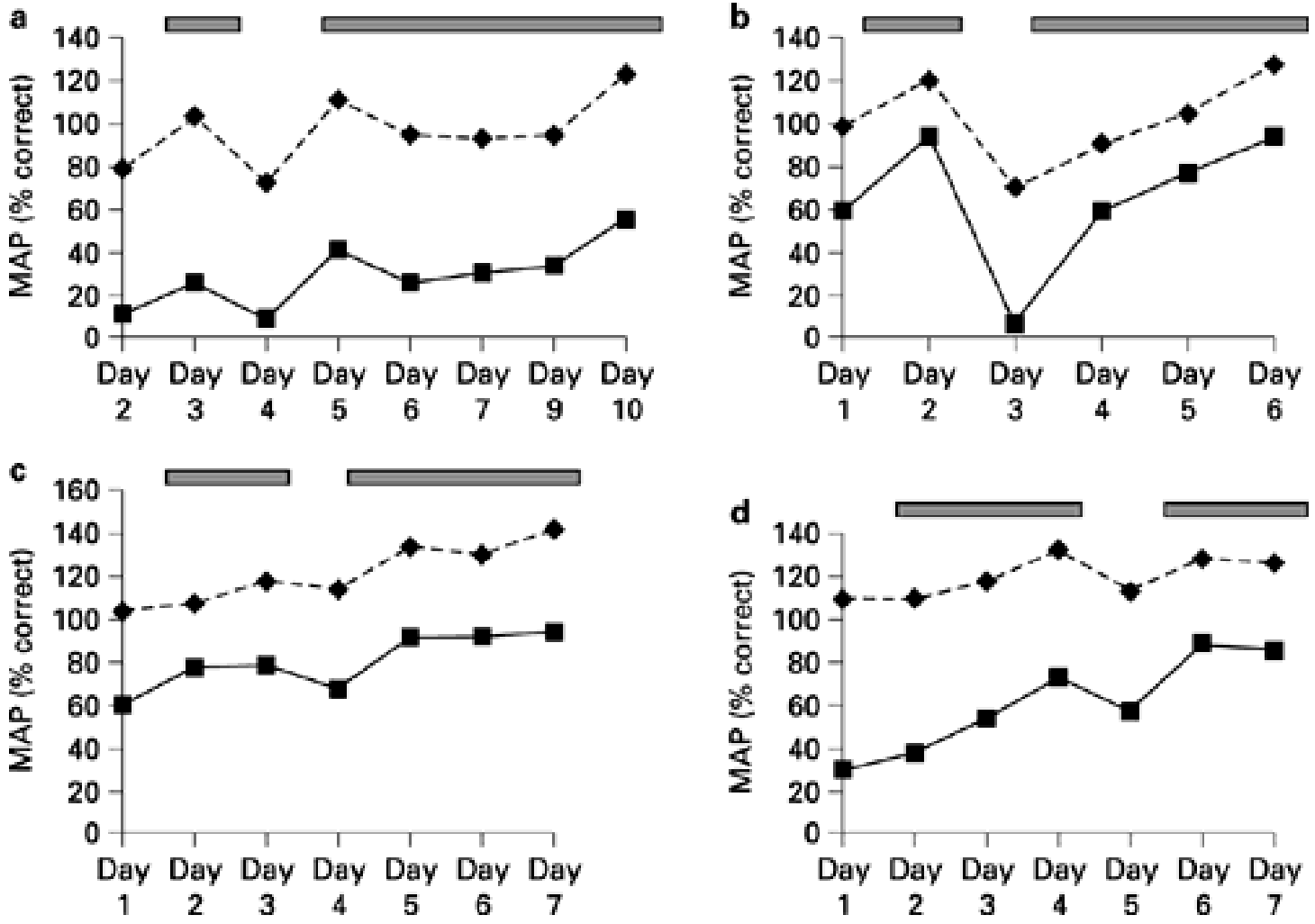


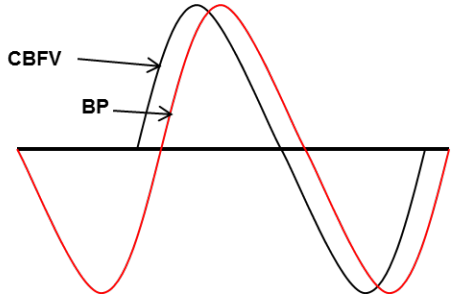
Fig. 2. Illustrations of the temporal relationship between MAP and performance on daily tests of cognitive function. ✦ = MAP; ■ = function. Note decrease in fxn when phenylephrine discontinued. A & b: picture naming, c & d: line cancellation.

Hillis AE et al Cerebrovasc Dis 2003;16:236-246

Dynamic Cerebral Autoregulation in Acute Stroke

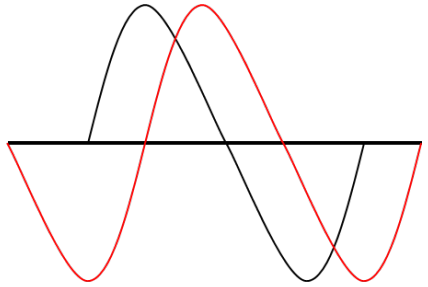
DCA: continuous monitoring of TCD and BP

LOW phase shift: poor autoregulation



20 degrees out of phase

HIGH phase shift: good autoregulation



80 degrees out of phase

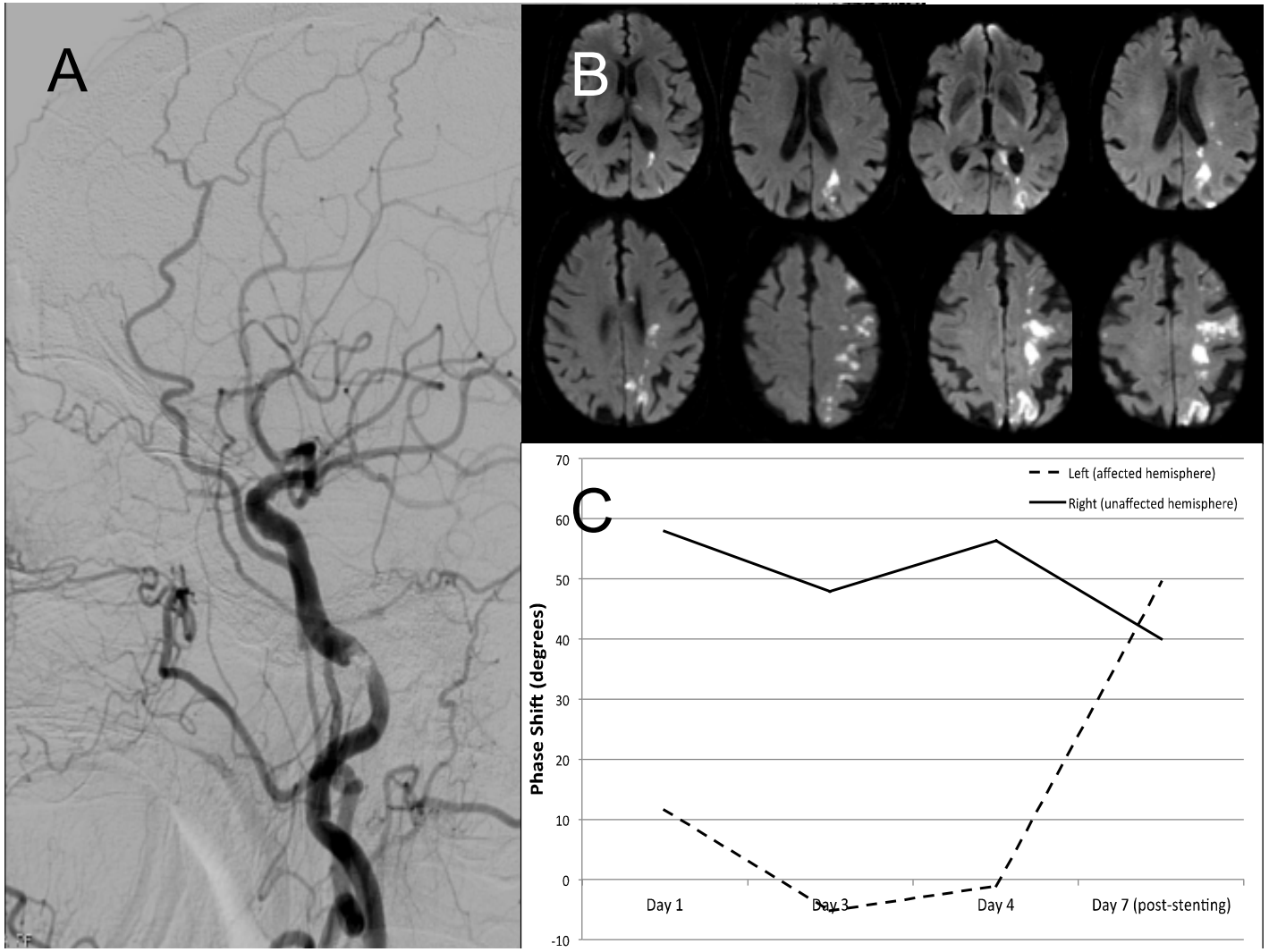
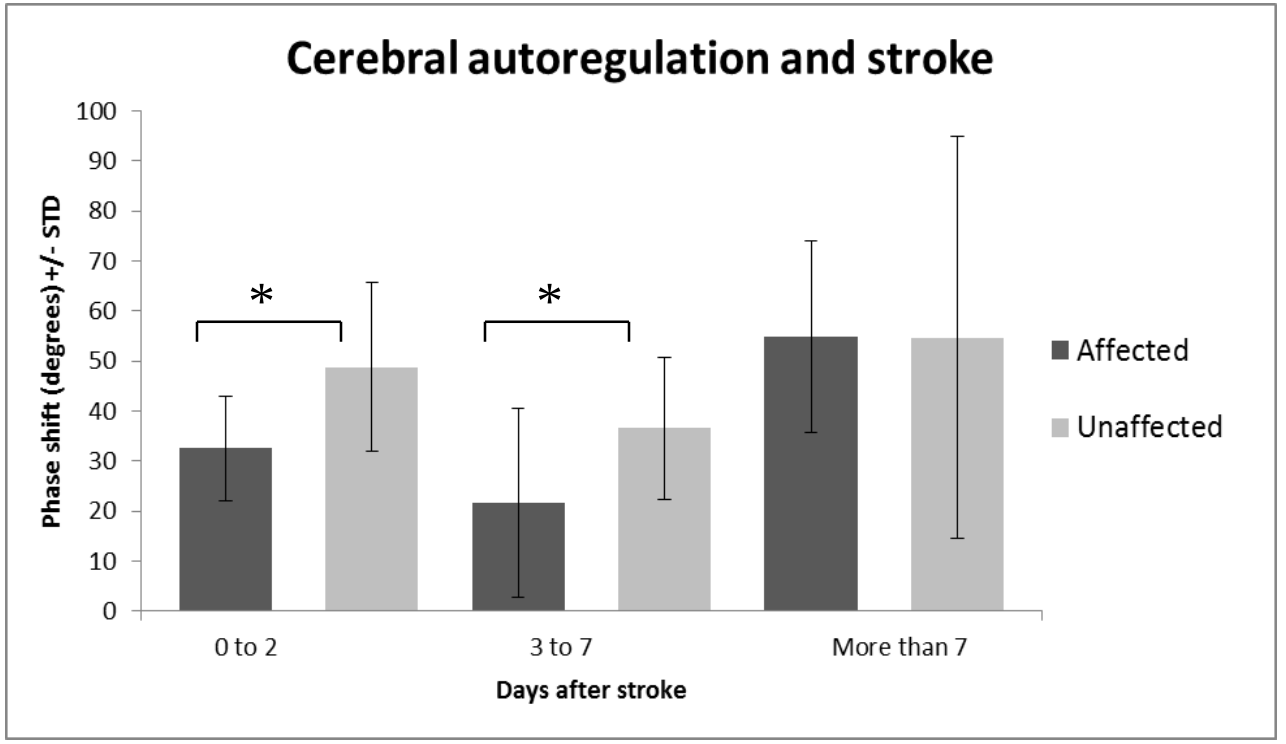


