Pressure-Flow Regulation in Cerebrovascular Diseases

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Cerebral Autoregulation

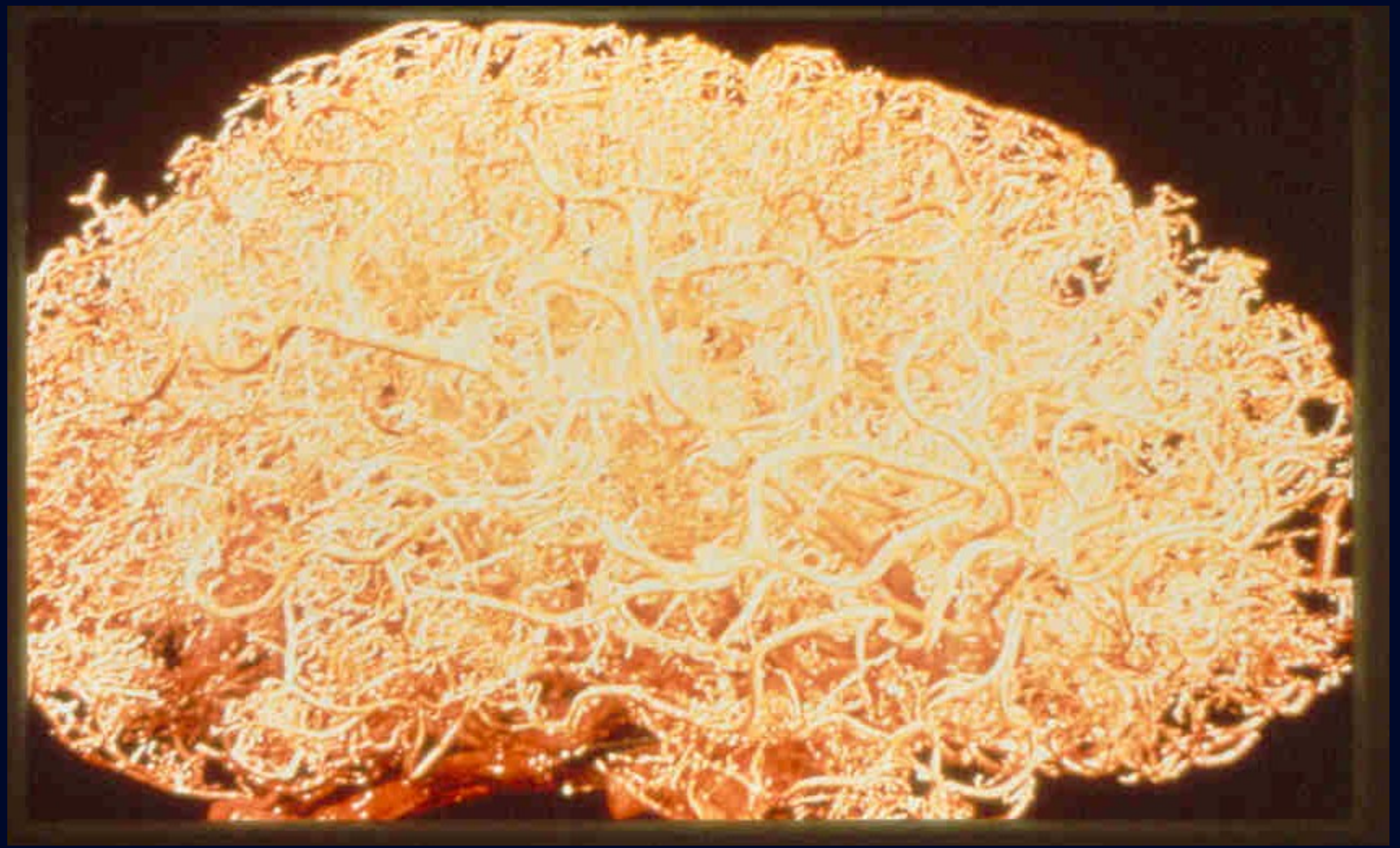
Cerebral autoregulation is the capacity of cerebral circulation to maintain adequate cerebral perfusion in response to metabolic demands and systemic blood pressure changes.

neurogenic myogenic metabolic

autoregulation is effective in MBP range 80 -150 mm Hg

CO_2 range from 25-50 mm Hg

Cerebral microvasculature



Cerebral vasoregulation

Metabolic: Regional balance of CBF and metabolism O_2, ATP, adenosine
Hypocapnia- hypercapnia pH - dependent vasoreactivity
NO synthase from cholinergic nerves, neurons, astrocytes, endothelium.

Myogenic: Intrinsic property of vascular smooth muscle to change resistance in response to beat-to-beat variations in arterial and intracranial pressures and transmural gradient.

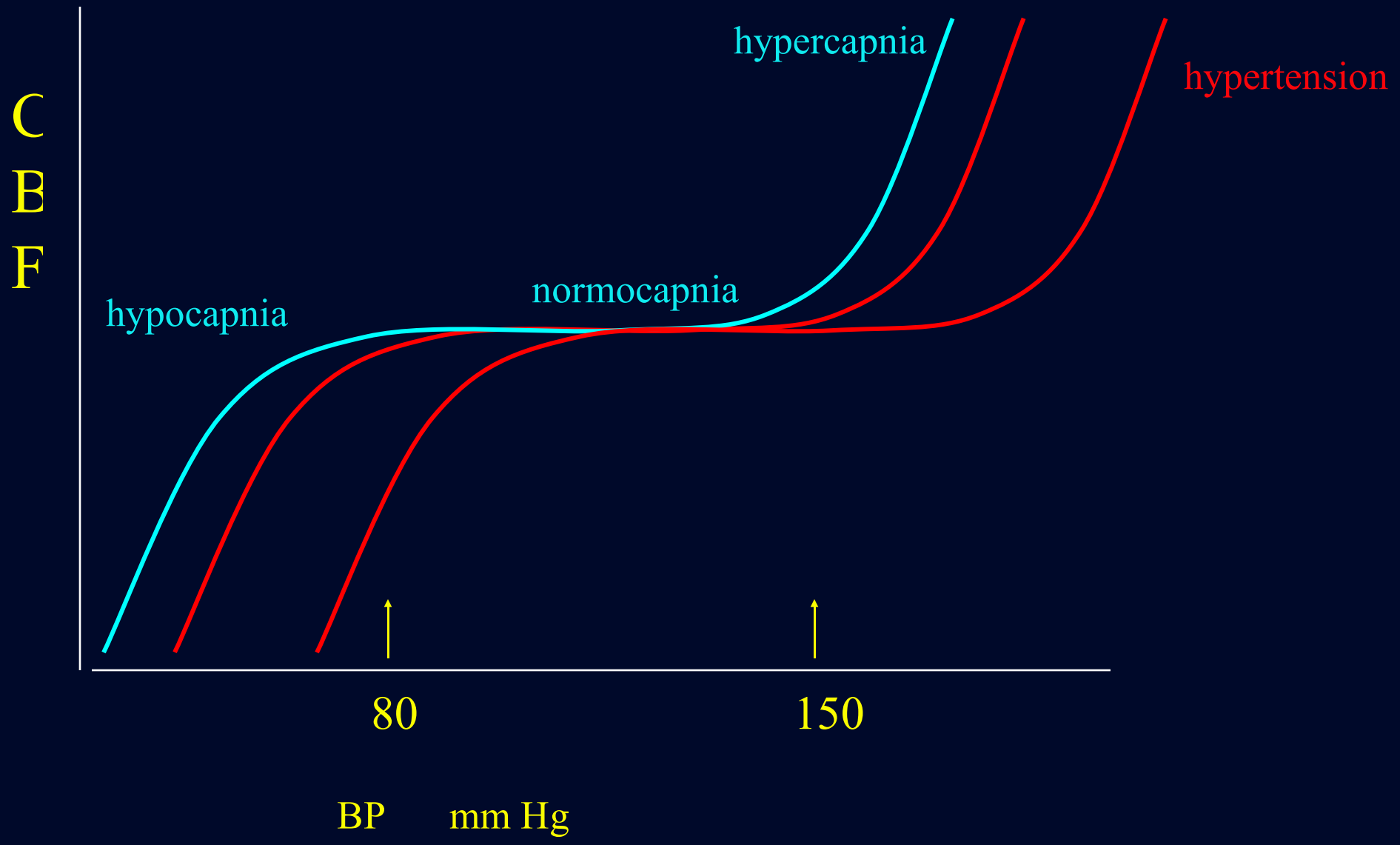
Neurogenic: Neural inputs from baroreflexes, sympathetic and cholinergic perivascular nerves and central autonomic network rhythms modulating vascular tone.

