Vascular Pathophysiology Revealed by Brain SPECT in Patients with Traumatic Brain Injry and Diabetes Mellitus

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Abstract

Background: Traumatic brain injury (TBI) is more sensitively revealed by combining both basal and perfusion-stimulated brain SPECT; however, few studies have attempted quantitative analysis of such findings or compared to disease with established cerebrovascualr pathophysiology.

Aims: Use brain SPECT to investigate vascular pathophysiology in TBI patients and compare to diabetes mellitus (DM) patients with expected vascular pathophysiology.

Methods: Among > 300 patients we identified those with TBI and DM to compare calculated SPECT indices of cerebral cortical perfusion (CPi), metabolism (CMi), total brain perfusion (BPi), metabolism (BMi) and a new Brain Flow Reserve index (BFRi) = b(Bpi)(BMi){Exp[CMi+CPi]}. Basal SPECT was performed before and stimulated perfusion SPECT after nitroglycerin 0.4-0.8 mg sl or similarly effective cerebral perfusion stimulants.

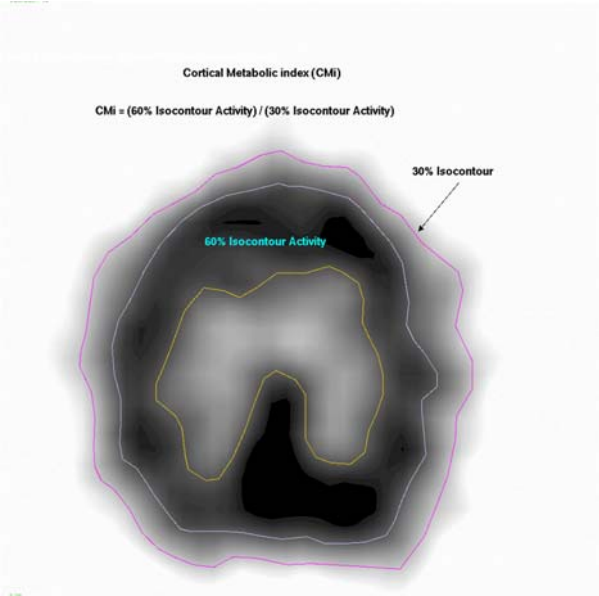
Results: Among > 20 TBI patient identified, decreased cerebrovascular flow reserve (CPi < CMi +5) was found in > 20%; however this was significantly ($p < 0.05$) less than the >50% of > 100 DM patients with decreased cerebrovascular flow reserve. Values of BFRi remarkably approximated expected physiologic flow reserve, maximally 1.33 for normal CMi near 60% and normal CPi near 70% and decreased for either pathologic decrease of CPi or CMi to < 50% or abnormal increase of CPi or CMi to >75%.

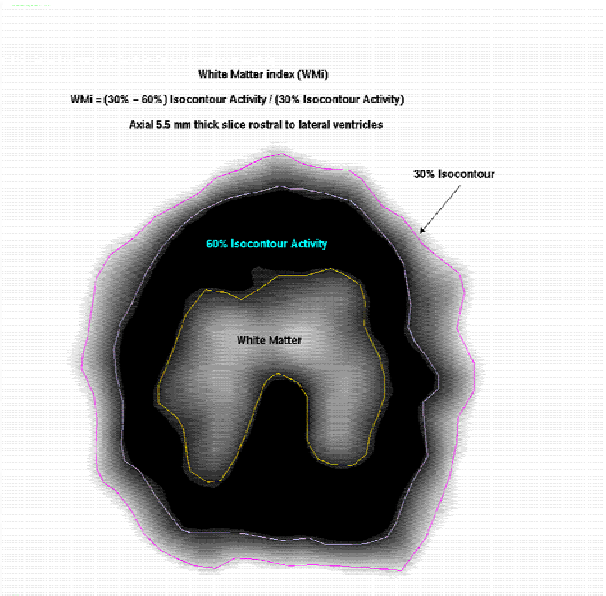
Conclusions: Brain SPECT analysis sensitively probes the pathophysiology of TBI and other diseases such as DM with significant vascular components and may provide further opportunity to study the mechanism by which TBI and/or DM may contribute to increased risk of Alzheimer's and/or mixed dementia.

1. Cortical Metabolic indices were calculated from basal metabolic SPECT images using a metabolic tracer such as 200 MBq F-18 fluorodeoxy-glucose, 560 MBq Tc-99m-ECD or 500 MBq Tc-99m-HMPAO IV, given in a quiet dark room. The dual head SPECT camera had 5.5 mm resolution using ultra high resolution parallel– hole collimators, sensitivity 6500 cpm/MBq, with images formatted in 128 x 128 matrices acquired at 5 to 60 sec/frame in 64 frames per 180 degrees.

