

BRAIN-HEART IMAGING WITH N-13 AMMONIA PET: A PRACTICAL CLINICAL PROTOCOL

Harold T. Pretorius, M.D., Ph.D.,[^] Dennis E. Menke, A.A.,[^] Nichole M. Richards, B.S., C.N.M.T.,[^] Betsy Budke C.N.M.T.

Objectives: Report a new, combined brain-heart PET protocol using potentially more widely available N-13 ammonia.

Methods: A 15 mCi N-13 ammonia dose was split into smaller, shielded doses given bolus IV to patients fasting and caffeine free > 9 hrs. Blood sugar was checked for FDG PET. Peak SUV/L extracellular fluid (ECF) = $Ht[\sqrt{Wt}]$ had Ht in m and Wt in kg. Cardiac stress used dipyridamole or regadenoson IV and aminophylline IV to reverse. Brain perfusion was stimulated by 0.4 to 0.8 mg sl. nitroglycerin. List mode PET was gated for stress and rest LVEF. Basal metabolic, stimulated perfusion and flow reserve indices used peak count normalized ROI analysis. Image statistical analysis was modified fractal. An Ecat Exact 47 PET (MIE) used 3D mode and Scintron software. Brain or heart SPECT used a Siemens ecam and Tc-99m-labelled tracers. Montreal cognitive assessment (MoCA) monitored cognition.

Results: Peak SUV/L of ECF was within SD 20% in most decay-corrected studies; outliers included suboptimal bolus or calibration errors. Among 20 studies reviewed, the best protocol was: 1) Chest transmission, 2) Cardiac stress, 3) Cardiac rest, 3) Brain basal, 4) Stimulated brain, 5) Brain transmission, done in < 50 min. A cardiac rest/stress dose ratio near the expected flow reserve index (often near 2) yields similar counts for both cardiac studies and less error from scattering or dead time. Since N-13 ammonia brain uptake peaks later than heart uptake, the stimulated brain scan needs no new dose. Similar rest-stress protocols are also possible, but backgrounds up to 50% were higher than < 25% backgrounds with the stress-rest protocol. Reconstruction was optimal with 16 to 48 subsets, 4 to 5 iterations and 5 to 9 mm Gaussian filters. LVEF from gated PET agreed within 5% with gated SPECT. PET often clarified equivocal coronary ischemia on SPECT. When needed, FDG metabolic PET adds about 30 more min, during which N-13, with < 10 min physical and < 3 min biological half-life, decays to a low background. Normalizing peak counts to 1.6 times average grey-white counts was more reproducible (<3% difference in indices expected similar) than simple peak count normalization. Abnormalities in cardiac flow reserve often coexisted with similar cerebral abnormalities, particularly for diabetics with microvascular disease. Modified fractal analysis of PET and SPECT brain scans correlated similarly with MoCA scores.

Conclusion: A practical, clinical, combined brain-heart N-13 ammonia PET protocol yields more diagnostic results in less time and with less radioisotopic dose, key issues for the increasing number of patients with abnormalities affecting both cerebral and cardiac functions.

1.

1. Fig. 1A: N-13 Ammonia PET Saggital Images for a 85 year-old type 2 diabetic (HbA1c 6.8%) man with memory loss and T-3 thyrotoxicosis on Armour thyroid (Serum T3 347, nml 71-180 ng/dl; Free T4 1.53, nml 0.82-1.77 ng/dl; TSH 0.013, nml 0.45-4.5 mIU/ml; rev T3 27.5, nml 9.2-24.1 ng/ml), suspicious for Alzheimer's disease.

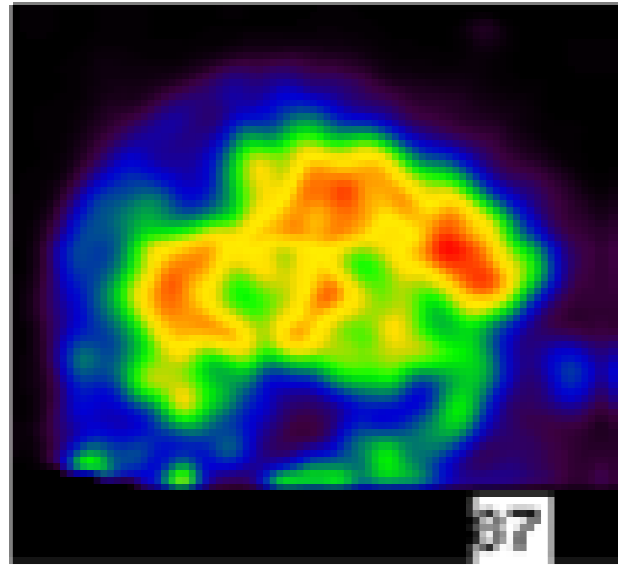


Fig 1B: Coronal Images for the same 85 year-old diabetic man did not show marked hippocampal perfusion or metabolism deficits and the high Neuron specific Enolase 23.4 (nml 0-12.5), relative renal hyperfusion (eGFR 81 vs age expected 55 ml/min/1.73 meter sq), as well as the hyperthyroidism, suggested increased stroke risk as did the low cerebral flow reserve (FRr) and fixed wedge-shaped parieto-occipital deficits, consistent with stroke rather than Alzheimer's disease. Vitamin B12 939 pg/ml, (nml 211-946) and vitamin D 60.6 ng/ml (ref 30-100 ng/ml) levels were normal.