Cerebral Autoregulation to BP

- Dynamic - rapid beat-to-beat fluctuations in ICP, BFV and BP
  - "A" waves "plateau waves (Lundberg 1960)
  - " B" waves - 0.5-2c/min in ICP
  - " M waves" 3-9c/min (correspond to Mayer waves in BP)
- Static - sustained levels systemic BP (e.g. hypertension) or metabolic acidosis or alkalosis
- Multifocal - regional and local metabolic demands (ATP, CO_2)

Autoregulation curve

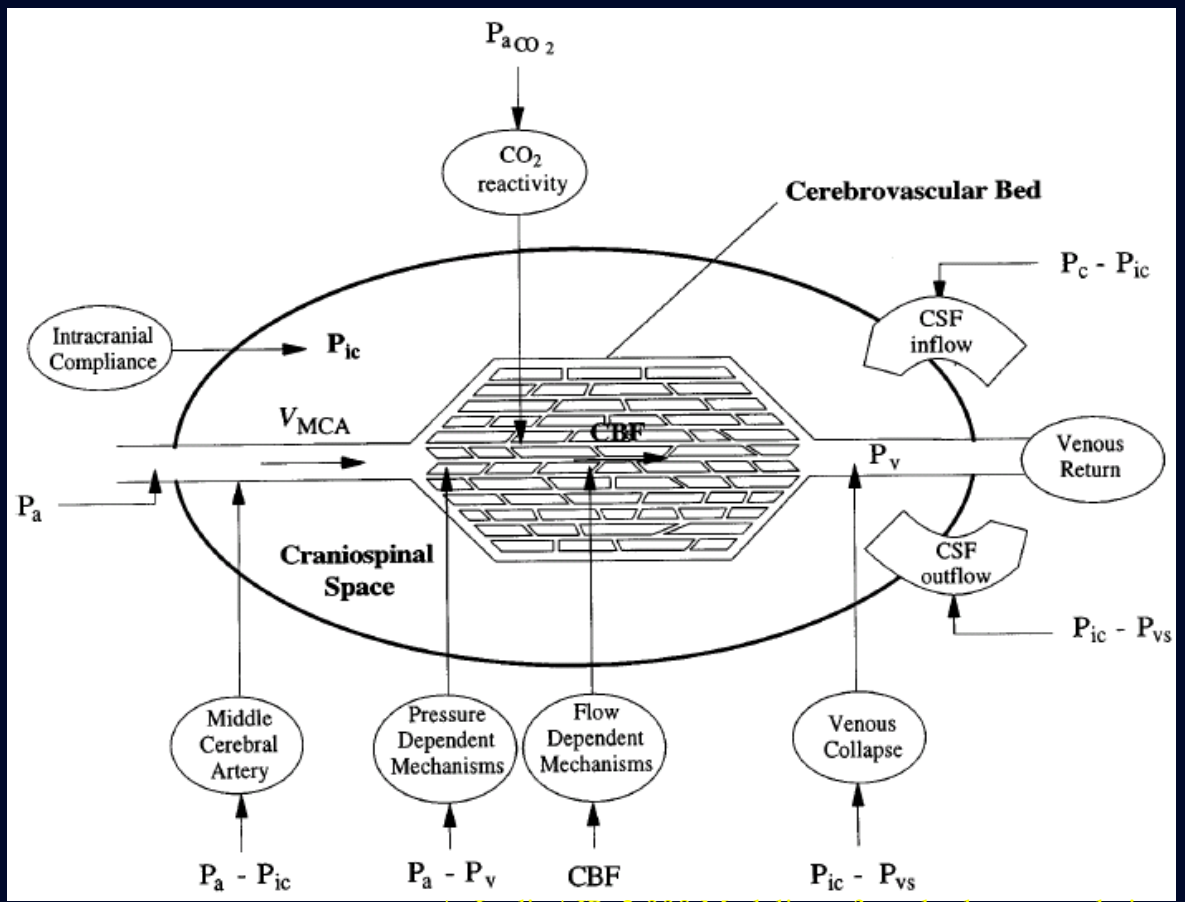
BP and CO_2 change simultaneously



Cerebral autoregulation

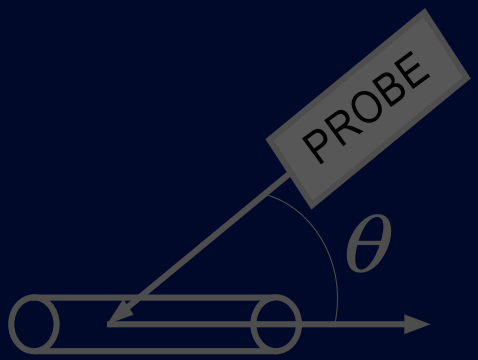
Several AR mechanisms act simultaneously to allow CBF redistribution to areas of increased metabolic demands (local regulation) or in response to systemic changes in

- BP
- CO2
- Glucose
- other metabolites



A. Lodi AJP ,2 998 Modeling of cerebral vasoregulation

Doppler ultrasound



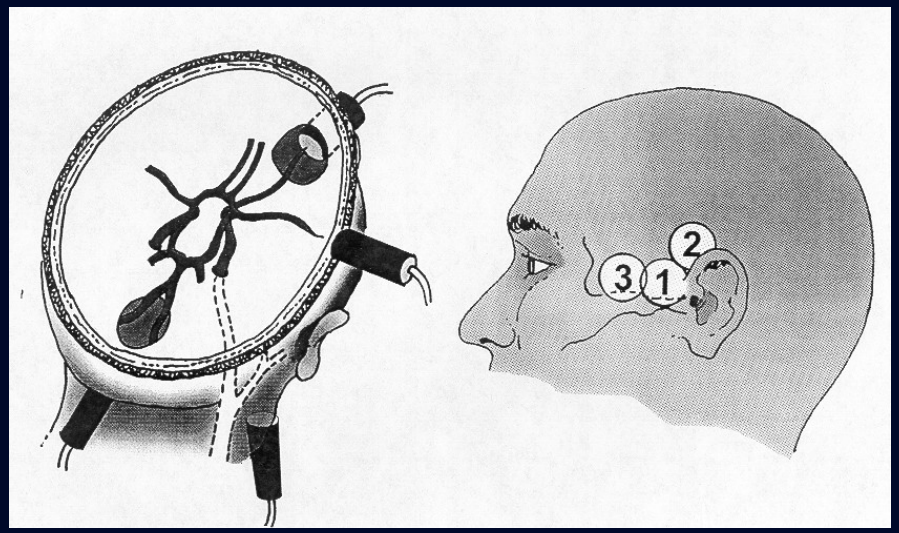
$$\Delta f = 2\frac{v}{c} f_t \cos\theta$$