Figure 2 A-C

DCA normalization 1 week after Acute Stroke

32 patients (mean NIHSS=10±7.3; age=62.9±16.9; 17F) with acute, (embolic, large) ischemic stroke in the middle cerebral artery territory. DCA was assessed on days 0-2, 3-7 and >7 after stroke. Transfer function analysis was applied to calculate average phase shift (PS) in the low frequency range (0.06-0.12 Hz). At mean 1.1±0.6 days after stroke the average PS in the affected hemisphere was **32.5**±10.4 degrees versus **48.8**±16.9 degrees in the unaffected hemisphere (p=0.026). At 4.6±1.3 days, the PS in affected and unaffected hemisphere was **21.6**±18.9 vs. **36.5**±14.3 degrees, respectively (p=0.029). At mean 10.3±2.1 days stroke there was no difference between affected and unaffected hemisphere (**54.8**±19.1 versus **54.7**±40.28 degrees, p=0.99).

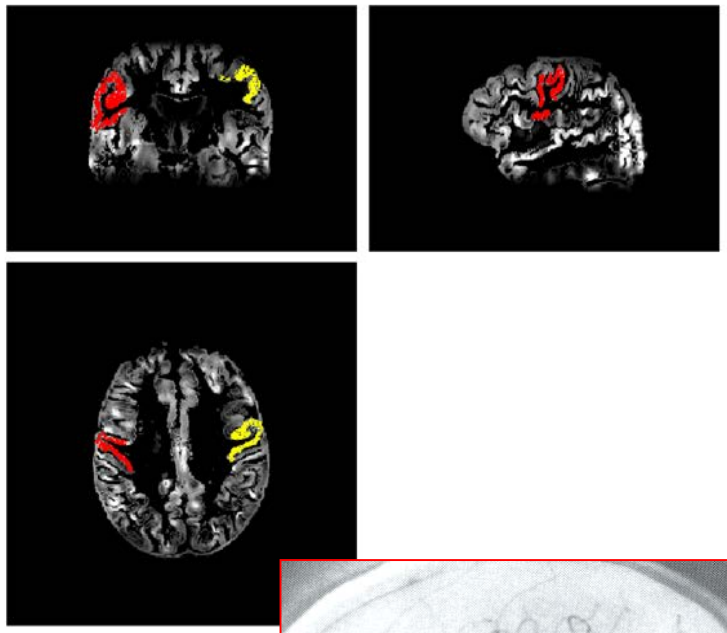


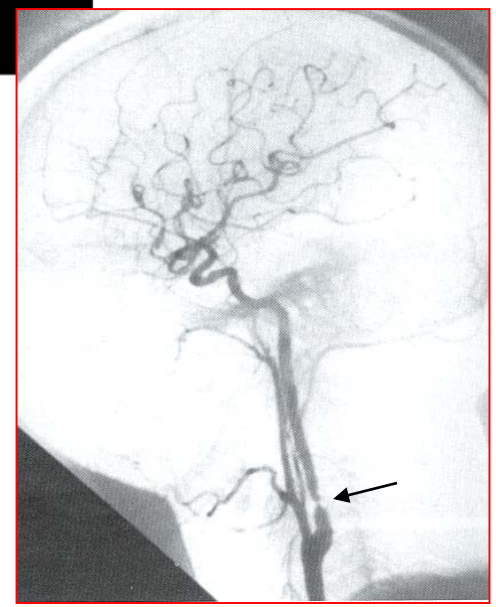
Petersen et al *Cerebrovasc Dis* 2015;39(2):144-50

Does Hypoperfusion Affect Function in the Chronic Setting?

Carotid Hypoperfusion and Cortical thinning

- **Background**: Cortical thinning is a biomarker for cognitive impairment.
- **Hypothesis**: cerebral hypoperfusion in the distal field of an asymptomatic ICA stenosis may play a role in the thinning process.
- **Method:** Co-registration of CBF and rCT in motor cortex (M1 -directly supplied by carotid arteries) and visual cortex (V1 - not supplied by carotid arteries directly)





Results 1: Comparing Means

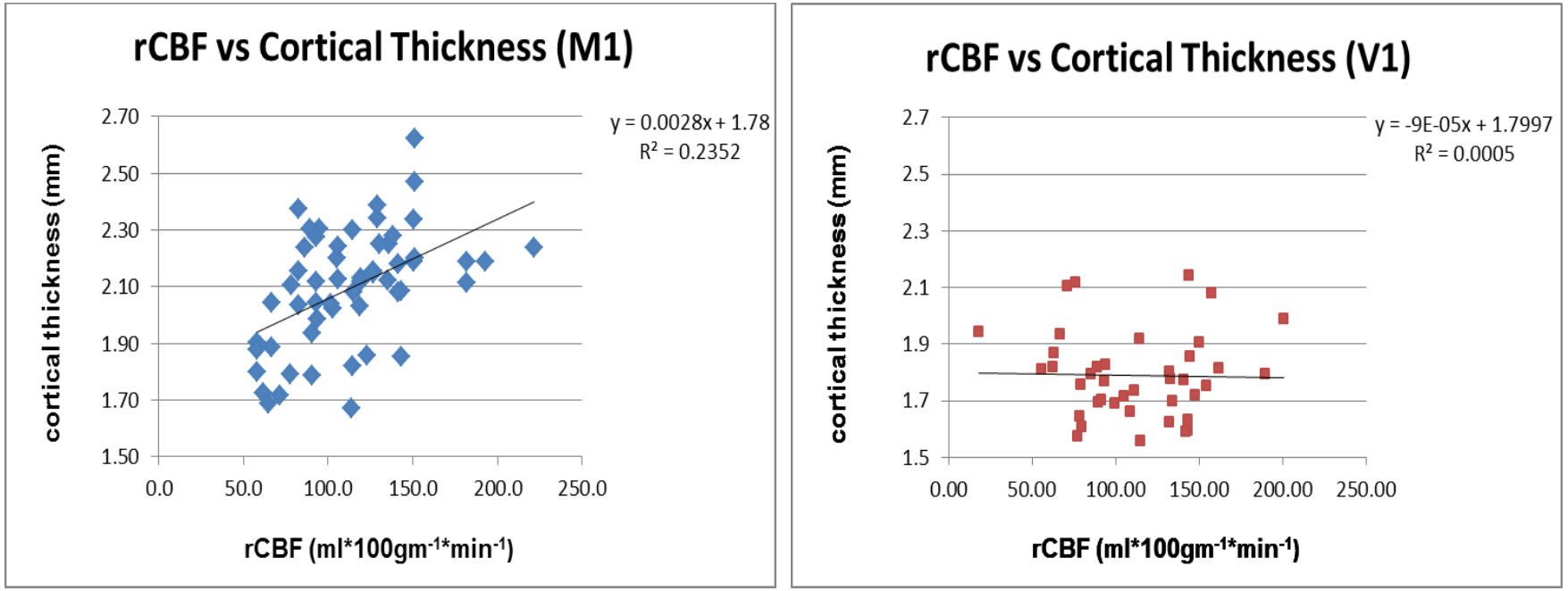
- GM CBF was significantly lower on the occluded side in M1 (115.2 $ml*100g^{-1}*min^{1}$ vs. 105.5 $ml*100g^{-1}*min^{-1}$, P<0.0001) and V1 (112.8 vs. 106.4 P=0.018).
- As reported previously, cortical thickness was significantly lower on the occluded side in M1 (2.07mm vs. 2.15mm P<0.001) but not in V1(1.78mm vs. 1.80mm, paired t-test P>0.2)), suggesting the ***ICA stenosis contributes to cortical thinning.***.

	M1 unoccl	M1 occluded	P-value	V1 unoccl	V1 occluded	P-value
GM-CBF ($100gm*ml^{-1}*min^{-1}$)	115.2	105.5	**0.0001**	112.8	106.4	**0.018**
Cortical Thickness (mm)	2.15	2.01	**0.0008**	1.80	1.78	0.6

Marshall RS et al *PLoS ONE* 2017 12(12):e0189727

Results 2: rCBF vs Cortical thickness in M1 and V1

Figure 2. Scatterplot of rCBF vs cortical thickness for M1 and V1. There is a linear correlation between rCBF and rCT in M1 (*both sides*), but not in V1 (GEE: p=.0002 for rCBF, p=.0020 for age).