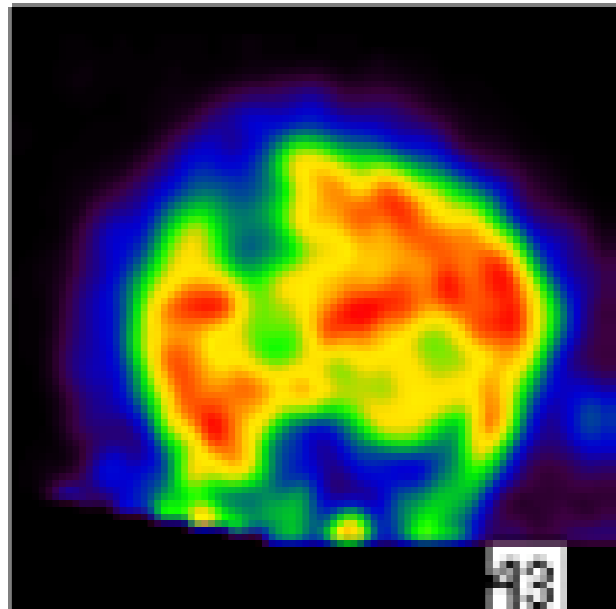
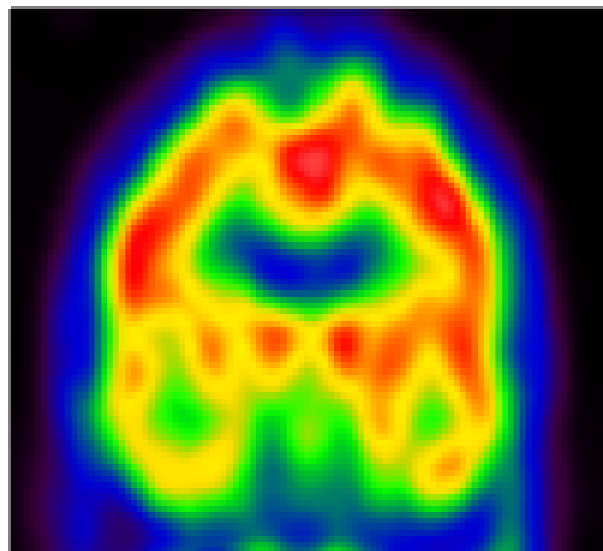
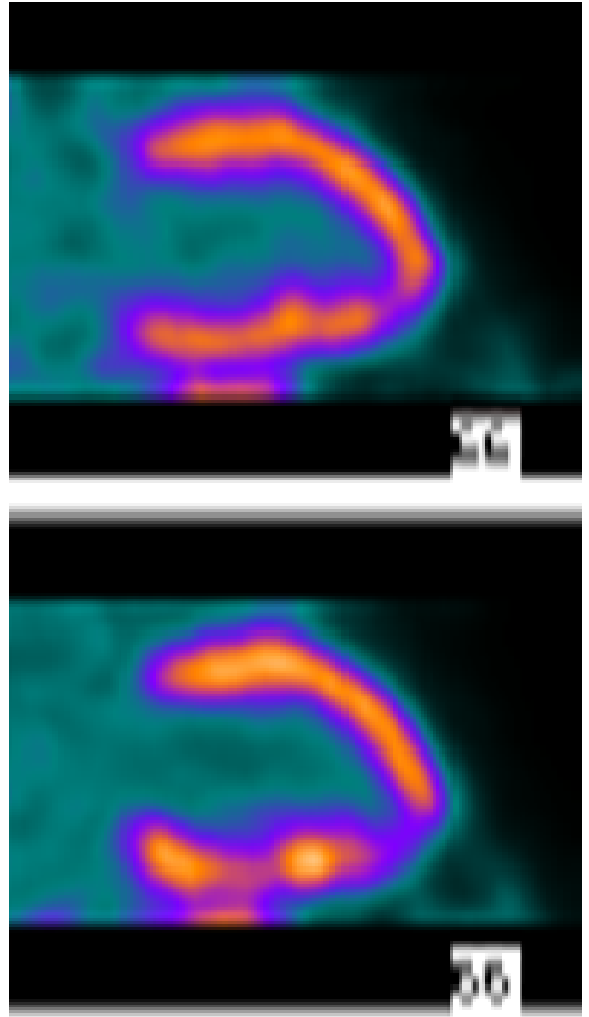


Fig 1C: Rest and Lexiscan stress N-13 ammonia PET images for the same 85 year-old man, obtained in a combined study, vertical long axis, showing inferoapical, subendocardial fibrosis and ischemia (reverse redistribution pattern) with dilated cardiomyopathy: rest LVEF 37% and stress LVEF 40% with global hypokinesis and abnormal coronary flow reserve index 1.25 ± 0.07 vs. normal approx. 3.0 ± 0.5 , consistent with diffuse microvascular or nearly balanced, multivessel CAD.. Abnormalities in both brain and heart studies are frequent, especially in elderly diabetics.