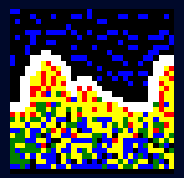
v = *velocity*

c = *sound speed*

f_t = *"carrier" = 2MHz*

θ = *angle*





Dopdoc.exe

Flow is dependent

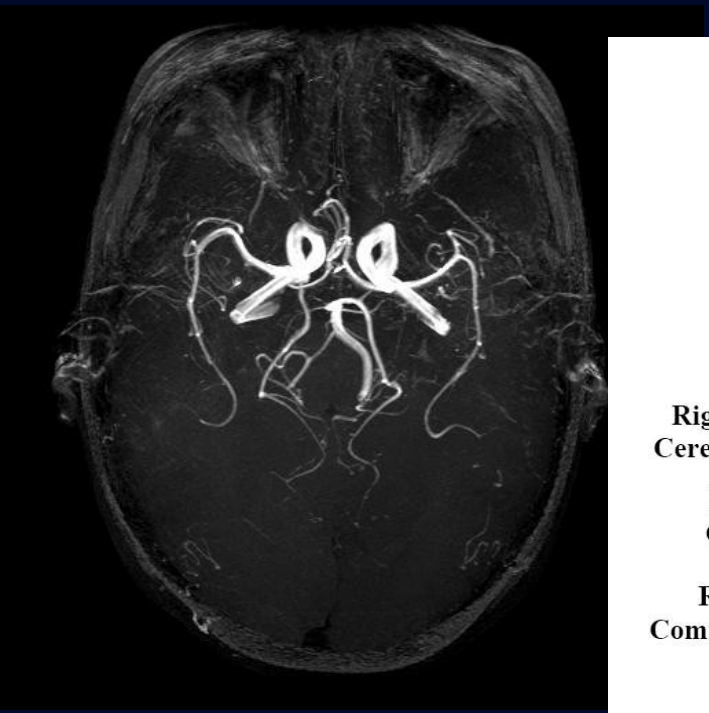
-pressure

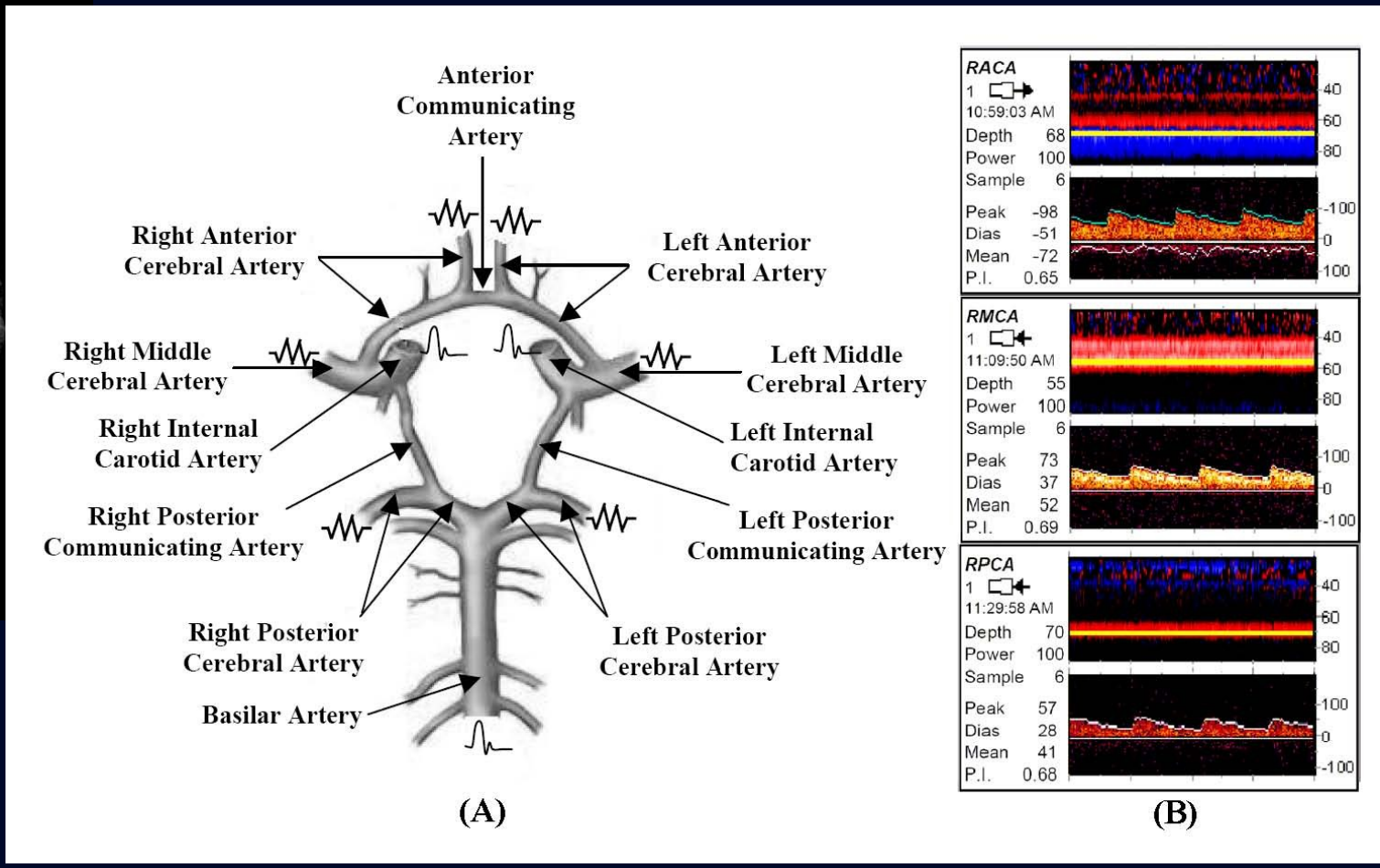
-resistance, vessel length and diameter

-viscosity

$$F \propto \frac{\Delta P \cdot r^4}{\eta \cdot L}$$

Circle of Willis





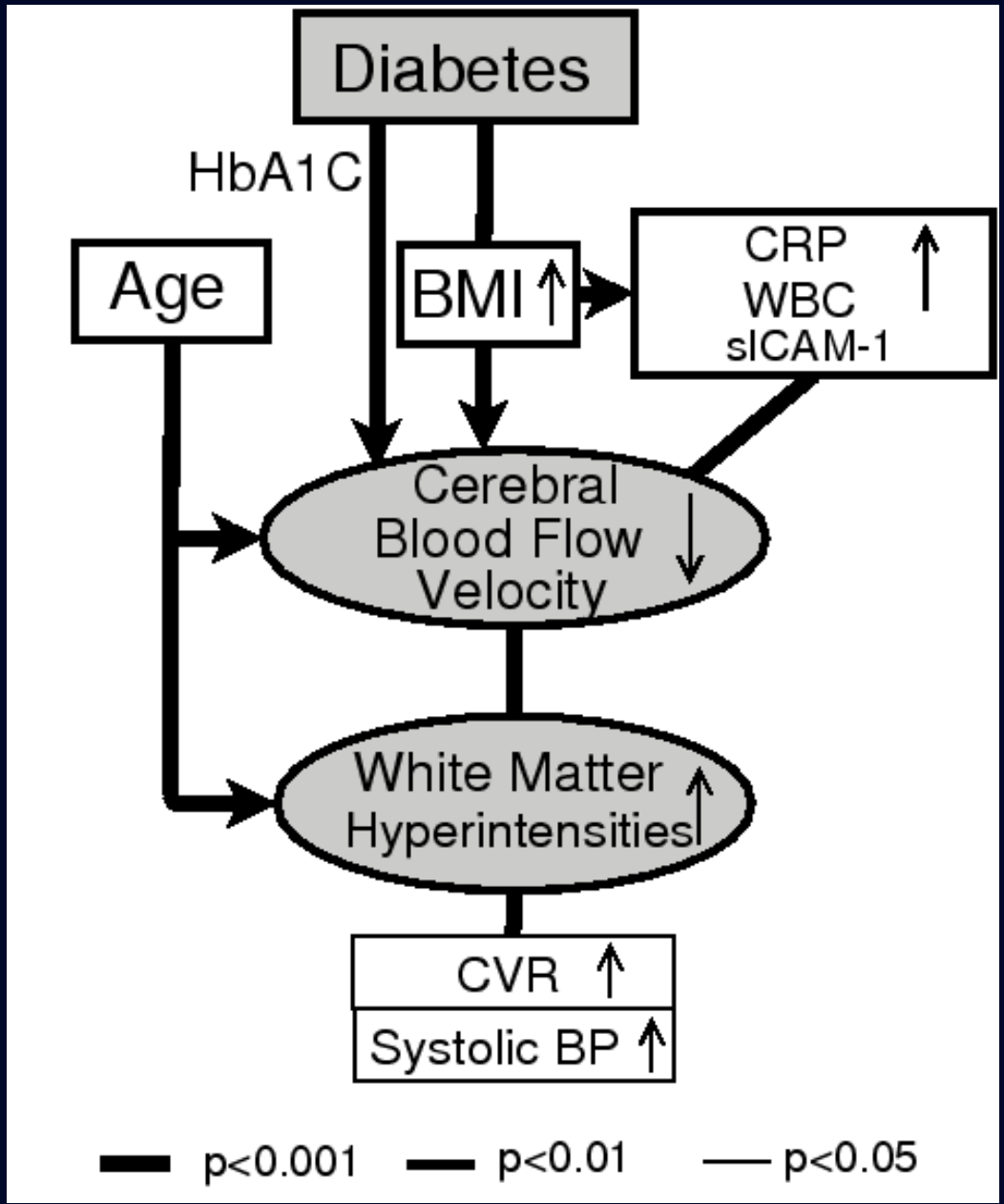
Cerebrovascular disorders

- Microvascular disease (diabetes, hypertension)
- Stroke
  - -small vessel (lacunar infarcts)
  - -large vessel atherosclerosis
  - -embolic
  - -hemorrhagic
  - - increased coagulability (hereditary, tumors)
  - - unknown
- Diabetes is a complex metabolic syndrome that affects 44 millions Americans and is among the major risk factors for stroke and dementia

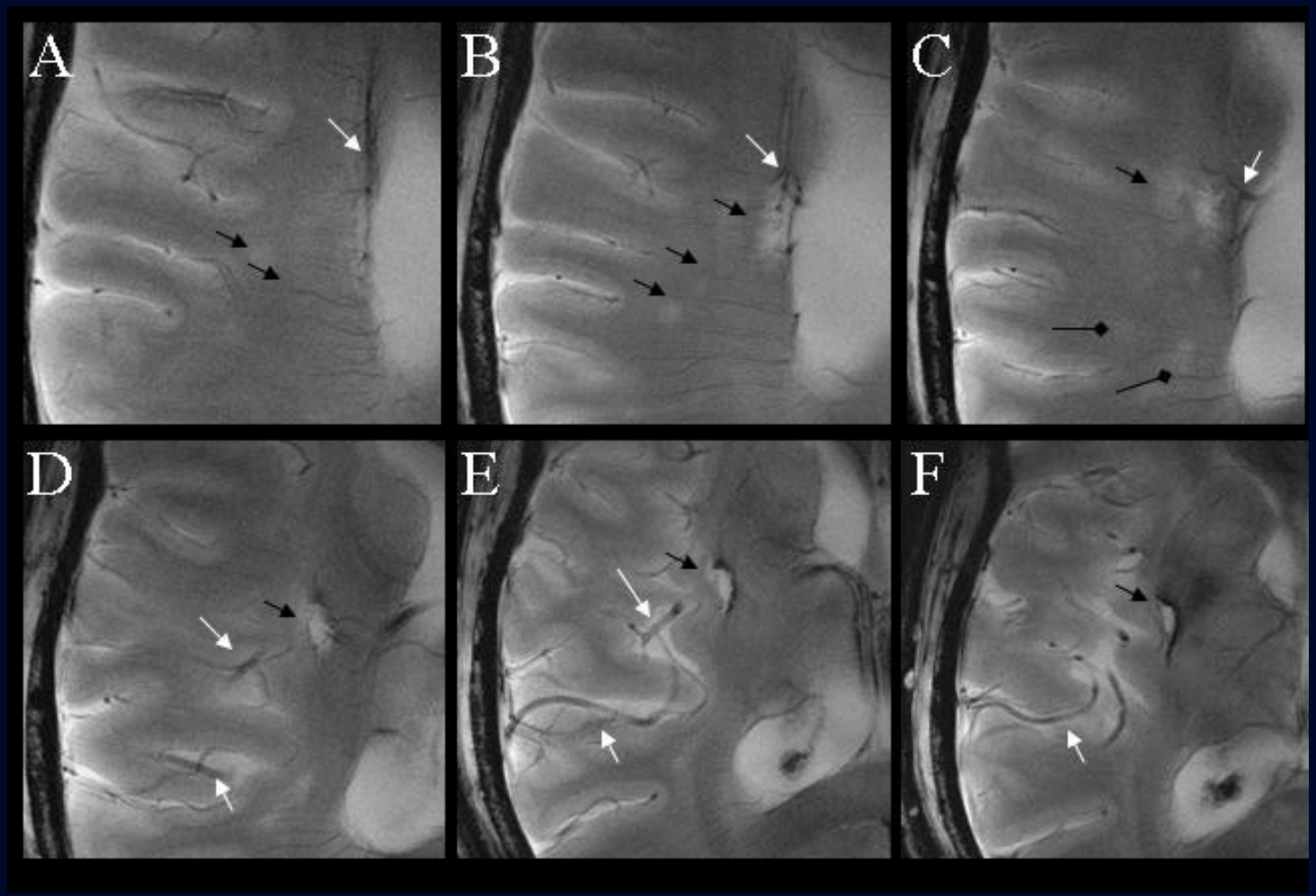
- Stroke is the third cause of death and the leading cause of disability in older adults
- Majority of ischemic strokes occur in vascular beds that have reduced vascular reserve due age, and vascular disease with HTN, DM