Interpretation: In addition to the hemispheral effect… greater athero burden in carotid system than VB system → greater arterial stiffness → greater transmission of damaging pulsatile flow into tissue bed

Marshall RS et al *PLoS ONE* 2017 12(12):e0189727

TCD Mean Flow Velocity vs Cognitive Z-score

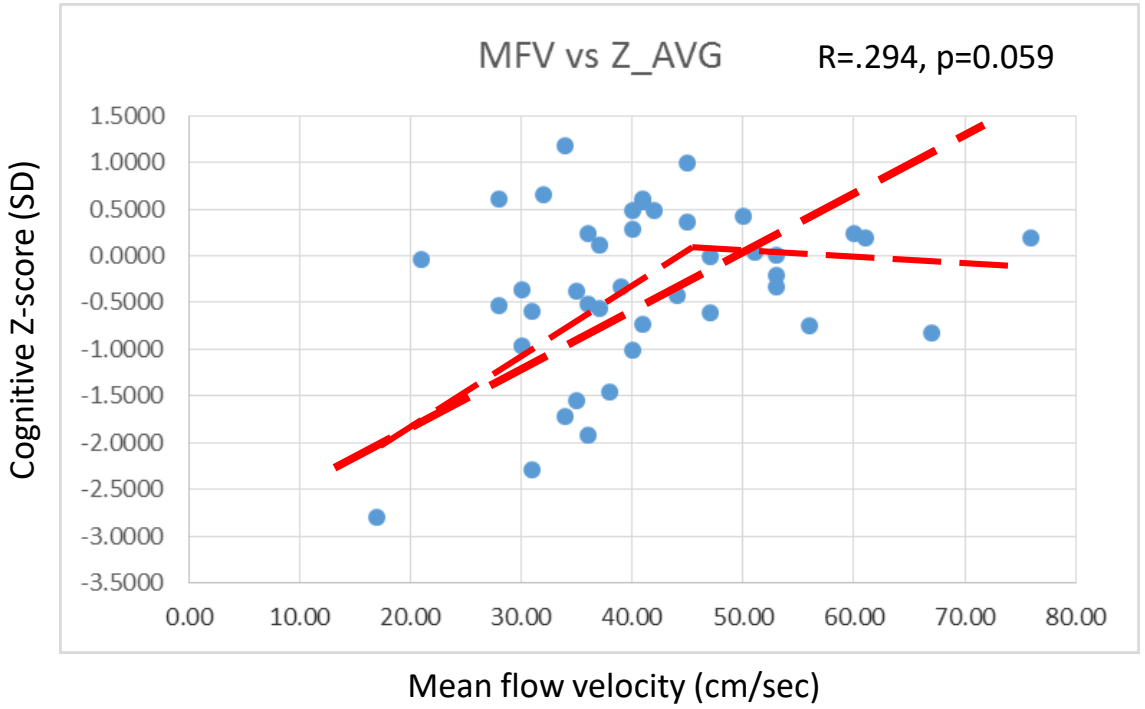


Figure 1: TCD mean flow velocity vs cognitive Z-score

The Davies test for non-zero difference-in-slope of a segmented relationship showed a single breakpoint at 45cm/sec

For MFV **< 45cm/sec**, the Z score increases 0.05SD per unit increase in MFV (95% CI: 0.01 to 0.10).

For MFV **> 45cm/sec**, the Z score showed no significant change per unit increase in MFV (95% CI: -0.07 to 0.05).

Marshall et al, 2018 CARNET mtg, Leuven, Belgium

What does all this mean?

Holy Grail of Cognitive Impairment

If:

Chronic hypoperfusion causes cognitive impairment and that impairment is reversible…

Then:

We have an alternative reason to treat patients with “asymptomatic” carotid artery stenosis.

(because they aren’t really asymptomatic)

CREST-H

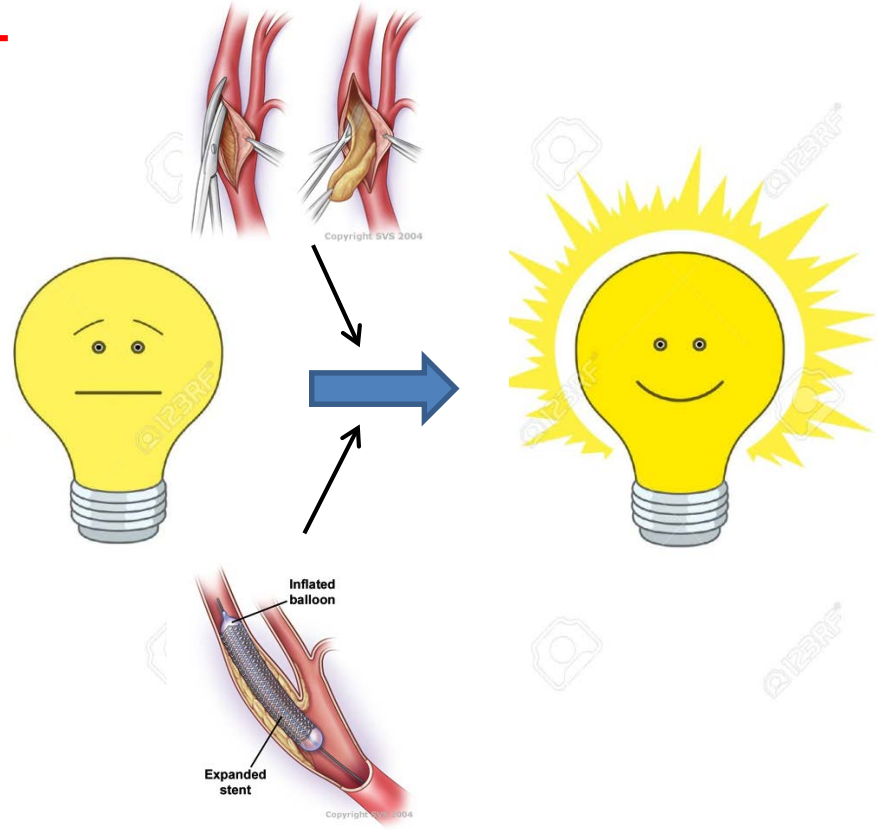
Carotid **R**evascularization **E**ndarterectomy and **S**tent **T**rial - **H**emodynamics

(an ancillary study to CREST-2)

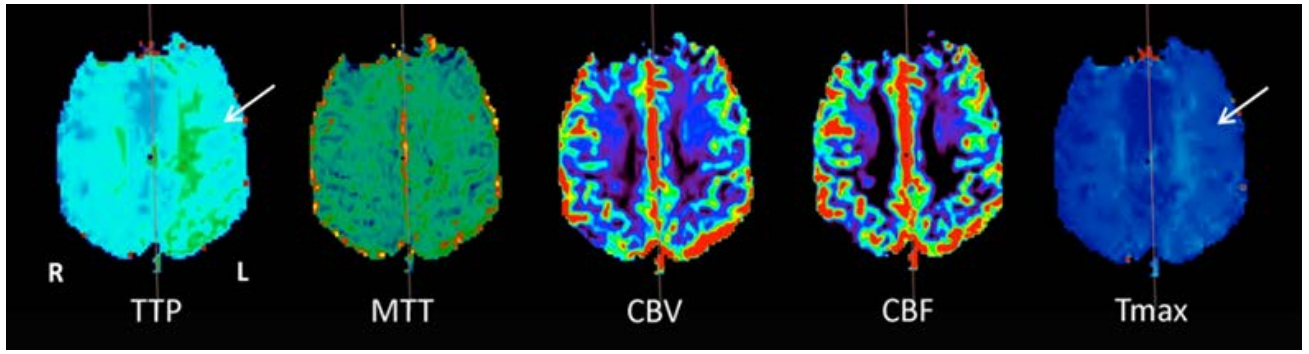
CREST-2

CREST-H Study Question

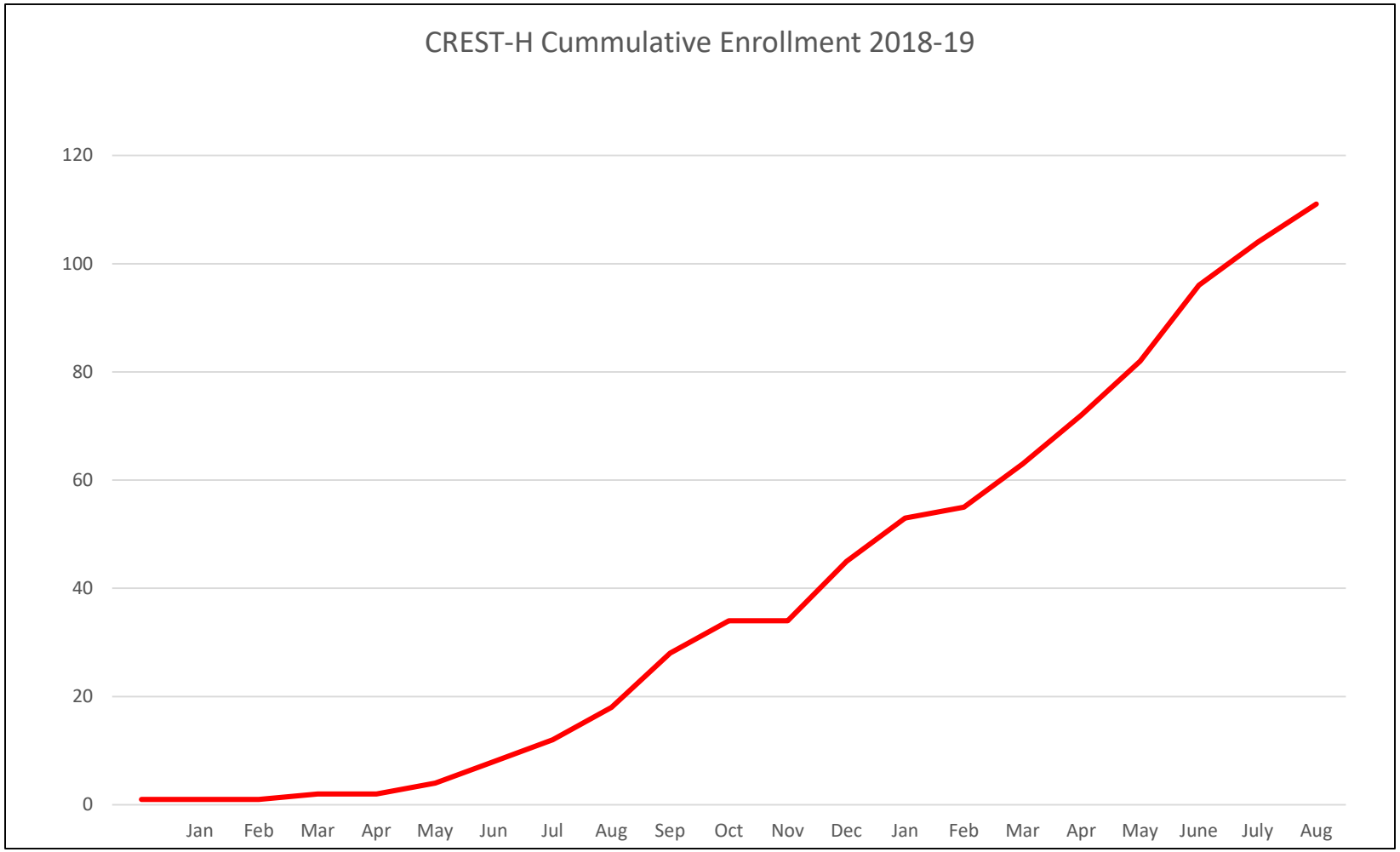
- Can revascularization (CEA or CAS) improve cognitive impairment among high-grade asymptomatic carotid stenosis patients with cerebral hemodynamic impairment?