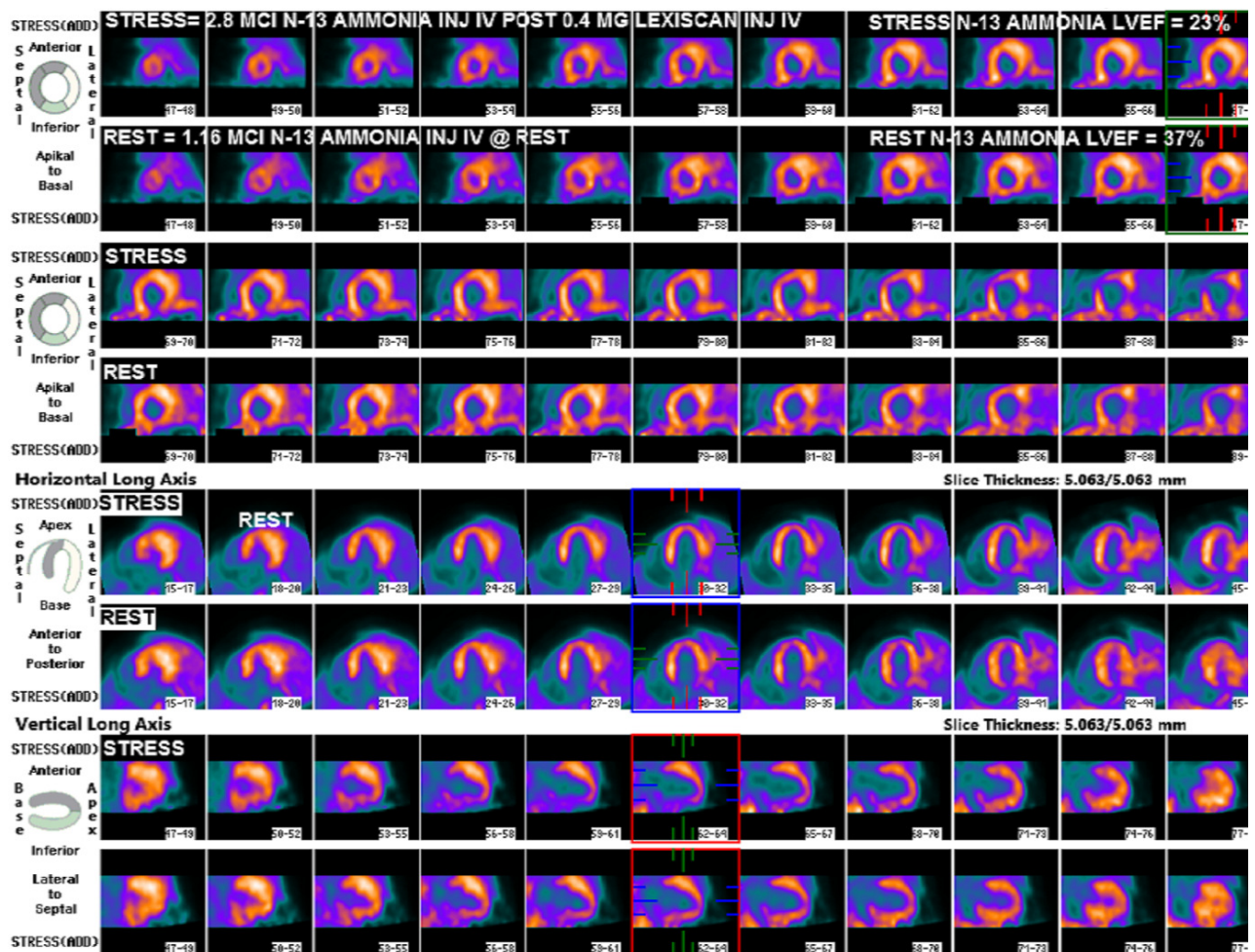
^ From Blue Ash Nuclear Medicine LLC, 4743
Cornell Rd, Cincinnati, OH, 45241 USA and
*The Christ Hospital, Cincinnati, OH, 45219,
USA.