Adverse effects on BFV and reserve capacity

- Age
- Body mass
- Inflammation
- Risk factors (HTN,smoking)
- Male sex
- Hereditary (notch 3)

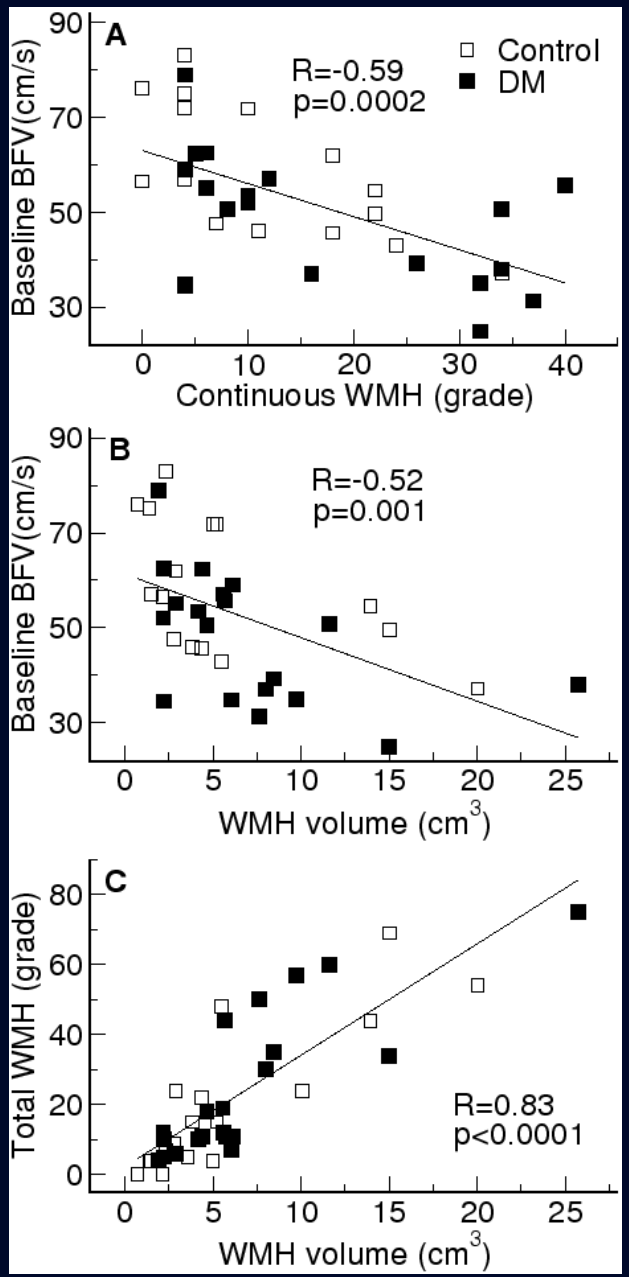


Small vessel lacunar infacrt



High resolution MRI at 8 Tesla

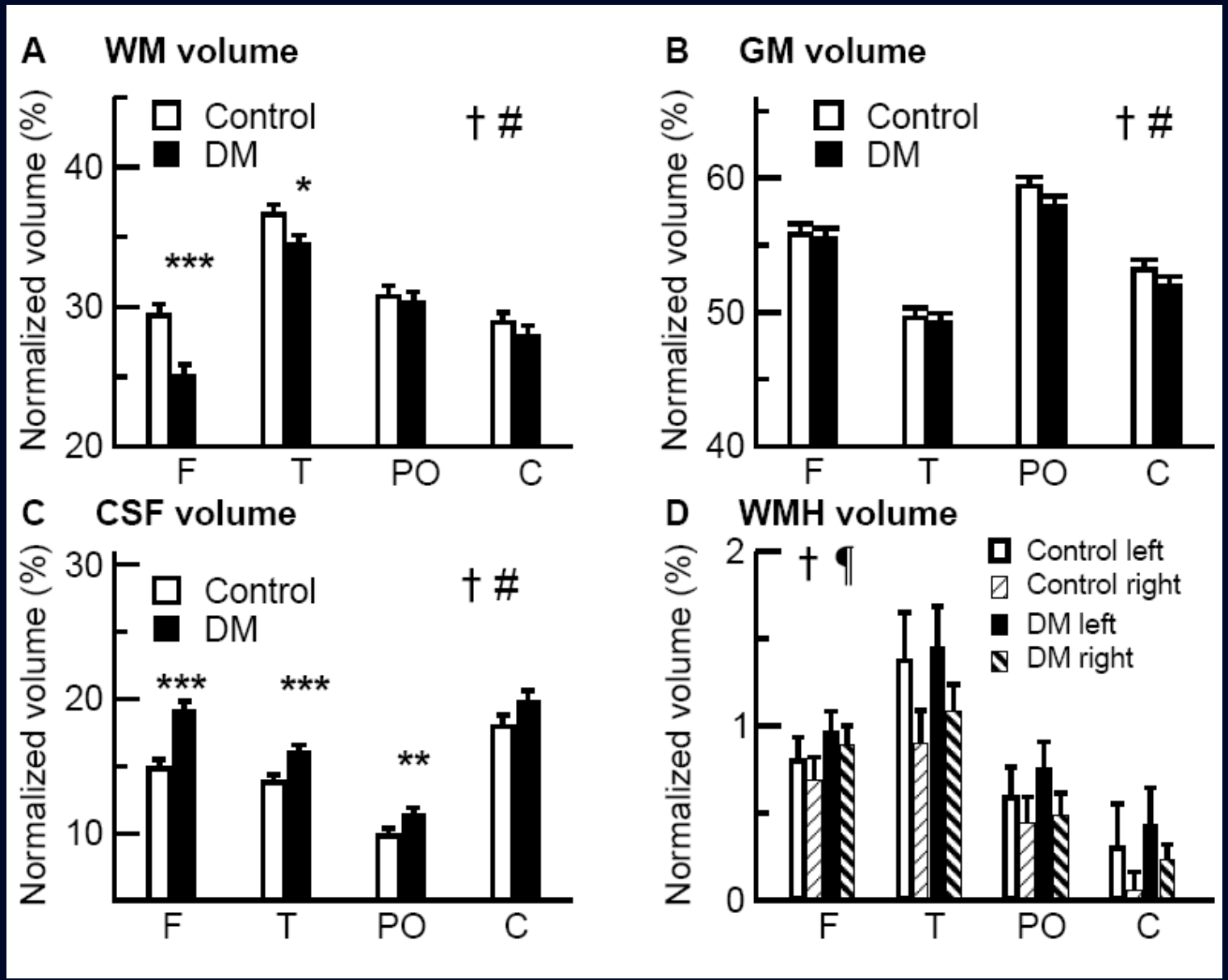
Novak et al 2005,
Magn Res. Imaging 23
539-548