Cortical Perfusion indices were similarly calculated using perfusion stimulants such as 0.8 mg nitroglycerin sublingual, 0.5 to 1.0 g acetazolamide IV, 10 g omega-3 unsaturated fish oil oral or 100 mg cilostazol oral and IV perfusion tracers such as Tc-99m-HMPAO or Tc-99m-ECD at suitable time intervals thereafter.

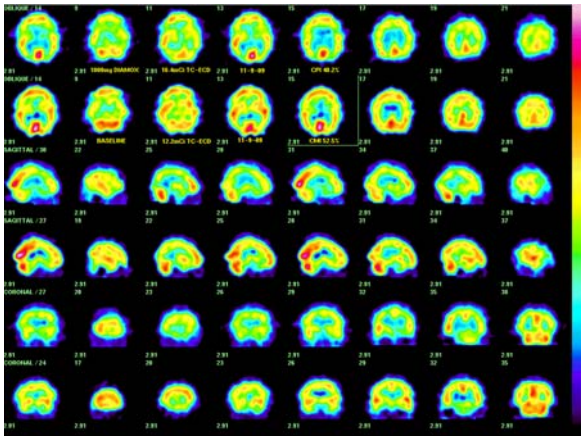
Brain Metabolic indices were defined as: BMi = (CMi)(WMi) / b where b is the cerebral ventricular activity as a % of peak brain activity, typically near 20%. The value of b was corrected for excess scattering by removing a fraction equal to twice the difference of 10% and 30% isocontours and thereafter normalizing by dividing the scatter-corrected b value into 0.2 and then multiplying by 0.2. This method causes the metabolic (and similarly calculated perfusion) indices to decrease when b decreases, as it does for larger ventricles with greater cerebral atrophy.

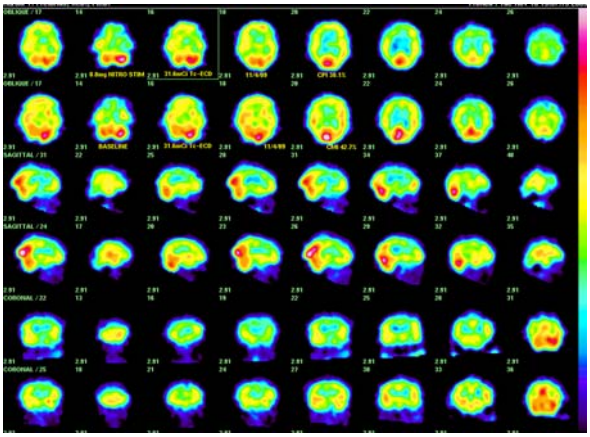




2. A new Brain Flow Reserve Index (BFRi) was calculated from the above derived parameters: BFRi = b(BPi)(BMi){Exp[CMi+CPi]}

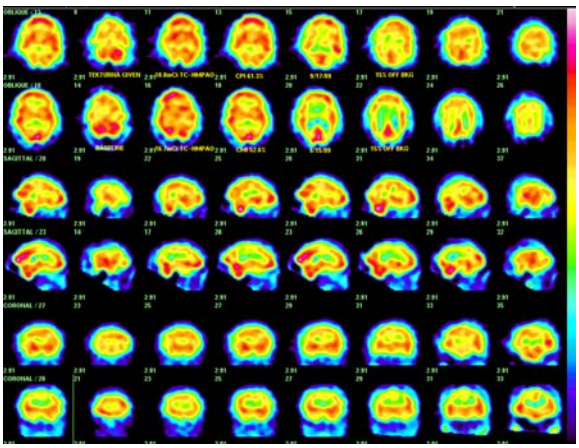
Shown below on the left is acetazolamide perfusion-stimulated brain SPECT (top row, each set of 3 image pairs) over basal brain SPECT (bottom row, each set of 3 image pairs) for a 54 year-old woman with frontal subarachnoid hemorrhage after falling down a flight of stairs, whose CMi 52.5%, CPi 40.2% and b 18%, with BFRi = 0.84 indicated a reasonable prognosis for recovery, which ensued over several weeks. Below on the right are similar SPECT images for a 59 year-old hypertensive, diabetic woman with memory complaints post two coronary angioplasties with CMi 42.7%, CPi 38.1%, b 27.9% and BFRi = 0.46 indicating lower recovery potential, despite normal urinary porphyrins, which do not correlate well with CPi in diabetics.