MRP / CTP



CREST-H Cumulative Enrollment through Sep 2019



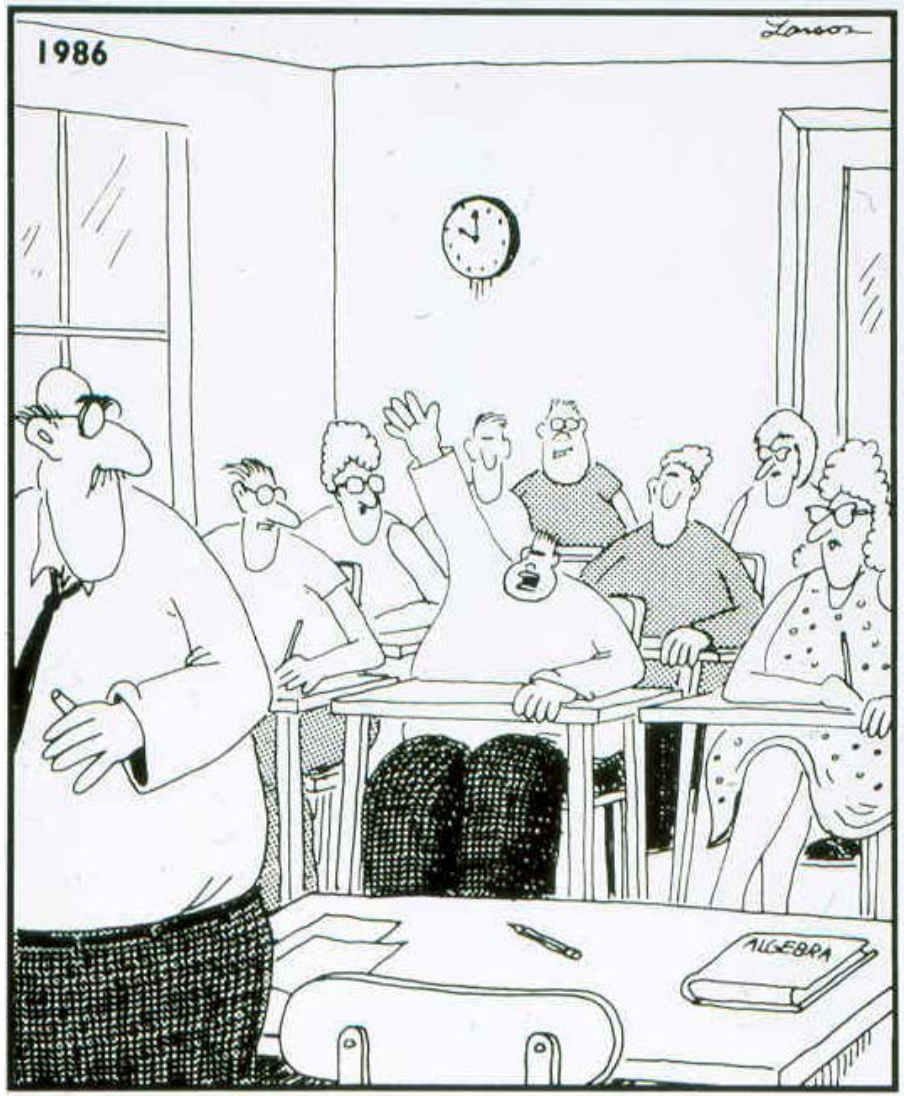
114 subjects enrolled as of October 18, 2019

51 Green-lighted Sites, 113 pts as of Oct 9, 2019

Thank you!

- Columbia (8)
- UPMC (6)
- Iowa (7)
- Maine Medical (7)
- Mayo Clinic Rochester (6)
- U Florida Shands (4)
- Michigan Vascular (4)
- USC/Keck (3)
- Mercy Medical St Louis (3)
- Kaiser Perm Los Angeles (3)
- Weill Cornell (2)
- Vancouver General (2)
- Yale (4)
- Gundersen (2)
- SUNY Buffalo (3)
- North Central Heart (1)
- U Washington Harborview (1)
- Ohio State (2)
- Mayo Clinic Florida (2)
- Overlake Hospital (1)
- University of Utah (2)
- St. Boniface(1)
- Ocshner(1)
- St.Josephs Barrow(1)
- Stanford(2)
- OhioHealth
- Huntsville Heart (2)
- U Wisconsin (1)
- U Minnesota (1)
- Univ Hosp Cleveland (5)
- Washington Adventist (1)
- Wake Forest (3)
- Novant Health (5)
- U Penn
- Houston Methodist
- MUSC(2)
- Northwestern
- Tennova Turkey Creek
- UCLA
- U Miami
- U Maryland
- Univ Alabama Birmingham
- VA Puget Sound(1)
- Intermountain Health
- Morton Plant(1)
- University of Chicago(1)
- University of Virginia
- Central Arkansas VA
- Inova (1)
- Louis Stokes(1)
- Kaiser San Diego

end



"Mr. Osborne, may I be excused? My brain is full."

Hemodynamics Projects

- Dysautoregulation in pre-ecclampsia (Miller K23)
- Arterial Stiffness and remodeling in brain aging (Gutierrez R01)
- White Matter Hyperintensities, PET amyloid and autoregulation (Brickman: R21, R01)
- Autoregulation in hypoparathyroidism (Walker R01)
- Altered hemodynamics in Cardiac Failure (Kodali, Lazar)
- Altered hemodynamics in LVAD (Willey R01 pending)
- Development of new autoregulation measures (Engineering Columbia, Petersen – Yale)
- CREST-H: flow failure subgroup in CREST-2 (Marshall, Connolly, Lazar, Liebeskind)

Orthostatic Hypotenstion and Dementia

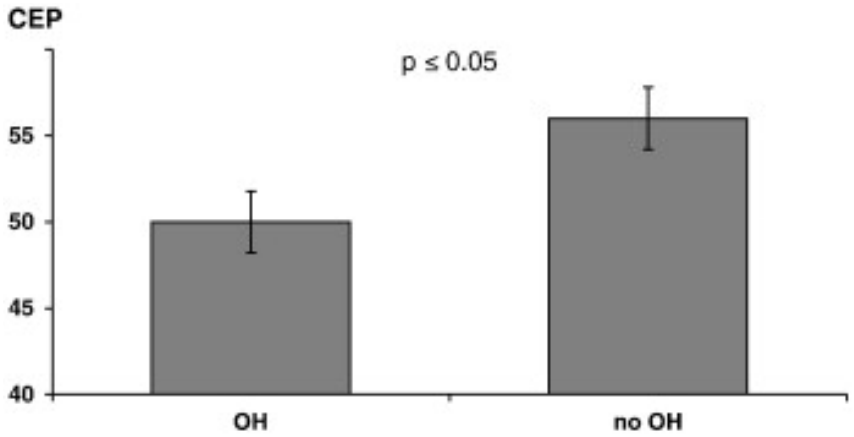


Fig. 1. Cognitive function in patients with and without OH (orthostatic hypotension) estimated by CEP (cognitive efficiency profile − mean scores ± SE). P ≤ 0.05, adjusted for age, education level, seated systolic blood pressure (SBP), seated diastolic blood pressure (DBP), weight and antihypertensive drugs.