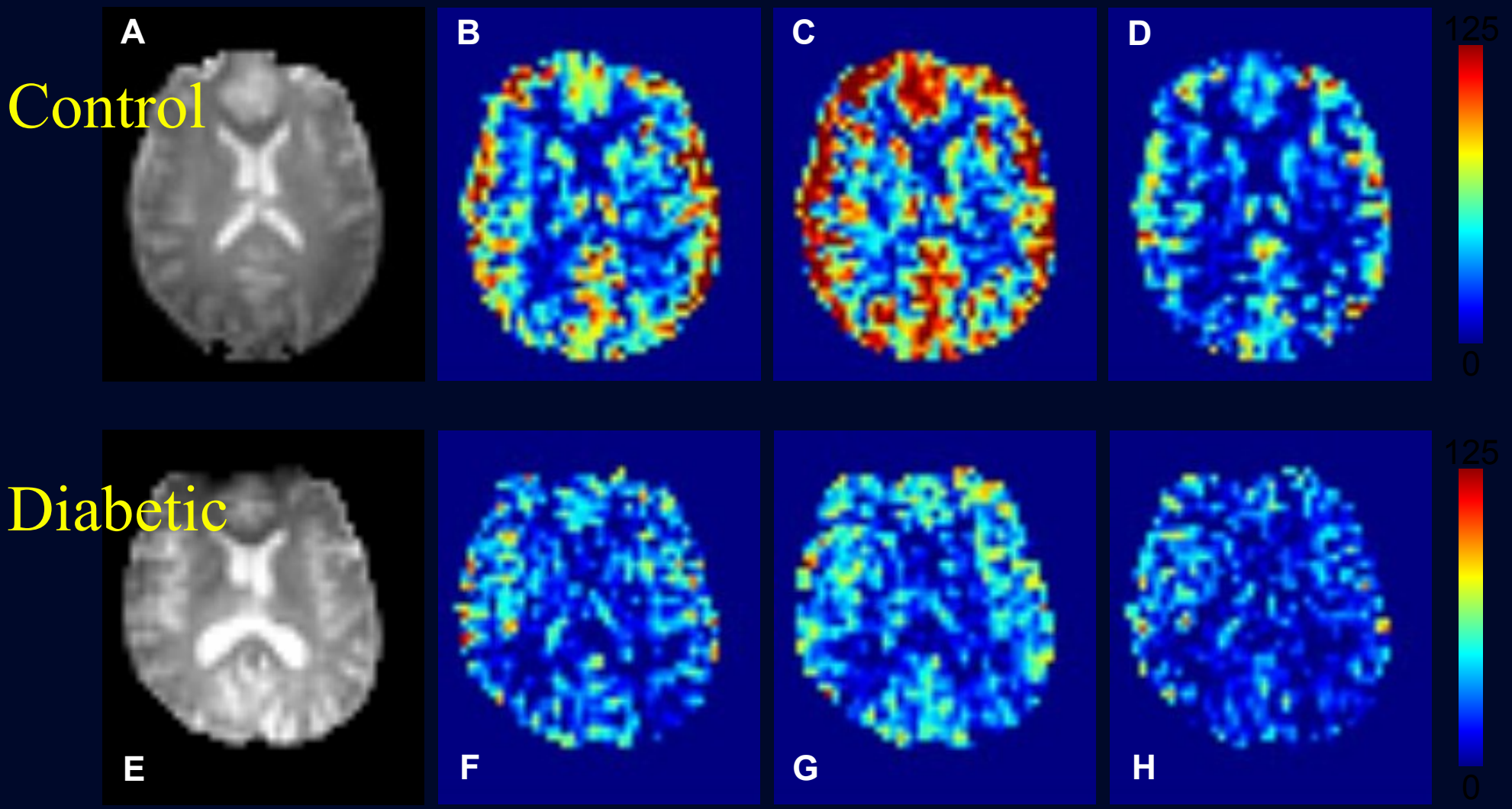
DM vs. Control

- WMH volume not different, between groups
- Regions: Frontal >temporal<parietooccipital
- WMH grade DM > frontal region (p=0.01)
  > parietooccipital (p=0.07)
- Hypertensive DM > Normotensive DM
  n=10 n=18
  > Periventricular WMH grade (p=0.02)
  > punctuate lesions in left temporal p=0.01
  >basal ganglia (p=0.02)
- CVR was positively associated with WMH normalized for brain volume ($p<0.0001$), HbA1c and BMI (0.0004) ($R^2=0.83$, $p<0.0001$).

Novak et al, Diabetes Care 29, 1529-1539,2006



Last D et.al Diabetes Care 2007



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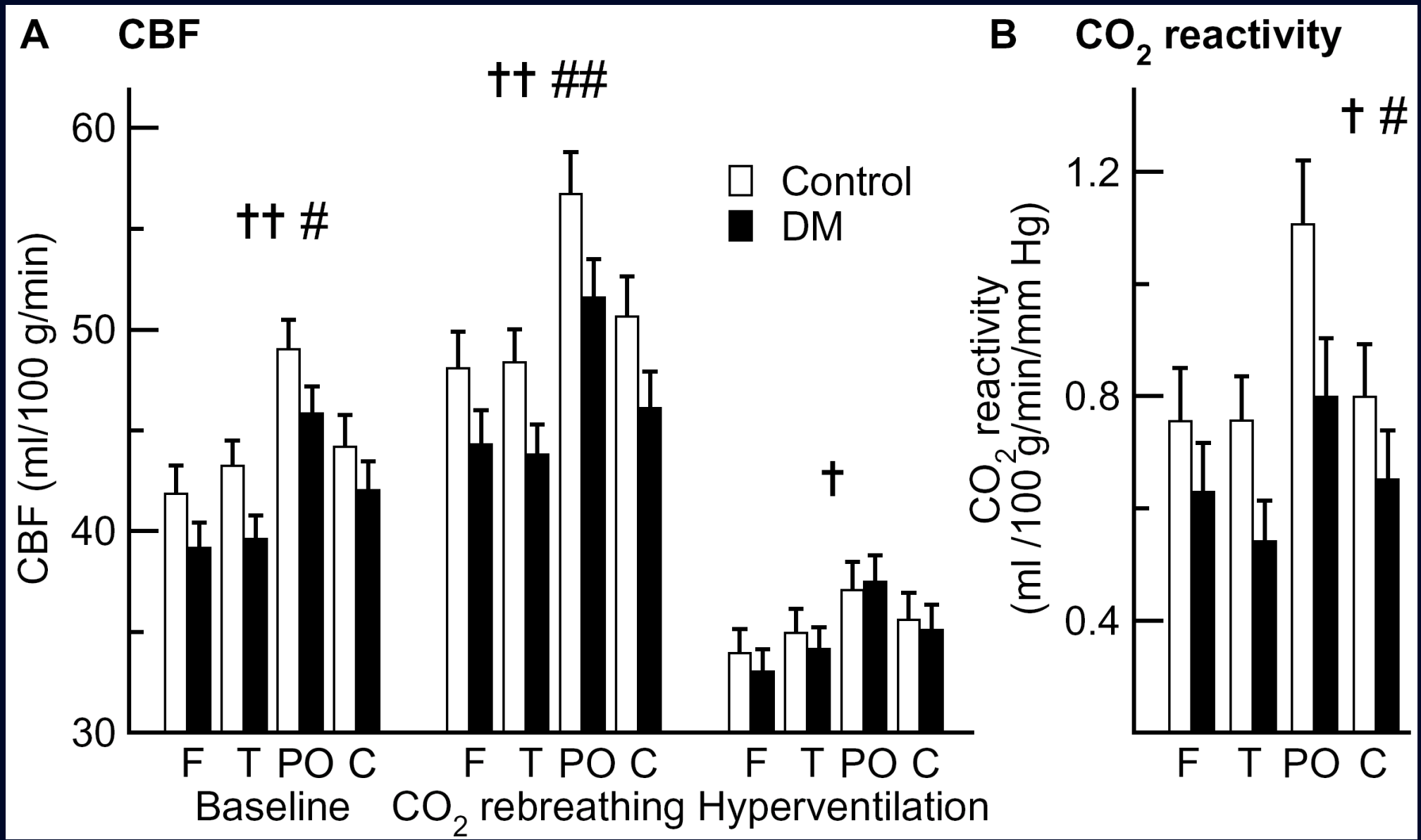