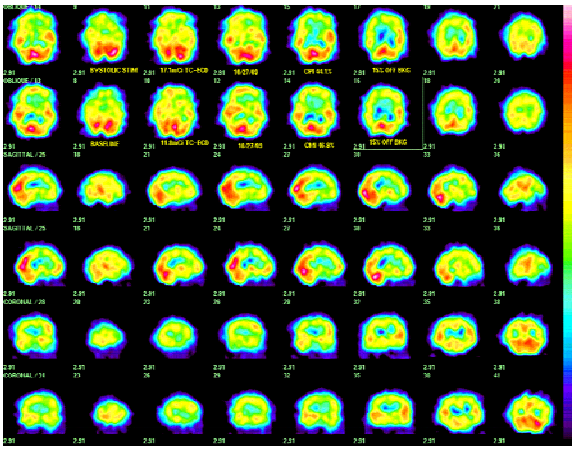




3. A 62 year-old insulin resistant, hyperlipidemic patient, disabled due to memory loss on neuropsychological tests, has brain SPECT, below on the on the left, showing perfusion stimulus effect of antihypertensives. Resting BP 158/90 for the basal scan improved to 148/86 for the stimulated scan two days after aliskirin 300 mg and telemisartin 80 mg oral daily, which we have also observed within an hour of acute BP control, comparable to other acute perfusion stimuli, favoring a same day protocol without change in BP or other physiologic variables.

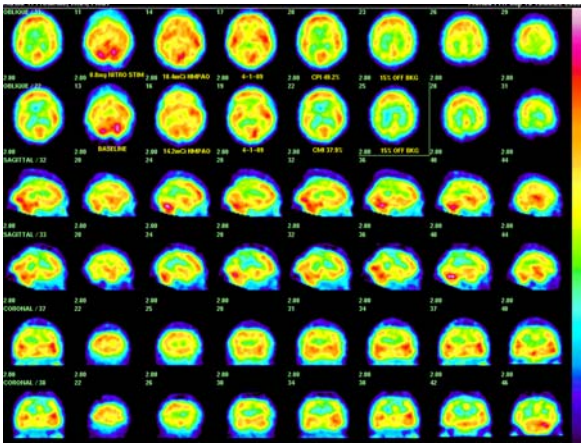
Below on the right is a brain SPECT for a 65 year-old hypertensive, hyperlipidemic, insulin-resistant man whose CPi 44.1% decreased vs. CMi 46.9% with acute decrease in BP from 142/90 to 130/82. Remarkably, the same fraction, 68.7% of insulin resistant patients and diabetics have CPi < (CMi + 5)%.

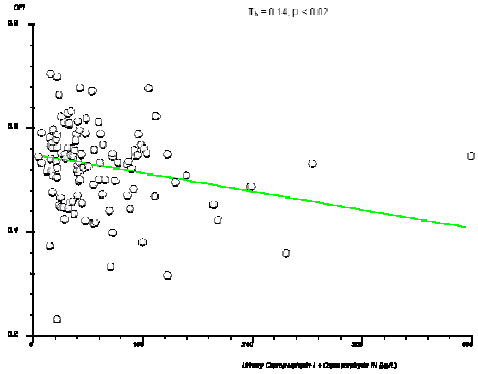




4. Traumatic brain injured patients initially showed significantly less marked abnormality in cerebrovascular flow reserve than diabetics; however, with further study the difference was spurious: in fact, among thirty five traumatic brain injured patients, twenty five had CPi < (CMi +5), or 71%, not statistically different than the 69% of diabetics or those with insulin resistant syndrome. Patients with traumatic brain injury were more likely to have seizure disorder.

Below on the right is the relation of urinary porphyrins (the sum of Corproporphyrin I + Corproporphyrin III), on the abscissa, to CPi, on the ordinate, for 116 memory complaint patients otherwise unselected (consecutive except for, insofar as we know, random nonadherence with protocol for porphyrin collections and obtaining SPECT scans) except that diabetics were excluded from this data set. Approximately the same relation holds for a smaller number of patients similarly analyzed with Corproporphyrin I alone as the dependant variable (data not shown here but reported recently at the American Thyroid Association International Meeting.





5. Below on the left is a subset of a similar nonparametric statistical analysis for traumatic brain injured patients (n = 24) showing statistical significance of the relation with quantitative fractionated urinary porphyrins, suggesting susceptibility of such patients to a component of oxidative stress, perhaps due to low-level body burden of toxic metals (eg. Hg, Pb, As).

Remarkably, a similar analysis for diabetic (diabetes mellitus) patients, shown below on the right, analytically shows no relationship, with p = 0.97 and the calculated nonparametric statistical regression line having a very nearly flat appearance (tau = 0.004), suggesting that diabetics, although very similar to traumatic brain injured patients in their overall extent of compromised cerebrovascular flow reserve, arrive at this pathophysiologic circumstance through a fundamentally different mechanism.

Summary

Patients with diabetes mellitus and even those with insulin resistant syndrome, which only leads to actual diabetes in about a third of cases, have a remarkably high rate, 69% of abnormal cerebrovascular flow reserve when monitored by perfusion-stimulated and basal brain SPECT. Patients with traumatic brain injury may also suffer a high incidence of at least transient insulin resistance and also have a similarly high rate of compromised cerebrovascular flow reserve, 71%. Initial analysis of the pathophysiologic mechanism producing these remarkably similar results suggests that fundamentally different aspects in diabetics or the much larger number of insulin resistant patients, who already are similarly compromised in cerebrovascular flow reserve, and patients with traumatic brain injury.