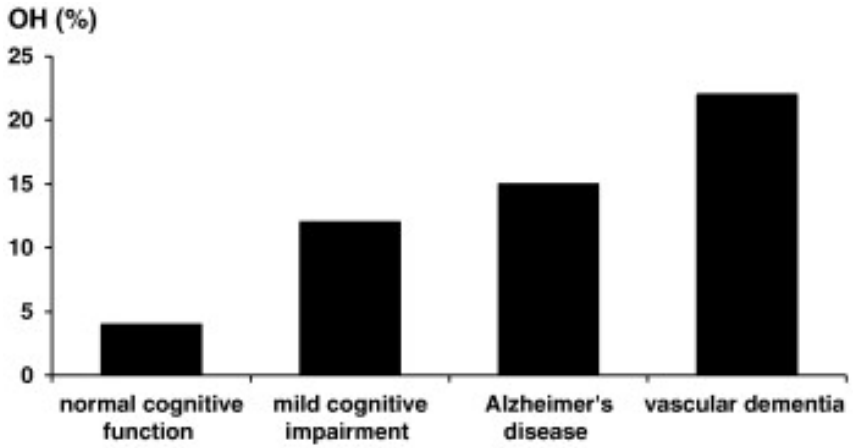


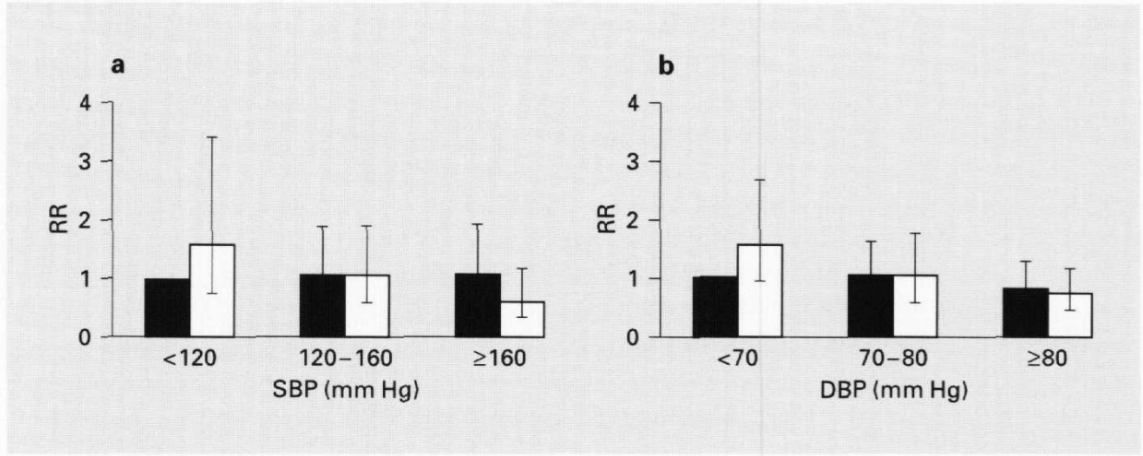
Fig. 2. Relationship between OH and cognitive status (normal cognitive function, mild cognitive impairment (MCI), Alzheimer's disease (AD) and vascular dementia (VaD)), adjusted for age, education level, seated systolic blood pressure (SBP), seated diastolic blood pressure (DBP), weight and antihypertensive drugs, P ≤ 0.01 for overall test.

n=495 with AD or VAD

Mehrabian S et al J Neurol Sci 2010;299:45-8

Risk of Hypotension in Dementia

Fig. 1. Antihypertensive medication use and relative risk (RR) of dementia. ■ = No antihypertensive medication; □ = antihypertensive medication. **a** Systolic blood pressure (SBP). Three categories of blood pressure level, stratified on medication use: <120, 120–160, ≥160 mm Hg; the lowest category without medication as reference. **b** Diastolic blood pressure (DBP). Three categories of blood pressure level, stratified on medication use: <70, 70–80, ≥80 mm Hg; the lowest category without medication as reference.



Ruitenberg et al Dementia Geriatr Cog Dis. 2001

Functions of autoregulation

- **Protection of brain from extremes of hypoperfusion and hyperperfusion**
- **Maintain homeostasis (dynamic): fluctuating perfusion pressures are continuously counter-regulated by changes in flow within normal range**
- **Neurovascular coupling to ensure adequate blood flow for neural activity**

Two-factor conceptual model

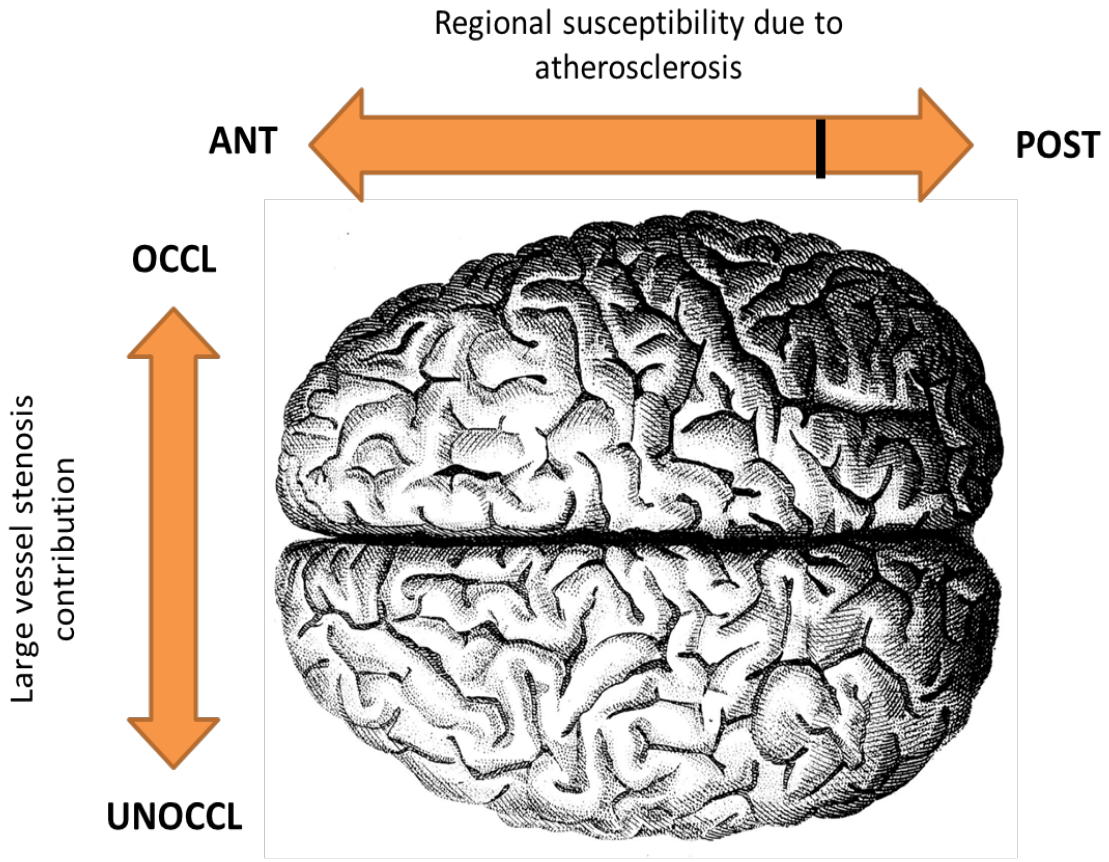


Figure 3. Two-factor model for the effect of altered hemodynamics on cortical thinning. We hypothesize a general susceptibility to thinning from atherosclerosis in the anterior circulation plus a hemispheral effect of cortical thinning due to restricted flow from the high grade carotid stenosis.

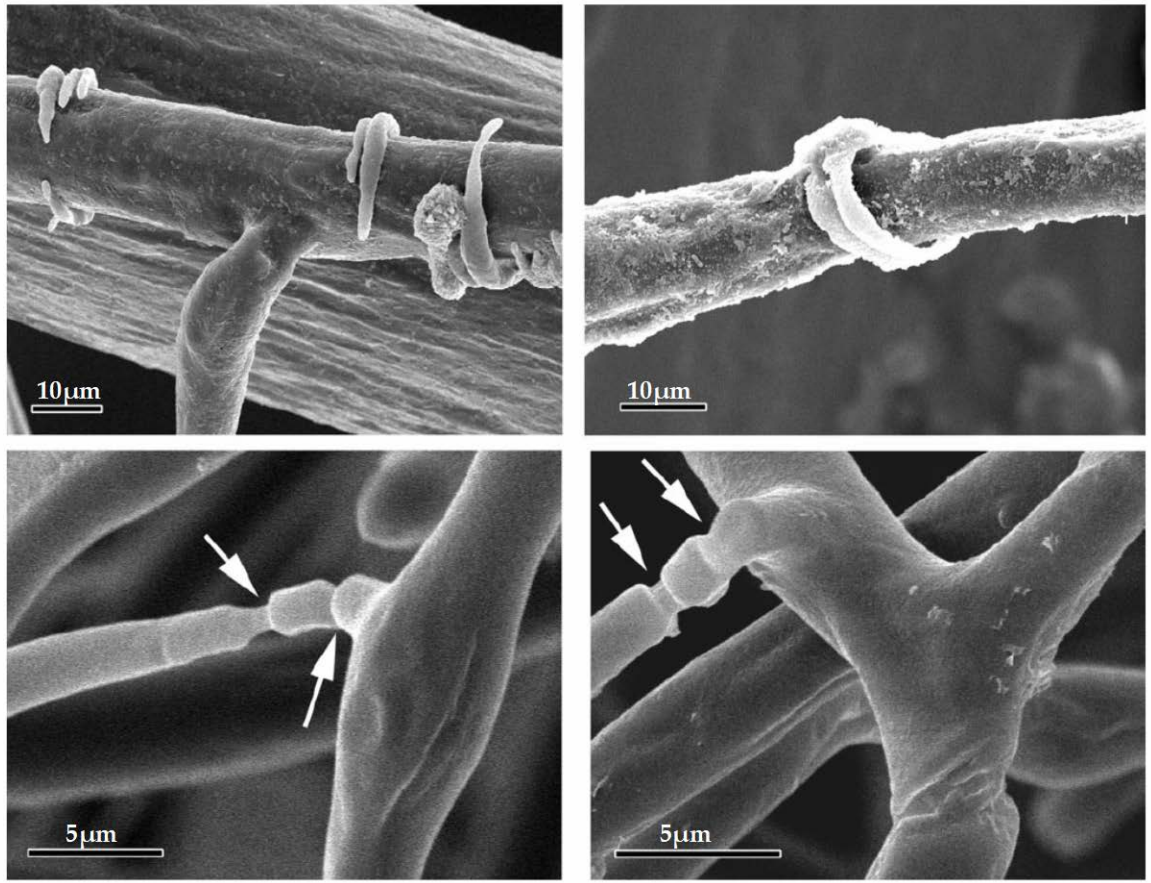
Marshall RS et al *PLoS ONE* 2017 12(12):e0189727

Mechanisms of autoregulation

- **Vasodilation and vasoconstriction**
  - Arterioles
    - “myogenic”: Resting tone – Ca++ mediated
    - “neurogenic”: Neurotransmitters – adrenergic (Zhang et al Circ 2002, Hammer et al Stroke 2010), and cholinergic (Hammer et al J Phys 2012)
    - NO to cause smooth muscle relaxation in response to acetylcholine and other stimuli
  - Capillaries
    - Pericytes constrict capillaries in response to noradrenaline