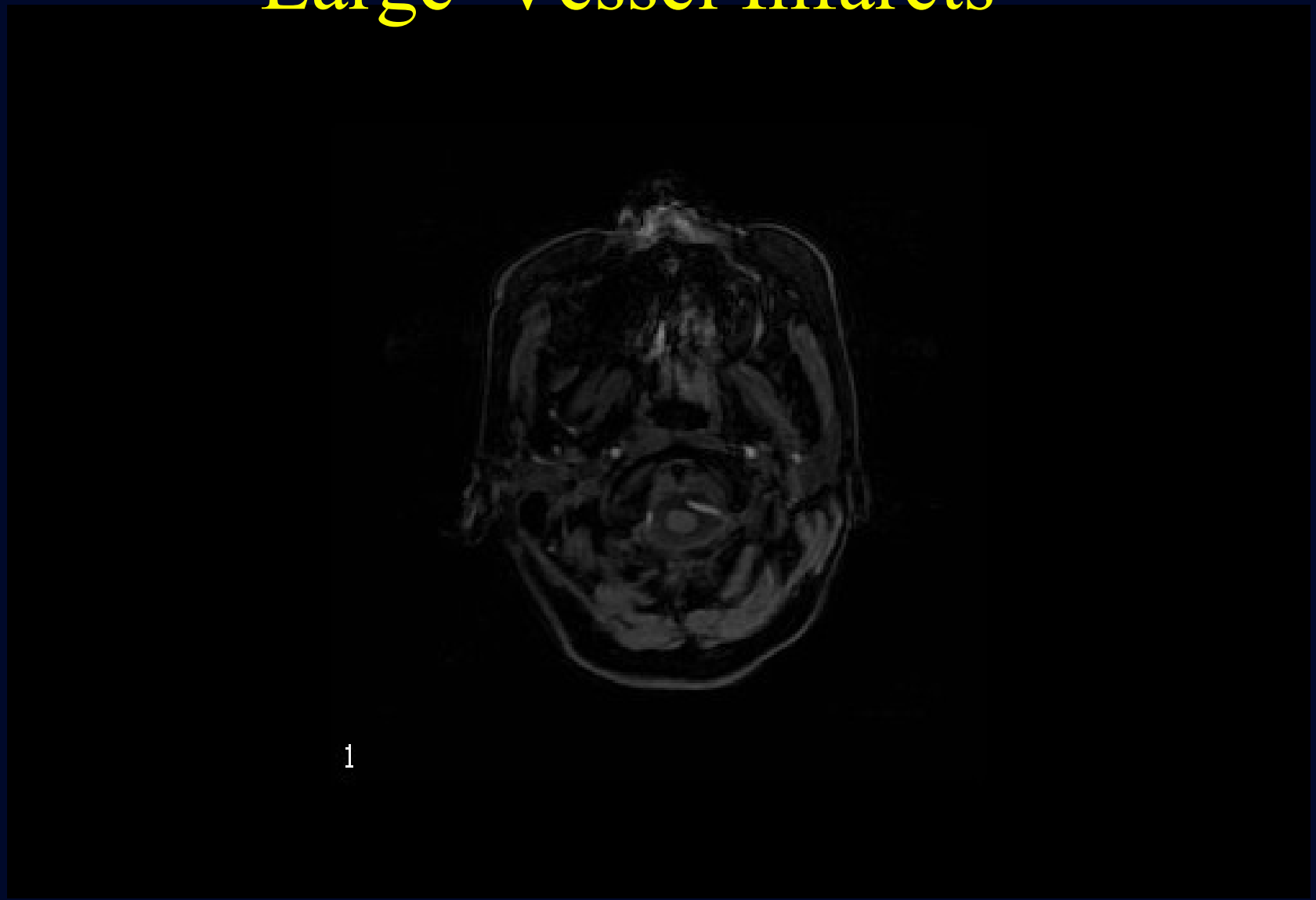
Last D et.al Diabetes Care 2007

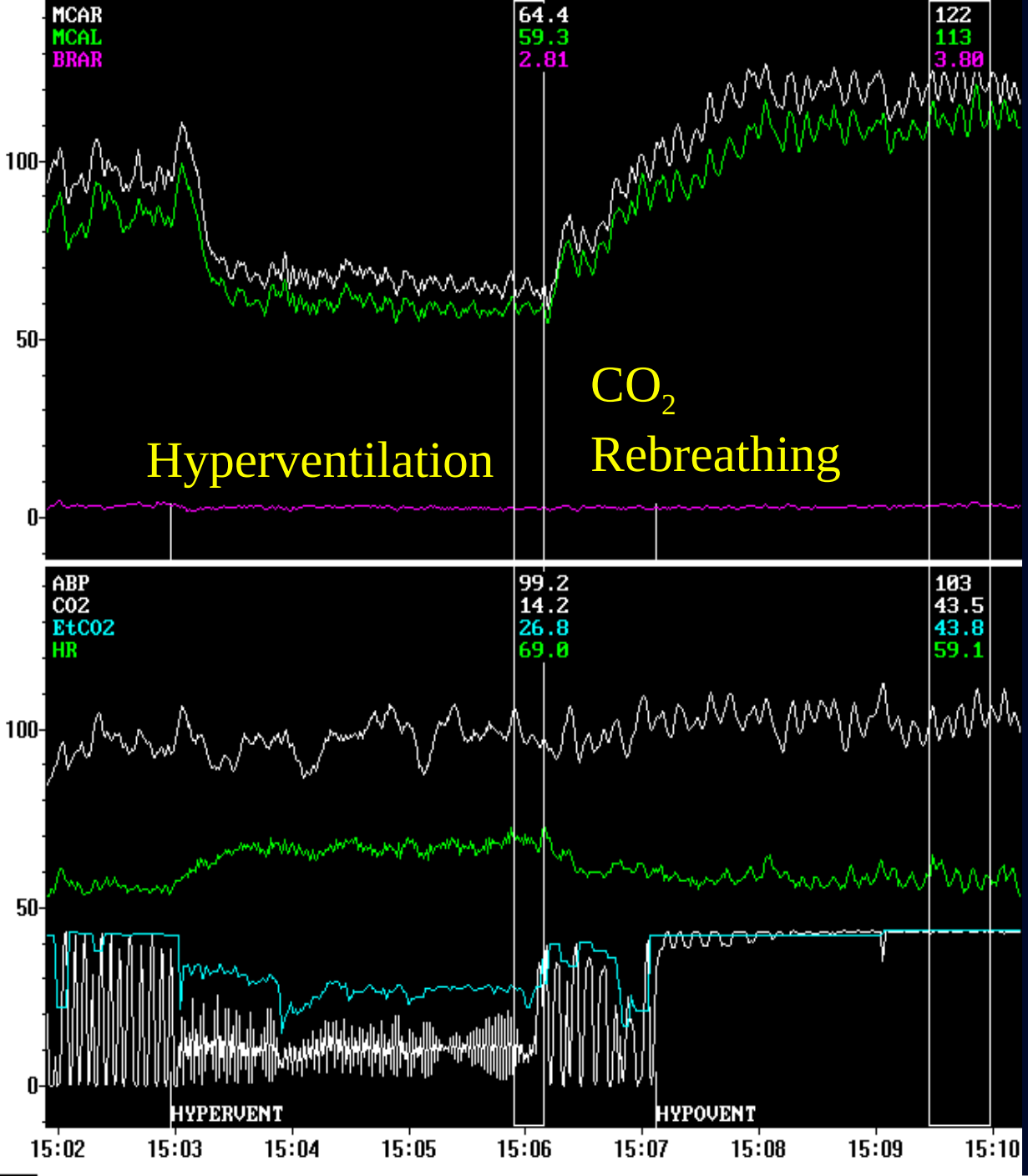
Ischemic Stroke

Ischemic response

- Vasodilatatory cascades counteract a sudden decline in blood flow and vasconstrictor cascades counteract sudden increases in pressure
- Increased collateral flow to ischemic areas
- Increased blood pressure
- Increased oxygen extraction
- if fails-cell death

