Blood Flow and Cognition

C Miller Fisher Neuroscience Visionary Award Address
NECC Boston 2019

Randolph S. Marshall, M.D., M.S.
Elizabeth K Harris Professor of Neurology
Chief, Stroke Division
Columbia University Irving Medical Center
New York
<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1R01NS076277 (Blood Flow Cognition)</td>
<td>NIH/NINDS</td>
</tr>
<tr>
<td>1R01NS097876 (CREST-H)</td>
<td>NIH/NINDS</td>
</tr>
<tr>
<td>1U24 NS10723 (StrokeNet RCC)</td>
<td>NIH/NINDS</td>
</tr>
<tr>
<td>1U01 NS086872 (StrokeNet NCC)</td>
<td>NIH/NINDS</td>
</tr>
<tr>
<td>Royalty Income</td>
<td>Elsevier</td>
</tr>
</tbody>
</table>
C Miller Fisher  
(1913-2012)
A Sample of Typical Titles
SENILE DEMENTIA—A NEW EXPLANATION OF ITS CAUSATION

Miller Fisher, B.A., M.D., F.R.C.P.(C.)
Memorial, Que.

DEMENTIA, in the older age groups is now being recognized as responsible for approximately one-third of all 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 Kline and Wilson has called "the sea of senility." 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 pursuing the most varied experiments, providing us with unique information concerning the substrata 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 anemia, tuberculosis, encephalitis, 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, pyknolymphatocysis, Alzheimer's disease, Pick's disease. The clinical and pathological criteria for each of these diagnoses have recently been reviewed by Miller Fisher, B.A., M.D., F.R.C.P.(C.).

They are unusually large.

The carotid arteries in the neck were examined in detail (Fig. 1). On the left side, the region of the bulb of the artery 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 bulb was firmly encased 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.

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 extracranial and intracranial segments, and the cervical and supraclavicular arteries. The mouths of the extracranial carotid arteries were slightly narrowed by arteriosclerotic 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 were densely localized to the parietal lobes. It is postulated that chronic cerebral ischemia due to occlusion and other collateral channels must have carried the entire blood supply to the brain. Had the carotid vessels not been examined, the dementia would otherwise have been considered as due to vascular disease. The case is therefore recorded here in detail.
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

**Cellular**
- Protein synthesis inhibition
- Anaerobic glycolysis
- Glucose metabolism declines, acidosis, edema, K+ / Ca++ transients
- Electrical failure
- Membrane failure

**Clinical**
- Higher cerebral dysfunction
- Hemiparesis
- EEG flattening in anesthetized patients
- Ischemic penumbra?
- Ischemic core
Cerebral Hemodynamics - Autoregulation

Loss of 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.
Dynamic Cerebral Autoregulation in Acute Stroke

LOW phase shift: poor autoregulation

HIGH phase shift: good autoregulation

DCA: continuous monitoring of TCD and BP

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.

<table>
<thead>
<tr>
<th></th>
<th>M1 unoccl</th>
<th>M1 occluded</th>
<th>P-value</th>
<th>V1 unoccl</th>
<th>V1 occluded</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM-CBF (100gm<em>ml⁻¹</em>min⁻¹)</td>
<td>115.2</td>
<td>105.5</td>
<td><strong>0.0001</strong></td>
<td>112.8</td>
<td>106.4</td>
<td><strong>0.018</strong></td>
</tr>
<tr>
<td>Cortical Thickness (mm)</td>
<td>2.15</td>
<td>2.01</td>
<td><strong>0.0008</strong></td>
<td>1.80</td>
<td>1.78</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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 \(\rightarrow\) greater arterial stiffness \(\rightarrow\) greater transmission of damaging pulsatile flow into tissue bed

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

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

Figure 1: TCD mean flow velocity vs cognitive Z-score
What does all this mean?
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)
Carotid Revascularization Endarterectomy and Stent Trial - Hemodynamics (an ancillary study to CREST-2)
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

- 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)
- Ochsner(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

Thank you!
“Mr. Osborne, may I be excused? My brain is full.”
Hemodynamics Projects

• Dysautoregulation in pre-eclampsia (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 Hypotension 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.
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.

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)
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

Causes of Cerebral Hypoperfusion
Blood flow and cognition in Asymptomatic Carotid Stenosis

Figure. Hemodynamic testing.

Blood flow variable:
- Hemispherical Blood flow
- Vascular reserve
- Dynamic homeostasis
- Neurovascular coupling

Property tested:
- CBF
- CVR
- DCA
- NVC

Test:
- ASL-MRI
- TCD CO2-reactivity
- TCD BP-CBFV independence
- ASL-PMRI hem response

Dependent variable:
- Cognitive impairment

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) hemisphere is shown to be lower than the left. PLD=1400ms.
Extracranial 80-90% ICA stenosis

TR 9/2000
Hemodynamics of Circle of Willis

\[ \text{rCBF} = \frac{\text{rCPP}}{\text{rCVR}} \]
**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|

Correlation of CBF with 3 behavioral patterns during BTO

![Scatterplot of CBF values by Behavioral Group](image)

<table>
<thead>
<tr>
<th>Behav. Gp.</th>
<th>CBF (cc/100g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>47.5</td>
</tr>
<tr>
<td>D-R</td>
<td>37.3</td>
</tr>
<tr>
<td>D-NoR</td>
<td>25.5</td>
</tr>
</tbody>
</table>

p = .003

CREST-H Study Design

CREST-2 enrolled patients

Flow asymmetry

- yes
  - yes 70
  - no 30
- no
  - yes 100
  - no 400

MCI

Treatment

- revasc
  - yes 35*
  - med 35*
- med
  - yes 15*
  - no 15*

* get 1-year follow up MRI (or CT)

Compare cognitive improvement diffs at 1 year
H1: red diff > black diff