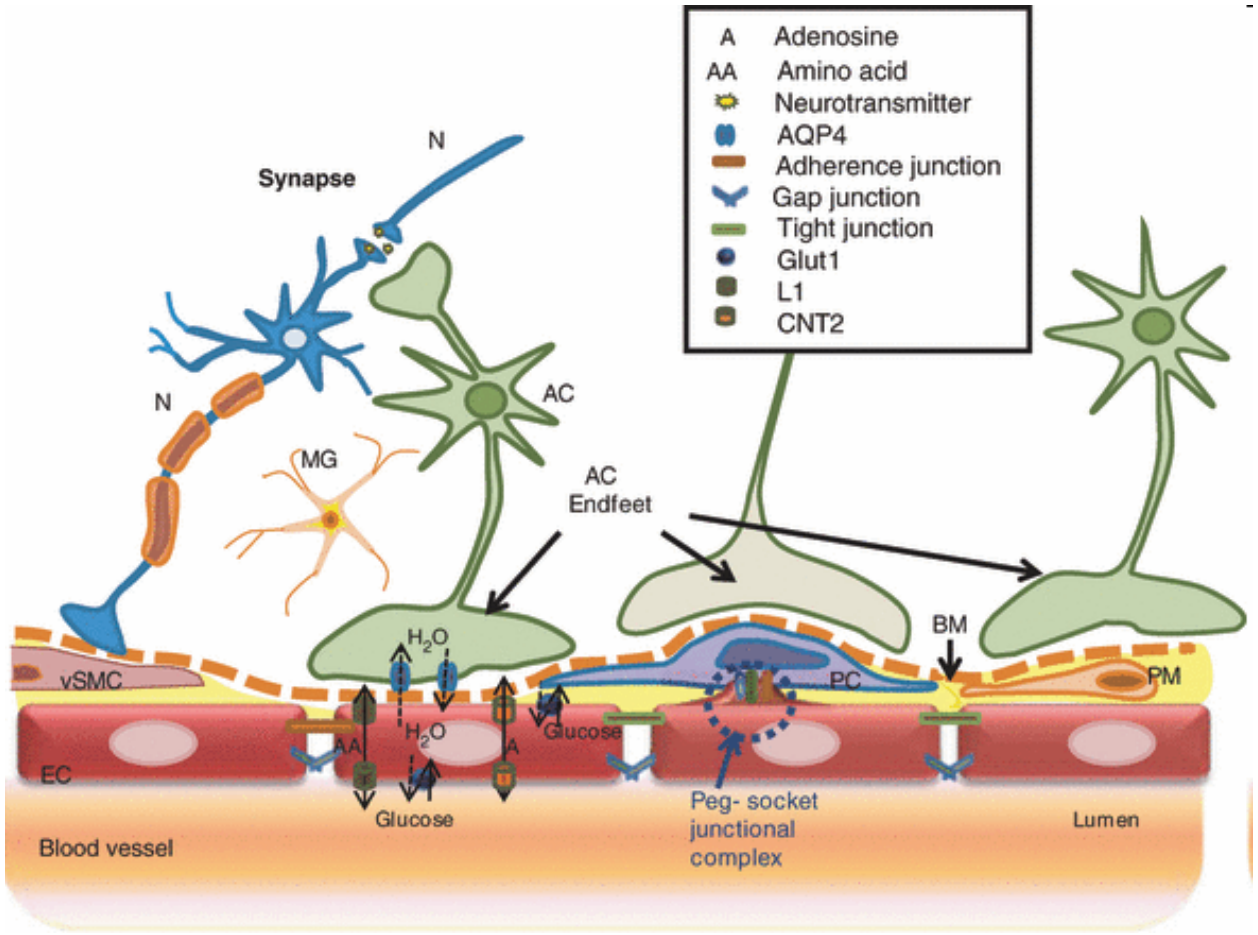
- **Neurovascular coupling**
  - Local effects on small vessels
    - NO: accumulates with neuronal activity, short-lived, potent vasodilator
    - Adenosine, arachidonic acid, and PGE2 may modulate vasodilation through astrocyte endfeet
  - Upstream regional effects to avoid passive reduction in flow elsewhere

EM of pericyte constricting a capillary



Harrison et al. (2002)

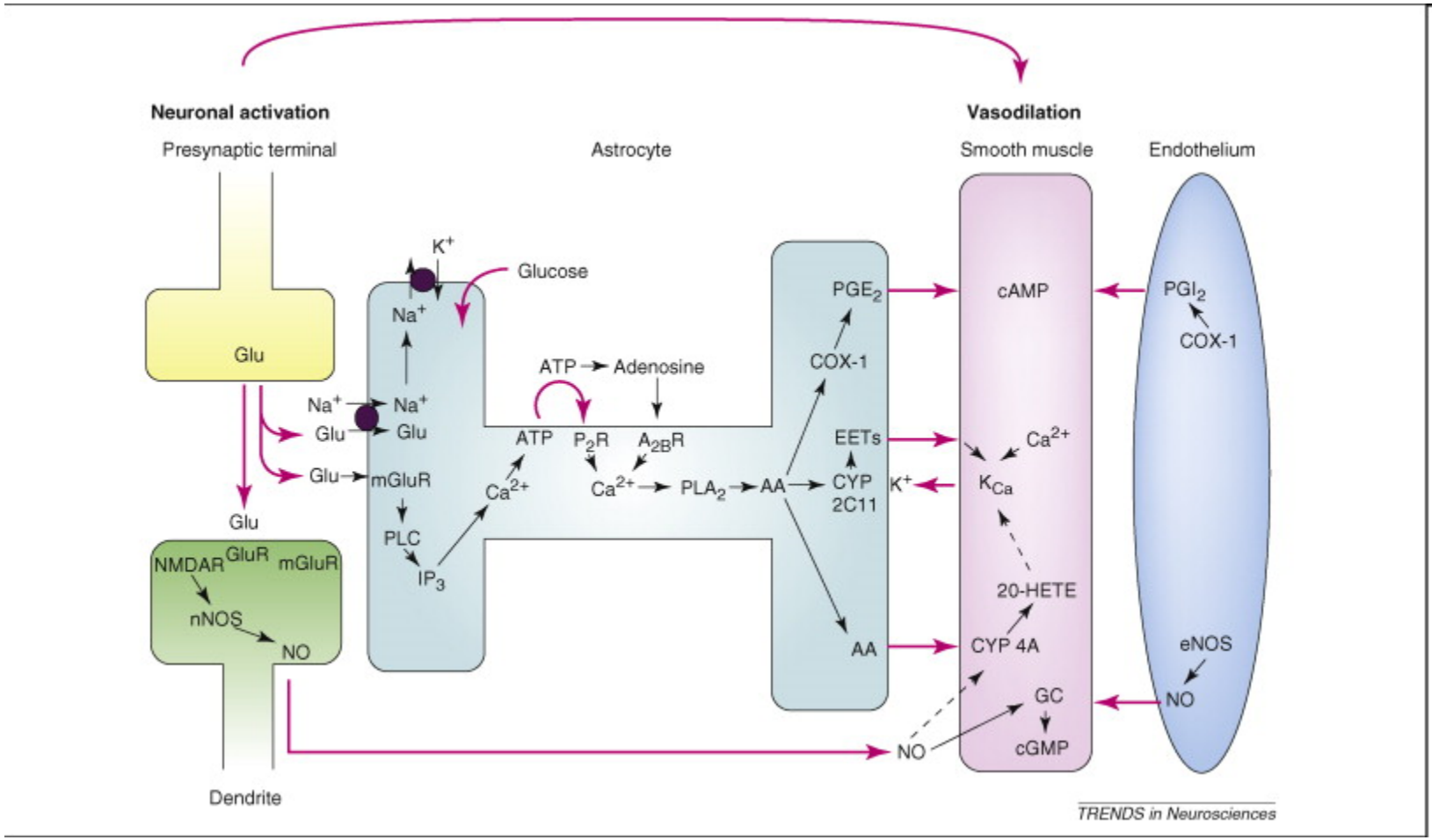
Cellular communication at the neurovascular interface



The neurovascular unit consists of neurons (N), endothelial cells (EC) astrocytes (AC), pericytes (PC), vascular smooth muscle cells (vSMC), microglia (MG) and perivascular macrophages (PM). Endothelial cells form a blood–brain barrier characterized by tight, adherence and gap junctions, as well as a specialized transporter system. Pericytes share basement membranes with blood vessels and directly contact endothelial cells via peg–socket junction complexes. Astrocytes stretch their endfeet toward blood vessels and neuronal synapses to integrate neuronal activity with the vascular response. A single astrocyte contacts $>10^5$ neurons.

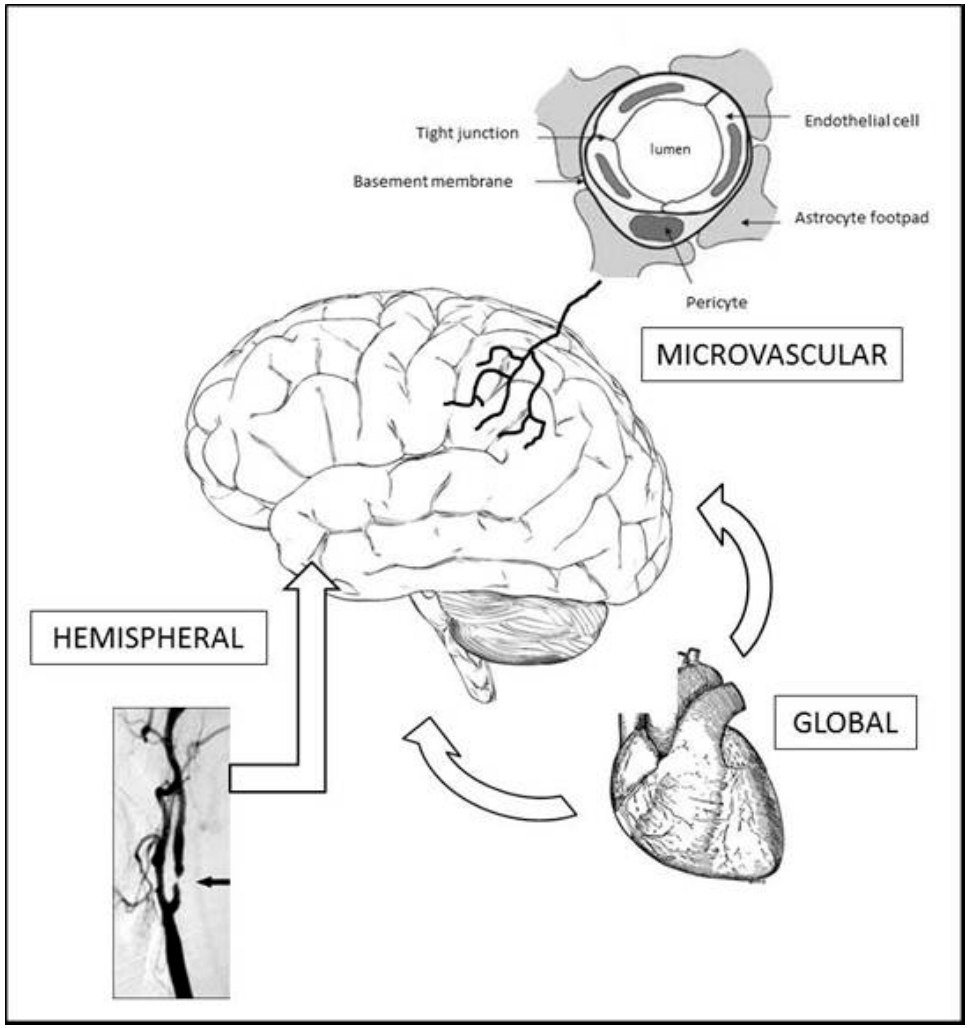
Lee et al. FEBS J. 2009 Sep;276(17):4622-35