Large Vessel Infarcts

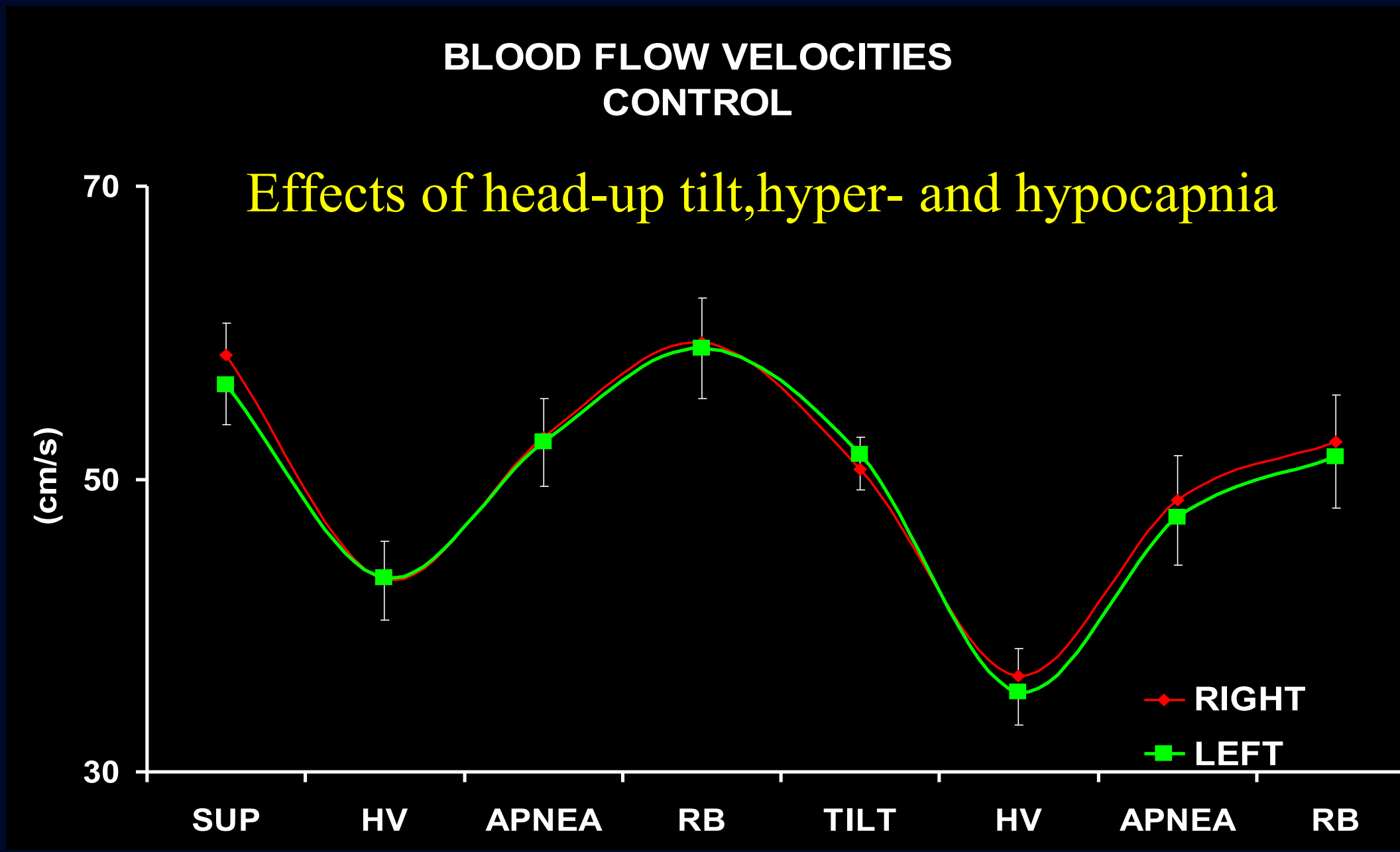


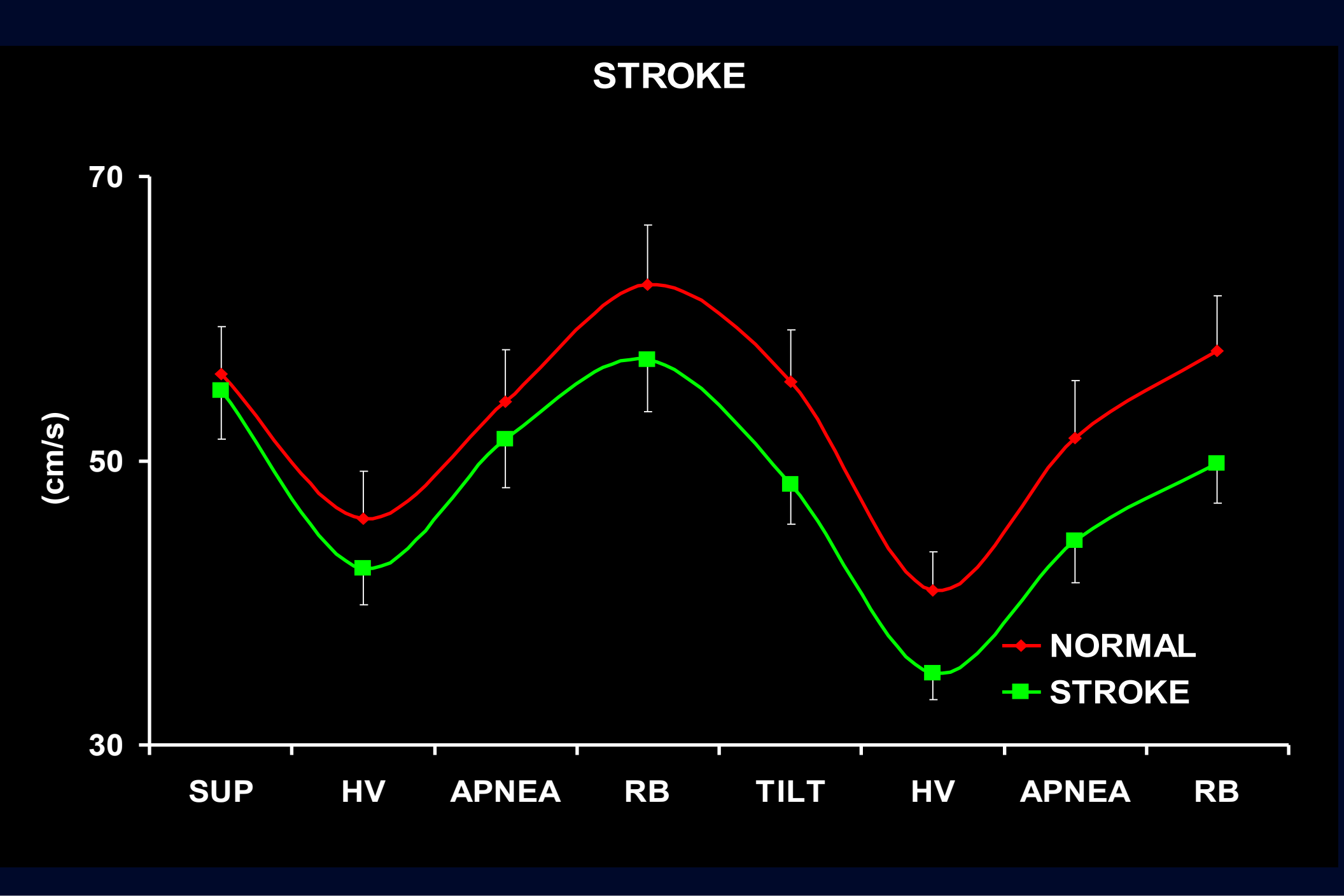


CO_2 Vasoreactivity Protocol

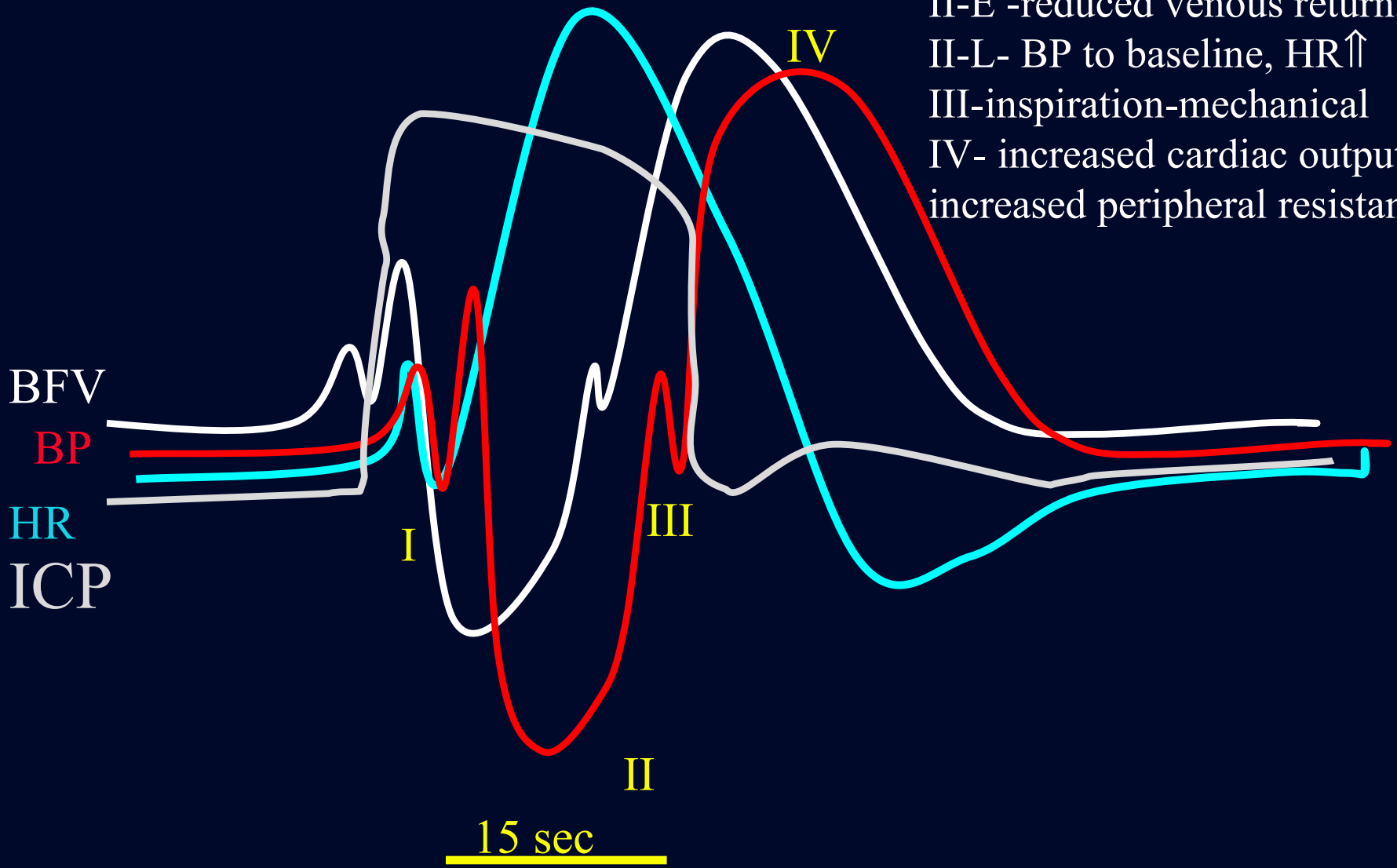
VMR = % change in BFV from min. during hyperventilation to max during 5% CO_2.

CO_2 Reactivity = slope of CVR/ETCO_2 during 5% CO_2 rebreathing.