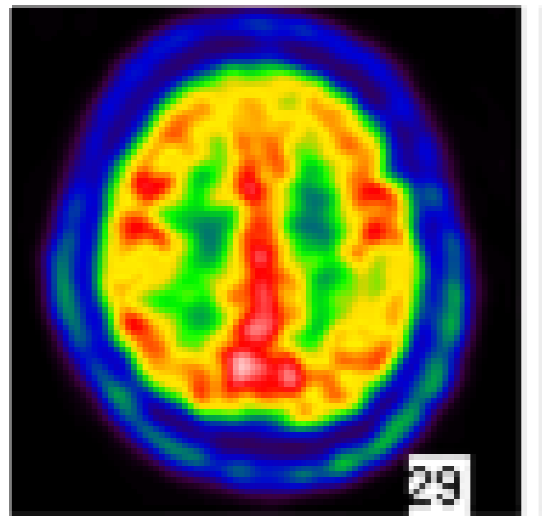
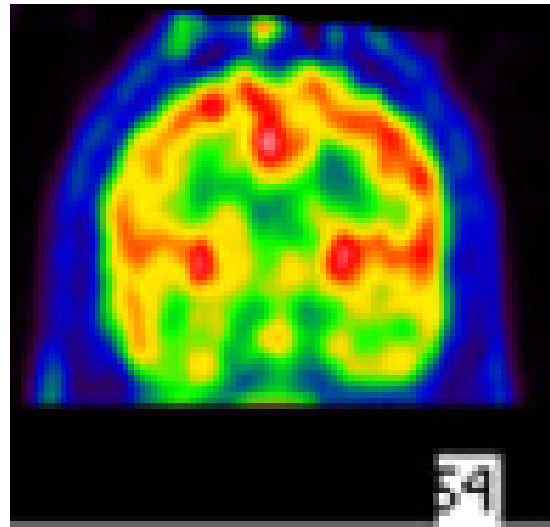
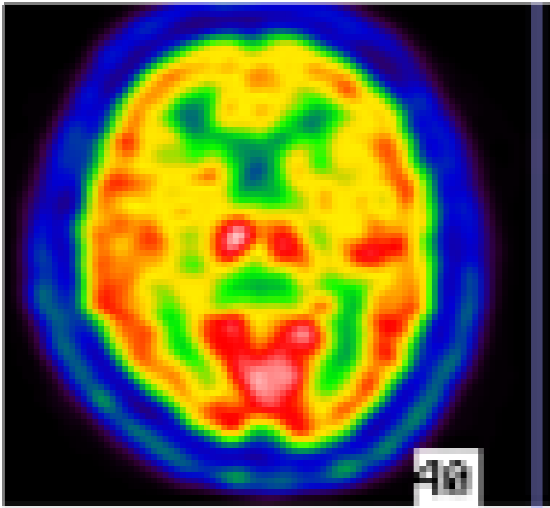


2.

Fig 2A: Brain N-13 ammonia basal images, Coronal (#54), and axial, parieto-occipital level (#40) and axial near superior ventricular level (#29), showing parieto-occipital deficits (cortical thinning) and patchy mesial and inferior temporal hypoperfusion. This 49 year-old male patient's modified fractal analysis revealed moderately severe cognitive impairment with Cortical Metabolic index 42.28% and Sn 0.982, comparable to Sn 0.974+0.143 in 92 other patients with moderately severe cognitive impairment and Montreal Cognitive Assessment (MoCA) 19.91+3.20. Among 17 near normal patients with MoCA 27.08+-1.21 the Sn was 0.354+-0.042.

Fig. 2B: Lexiscan stress and rest cardiac images showing mild posterobasal ischemia, systolic CHF with rest LVEF 37%, stress LVEF 23% and increased pulmonary uptake several weeks after angioplasty of the right coronary artery for the same 49 year-old man of Fig 2A who has history of nine angioplasties, at least one myocardial infarction, hypertension, type 2 diabetes mellitus, hyperlipidemia, hypothyroidism and smokes cigarettes. His coronary flow reserve index was 1.44+-0.2 less than expected normal approx. 3.0+-0.5. N-13 ammonia PET helped quantify the degree of mild ischemia in this patient, whose myocardial perfusion SPECT (not shown) actually appeared more severely compromised owing to posterobasal attenuation artifact.





3.