Cerebral autoregulatory pathways involving the astrocyte



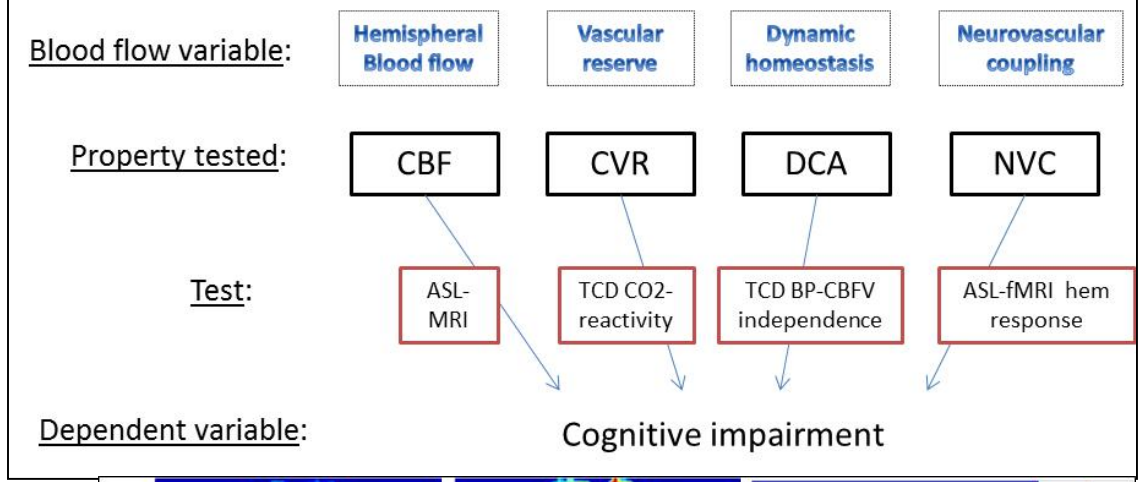
Koehler RC et al. Trends Neurosci. 2009 Mar;32(3):160-9

Causes of Cerebral Hypoperfusion



Blood flow and cognition in Asymptomatic Carotid Stenosis

Figure. Hemodynamic testing.



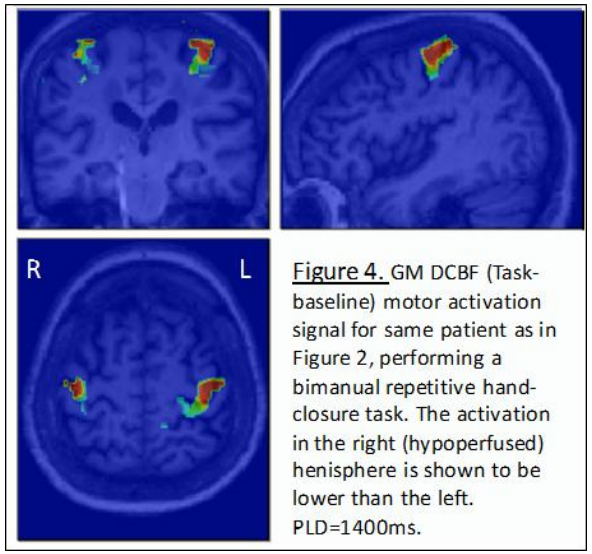
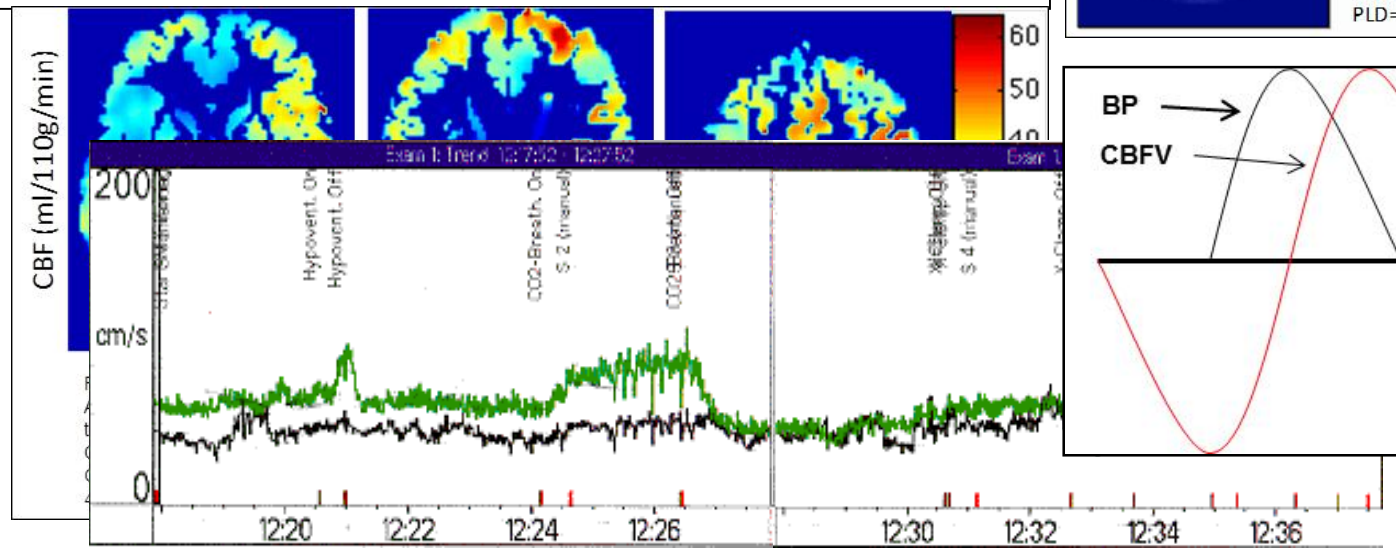


Figure 4. GM DCBF (Task-baseline) motor activation signal for same patient as in Figure 2, performing a bimanual repetitive hand-closure task. The activation in the right (hypoperfused) henisphere is shown to be lower than the left. PLD=1400ms.



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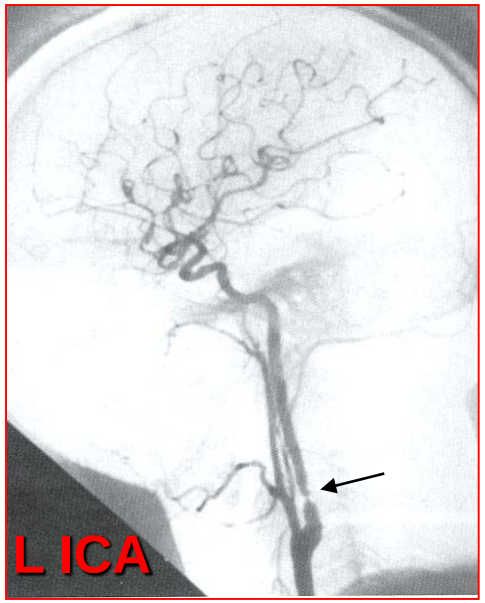
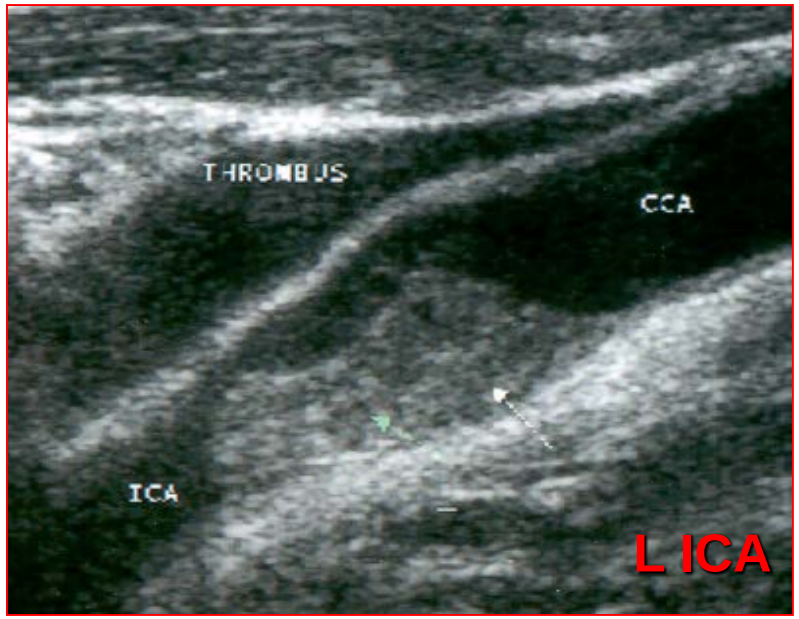
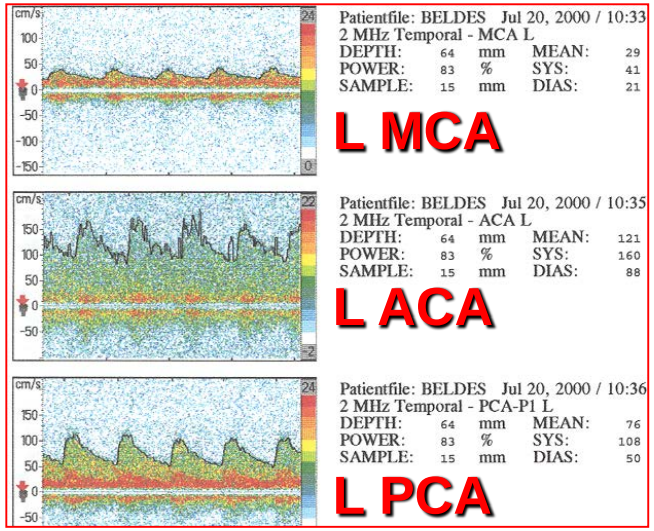
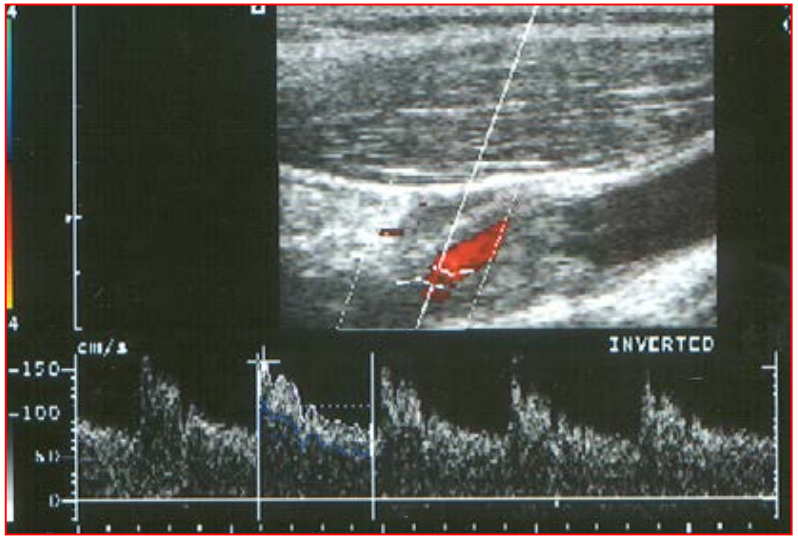
Extracranial 80-90% ICA stenosis