BLOOD FLOW VELOCITIES
CONTROL
Effects of head-up tilt,hyper- and hypocapnia
70
50
30
(cm/s)
RIGHT
LEFT
SUP
HV
APNEA
RB
TILT
HV
APNEA
RB


STROKE
70
50
30
(cm/s)
NORMAL
STROKE
SUP
HV
APNEA
RB
TILT
HV
APNEA
RB

Valsalva Maneuver



Blood pressure

I- inspiration - mechanical

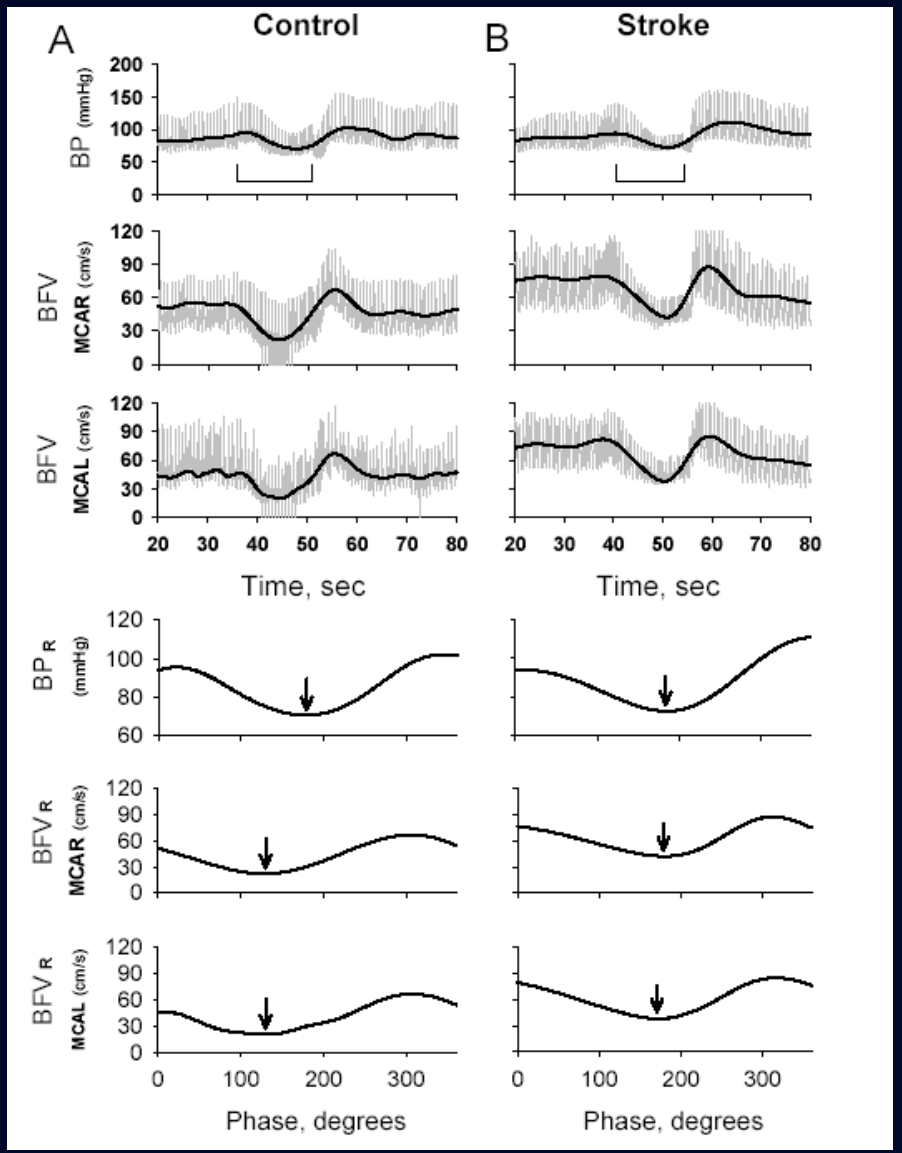
II-E -reduced venous return, BP falls

II-L- BP to baseline, HR⇑

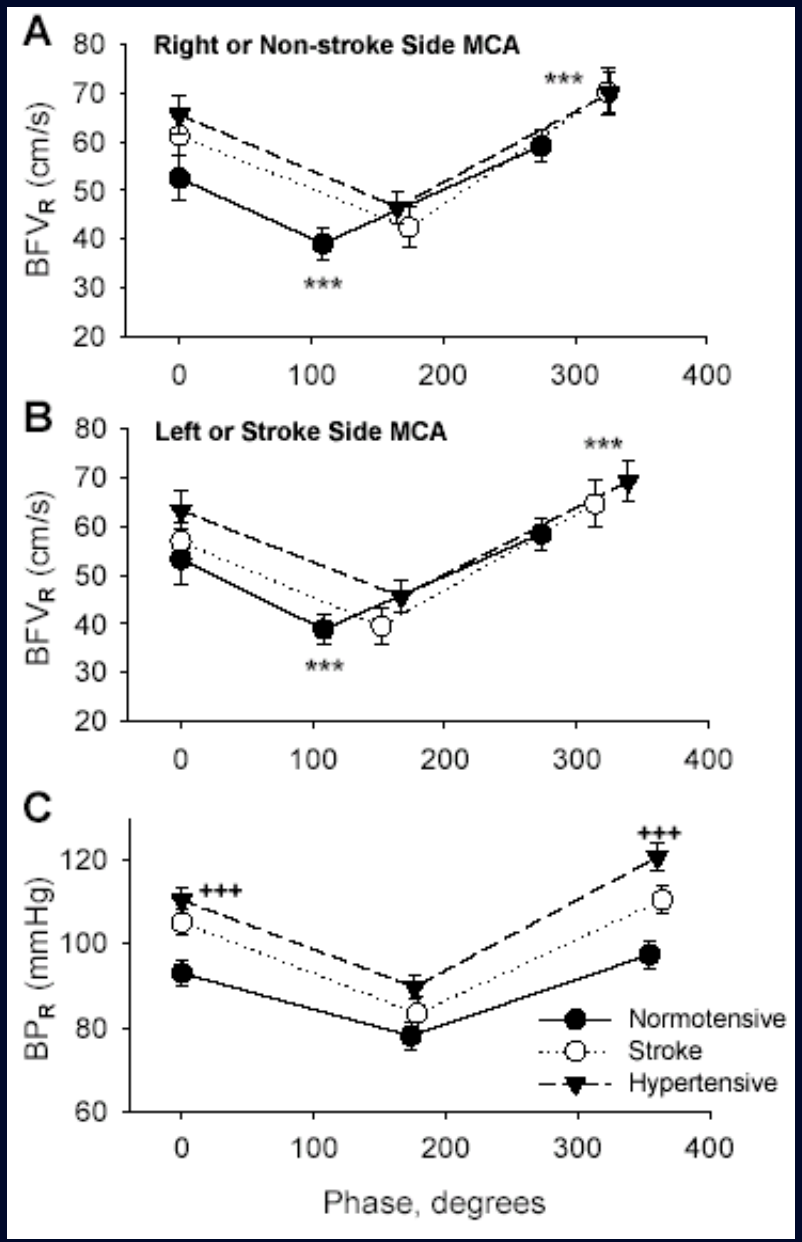
III-inspiration-mechanical

IV- increased cardiac output and increased peripheral resistance, HR⇓

Assessing Autoregulation with the Valsalva Maneuver (Multimodal Pressure Flow Method)



- BP and BFV response to 4 phases of the Valsalva Maneuver in a control (A) and stroke (B) subject.
- The thick black line indicates the BP_R and BFV_R (intrinsic modes) that reflect the characteristic VM oscillation.
- Continuous phase diagrams: Arrows indicate phases at the BP_R and BFV_R minima.
- With normal autoregulation, BFV_R minimum precedes the BP_R minimum (A).
- With abnormal autoregulation BFV_R minimum is similar to BP_R minimum (B).



Novak V, Biome Med Eng Online, 3:39,2004

Transcranial Doppler, assumptions /limitations

- CBF is constant despite changes in perfusion pressure (CPP)

  CPP= ABP (head)-ICP (head)

  CPP= (ABP finger)-constant (ICP)
- Diameter of main vessels remains constant (??) and does not change with vasomotion and from segment-to-segment (false with large vessel intracranial atherosclerosis).
- Autoregulation and vasoreactivity are dependent on vessel resistance and diameter and thus are vary in in different vascular beds

MRI limitations

- Cannot be used at bed side and for prolonged monitoring
- Low signal to noise ratio- averaging
- Cannot used for assessment of dynamic CAR
- Invasive (gadolinium) vs. non-invasive measures (lower sensitivity)
- Expensive

Clinical applications of models

- Predict variables that cannot be measured, e.g. intracranial pressure
- Evaluate simultaneously pressure and CO2 interactions

- Separate physiological mechanisms contributing to autoregulation
- Predict vascular patterns and autoregulation in multiple beds

- Predict autoregulation in vascular beds that are difficult to measure

- Assess hemodynamic effects of stenosis

- Identify vascular segments with impaired autoregulation

- Predict Outcomes

Conclusions

Cerebral autoregulation declines with aging and impairment is augmented by presence of cardiovascular risk factors ands troke.

With impaired autoregulation, cerebral blood flow depends on perfusion pressure.

Mathematical modeling may be useful in determination of individual risk for stroke, in the assessment of new treatment strategies and risk factors modifications.

Co-investigators and collaborators

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8 Tesla MRI

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