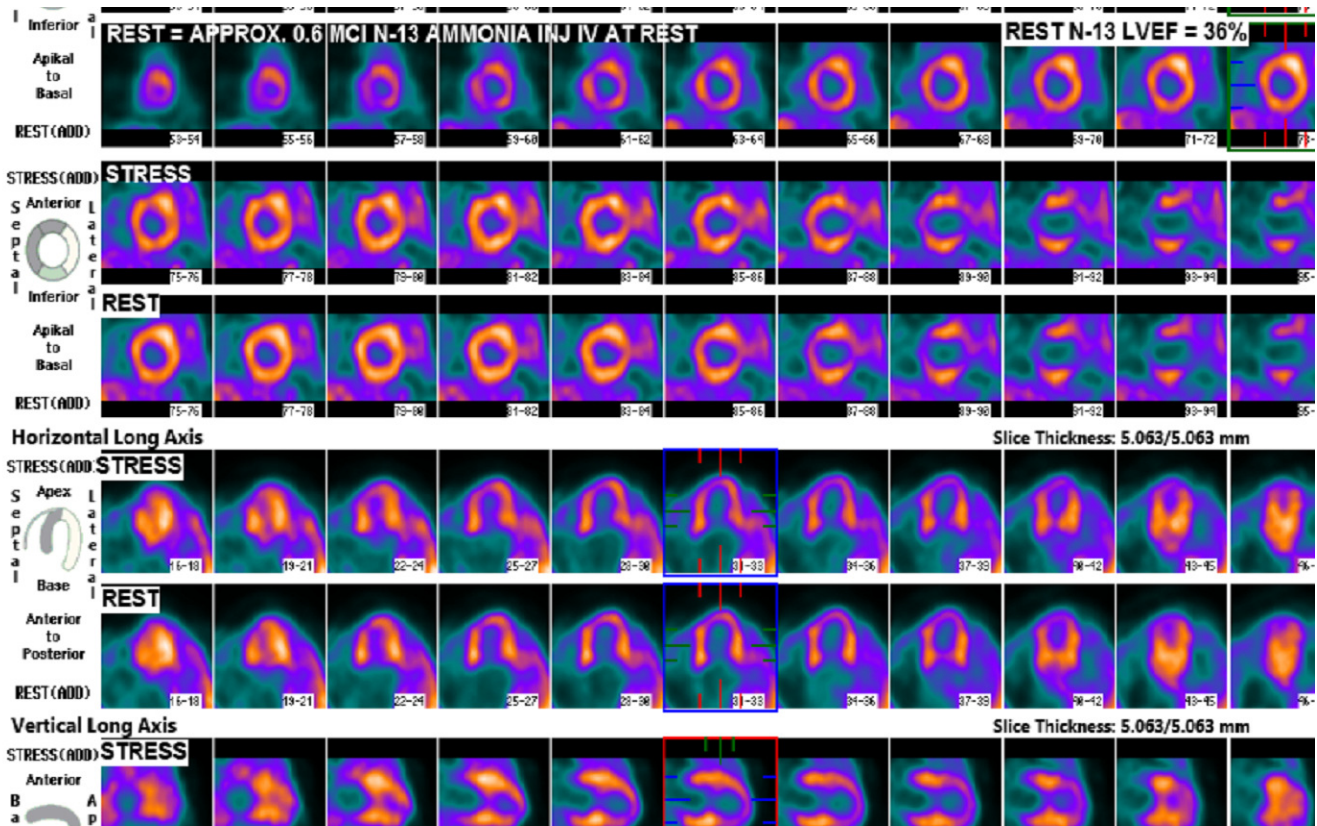


Fig. 3A; Above: N-13 Lexiscan stress and rest cardiac images for a 66 year-old hypertensive man with 40 lb weight loss in the last six months, newly diagnosed hepatitis C, hepatic cirrhosis who smokes cigarettes and is post automatic cardiac defibrillator insertion as well as coronary angioplasty in 2012. No evidence of Lexiscan induced ischemia was noted; however, his coronary flow reserve index 1.38 ± 0.1 was consistent with multivessel CAD and systolic heart failure: rest LVEF 31% and stress LVEF 26% (reprocessed from stress artifact shown).

Fig. 3B; Below: Saggital images for N-13 basal (#63, on the left) and sl. Nitroglycerin-stimulated (#62, on the right) brain PET showing resolution of a dorsolateral deficit and increased brain to sinus activity after perfusion stimulation. His cortical metabolic index was 55.11% , similar to CMi (49.59-66.96)% in 33 near normal patients, with cortical perfusion index (CPi) 50.22%, decreased vs. Cpi (57.75-81.02)% in 33 near normal patients. His cerebral flow reserve index – 4.89% was also abnormal vs. (+4.29 to +17.93)% in 33 near normal patients. Modified fractal Sn was 0.821+-0.048, consistent with moderately severe cognitive impairment (Sn was 0.345+-0.042 in 17 near normal patients).