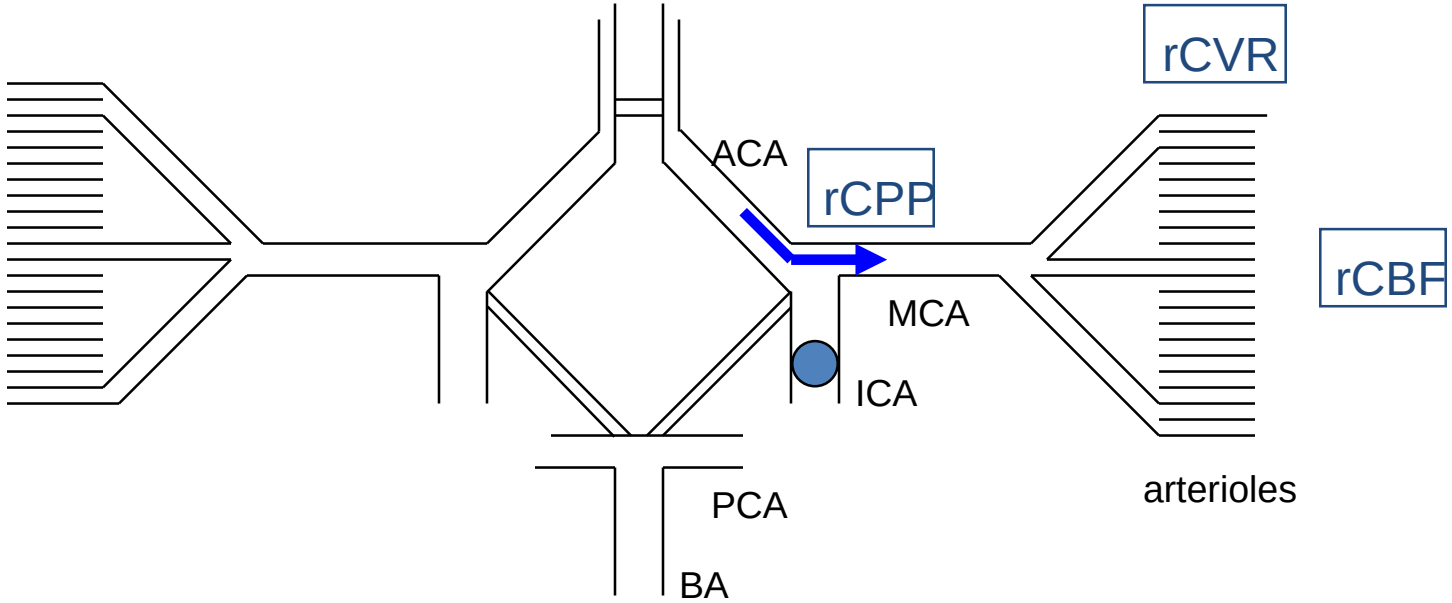




TR 9/2000

Hemodynamics of Circle of Willis

- rCBF = rCPP / rCVR



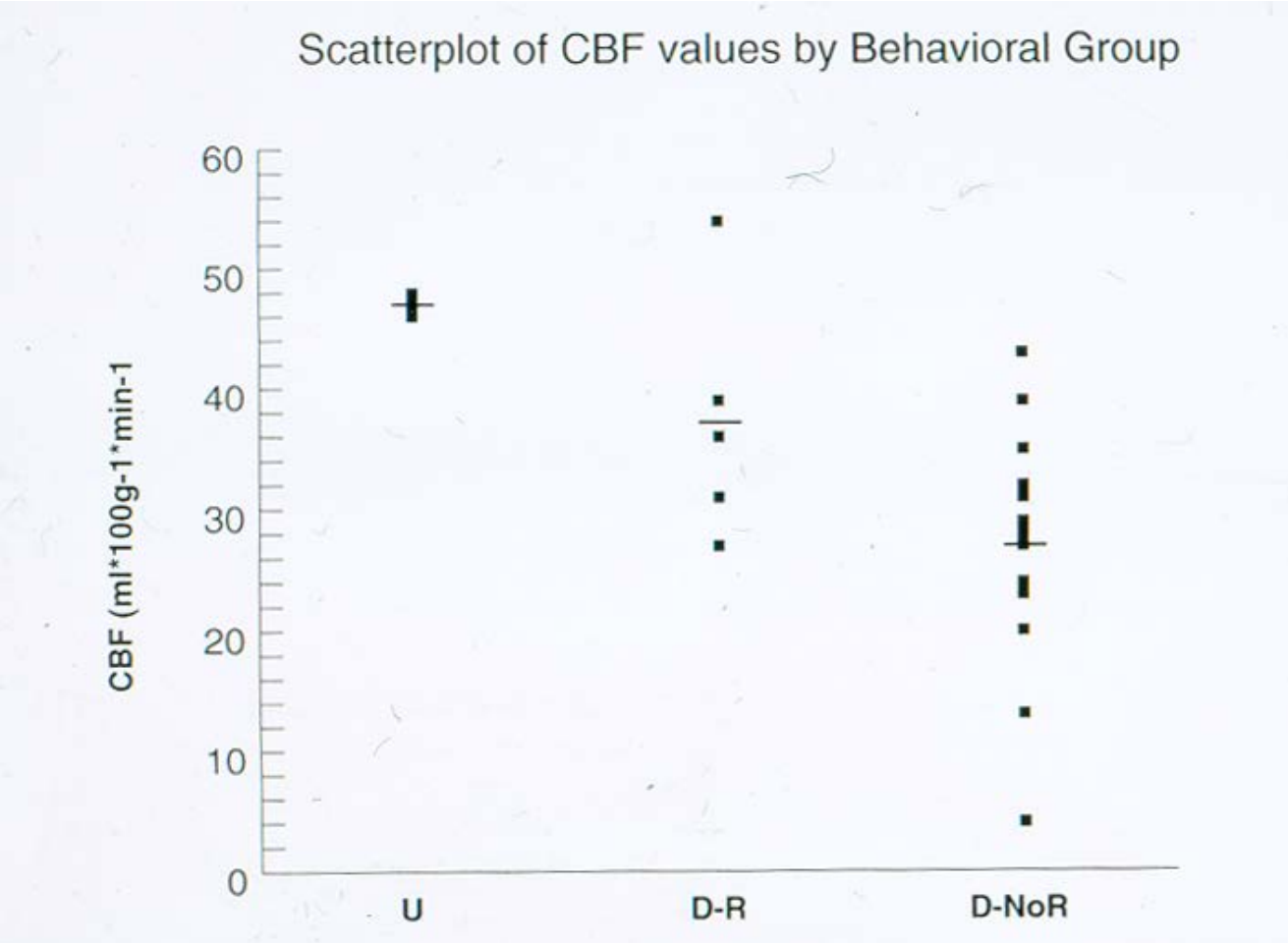
RECON Baseline Cognitive Status OEF effect:

Multiple Regression on Composite Neurocognitive Scores, stratified by Event type (TIA shown here, n=32)

Variable	Estimate	Standard Error	95% Confidence Limits		Pr > |t|
Intercept	-0.973	2.120	-5.370	3.424	0.651
CESD	-0.008	0.012	-0.033	0.016	0.501
PET ratio dichotomized (0=abn, 1=nl)	-1.100	0.503	-2.143	-0.057	**0.040**
Age	-0.050	0.017	-0.085	-0.014	**0.008**
Gender (1 for Female, 0 for Male)	0.196	0.307	-0.442	0.833	0.531
Education (0 for 8th, 1 for HS, 2 for Col)	0.489	0.289	-0.111	1.089	0.105
ICA Side (1 for Right, 0 for Left)	-0.703	0.330	-1.387	-0.019	**0.044**
Previous Stroke (1 for Yes, 0 for No)	-0.298	0.342	-1.007	0.412	0.394

Marshall, et al. *Neurology* 2012; 78:250-5

Correlation of CBF with 3 behavioral patterns during BTO



Behav. Gp.	CBF (cc/100g/ min)
U	47.5
D-R	37.3
D-NoR	25.5

p=.003

Marshall, Lazar, et al, Brain 2001

CREST-H Study Design