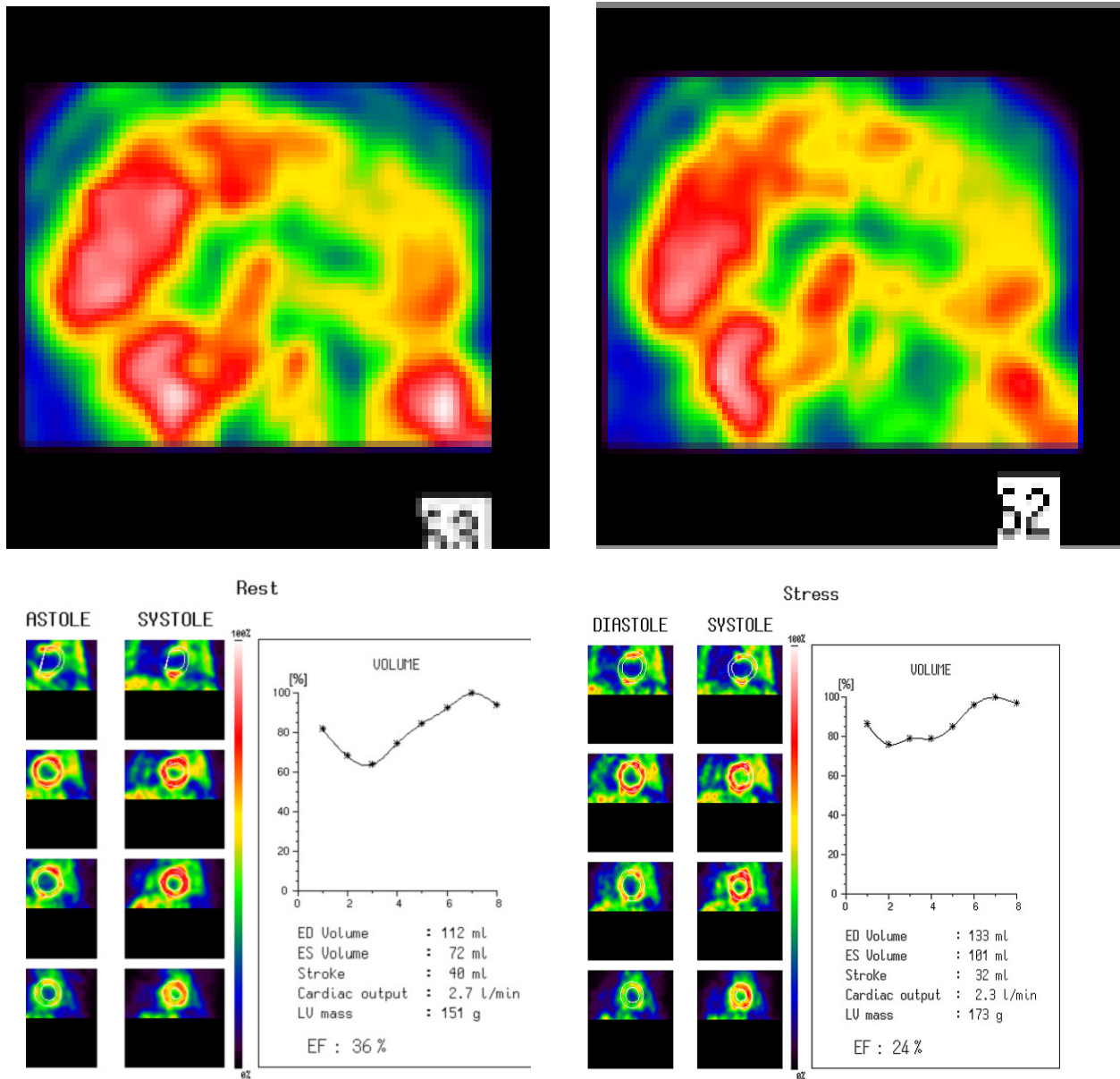
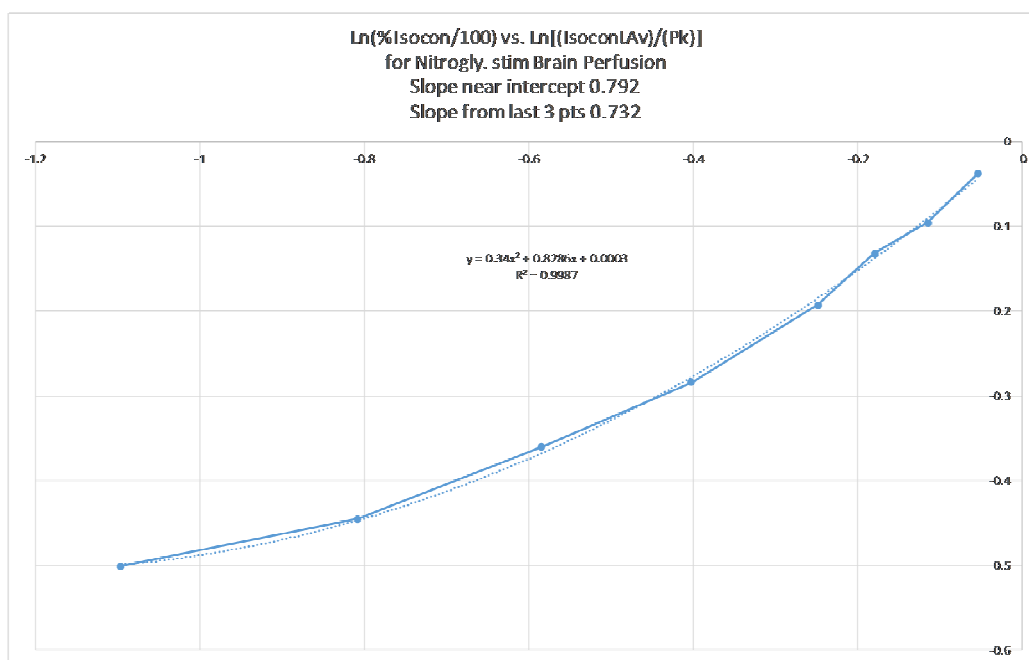
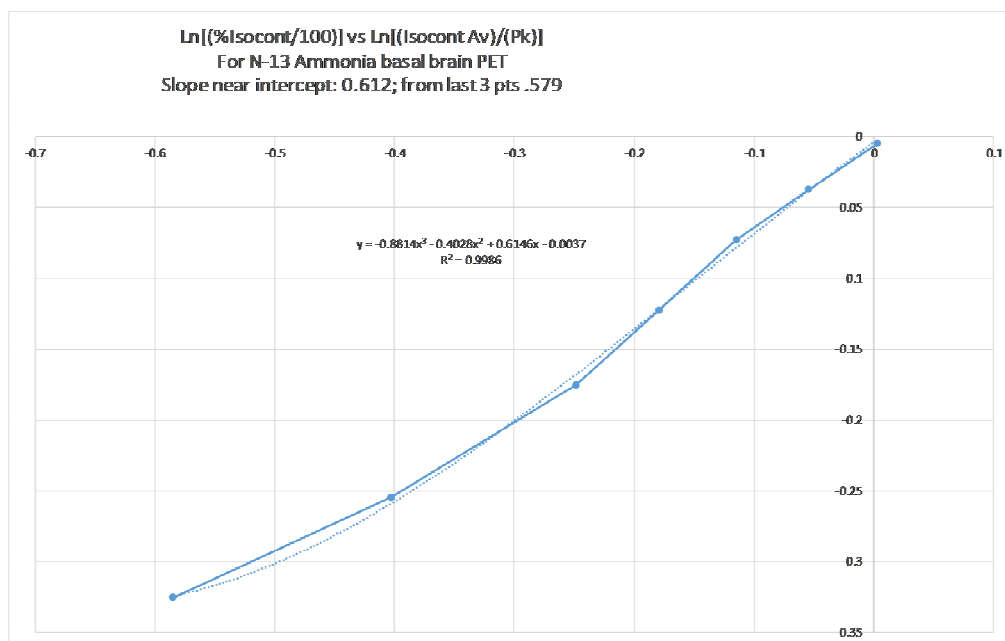


Fig 3C; Above: Log-log plots for modified fractal analysis are not linear since inhomogeneity of brain function by PET is not a simple fractal relation. Steeper slopes indicate more inhomogeneity in tracer distribution and usually are associated with lower cortical indices and more severely compromised cerebral function. Intercept is (0,0) since $\text{Ln}(100\% \text{ isocontour}) = \text{Ln}(1) = 0$ and Av isocontour activity approaches peak activity at an isocontour of 100%, hence the ratio of Av/Pk isocontour activity also approaches 1, whose $\text{Ln} = 0$. This method helps avoid normalization errors since extrapolation is not near the intercept if the image is normalized improperly to, for example extracerebral activity such as sinus inflammation or relative pituitary hyperperfusion, both of which are quite common with N-13 ammonia. Pituitary hypermetabolism is much less common, and more likely pathologic with FDG PET.



4.

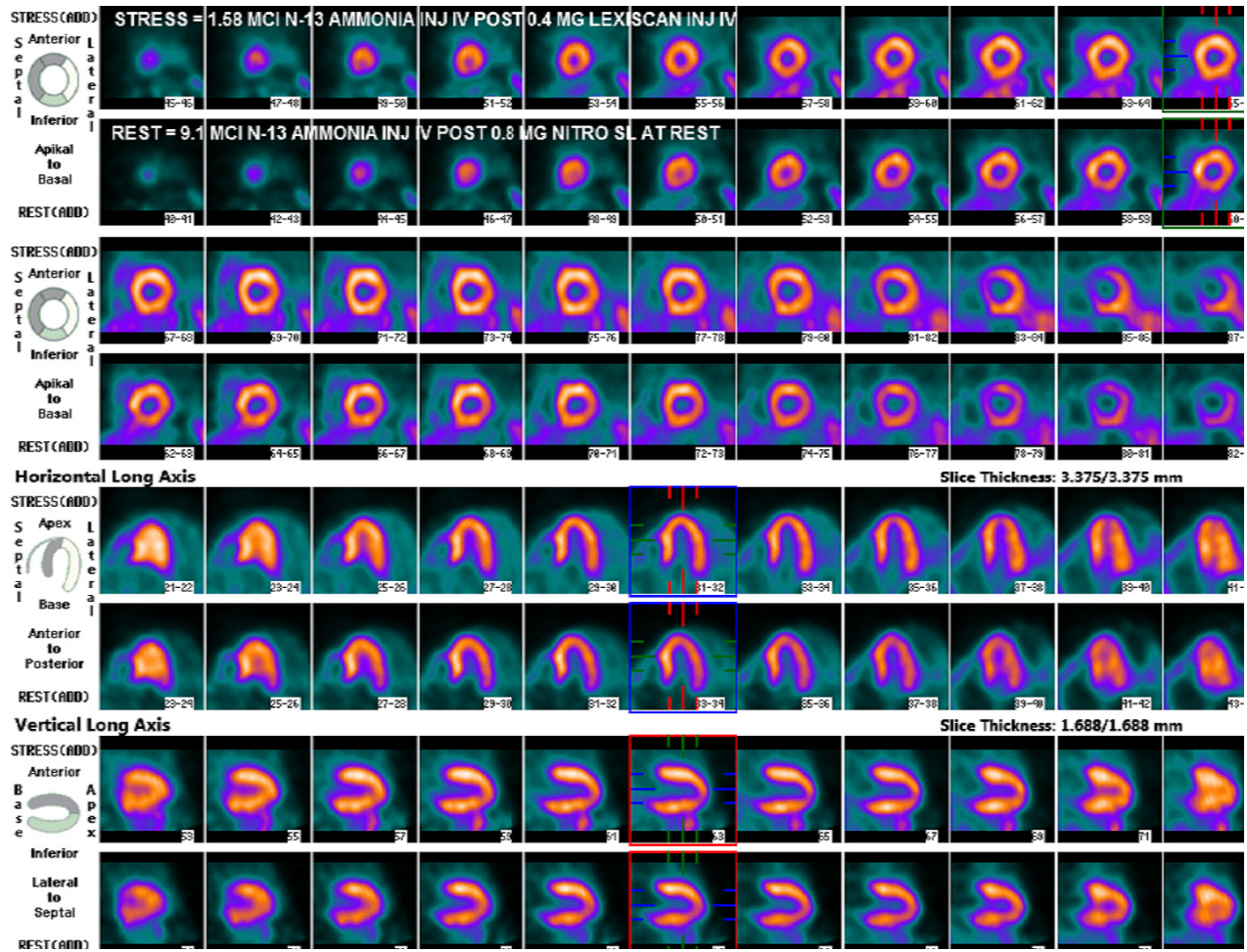


Fig 4B: Above: Use of nitroglycerin for rest brain images precludes accurate coronary flow reserve calculation but may enhance sensitivity for CAD. Image alignment is imperfect in this patient, done before we fully understood how to rebin list mode images, which facilitates optimal alignment, but suggests minimal, inferoapical, subendocardial ischemia.

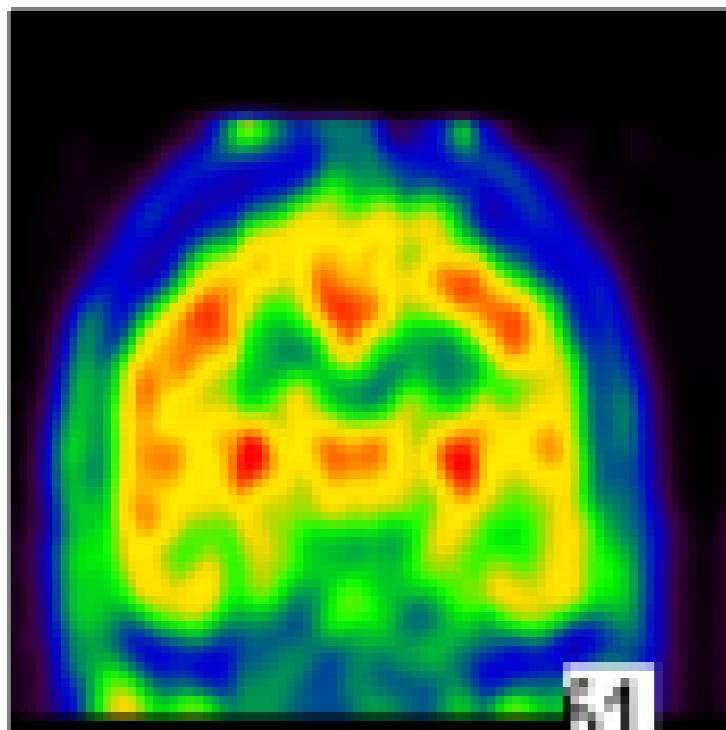
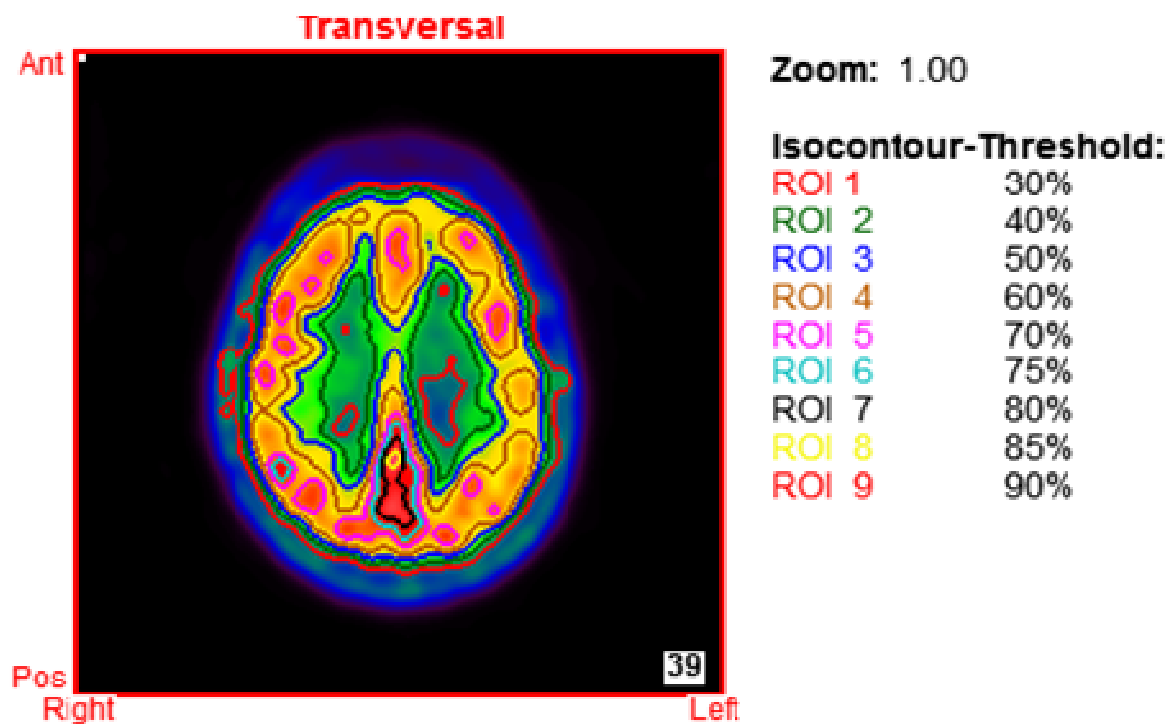
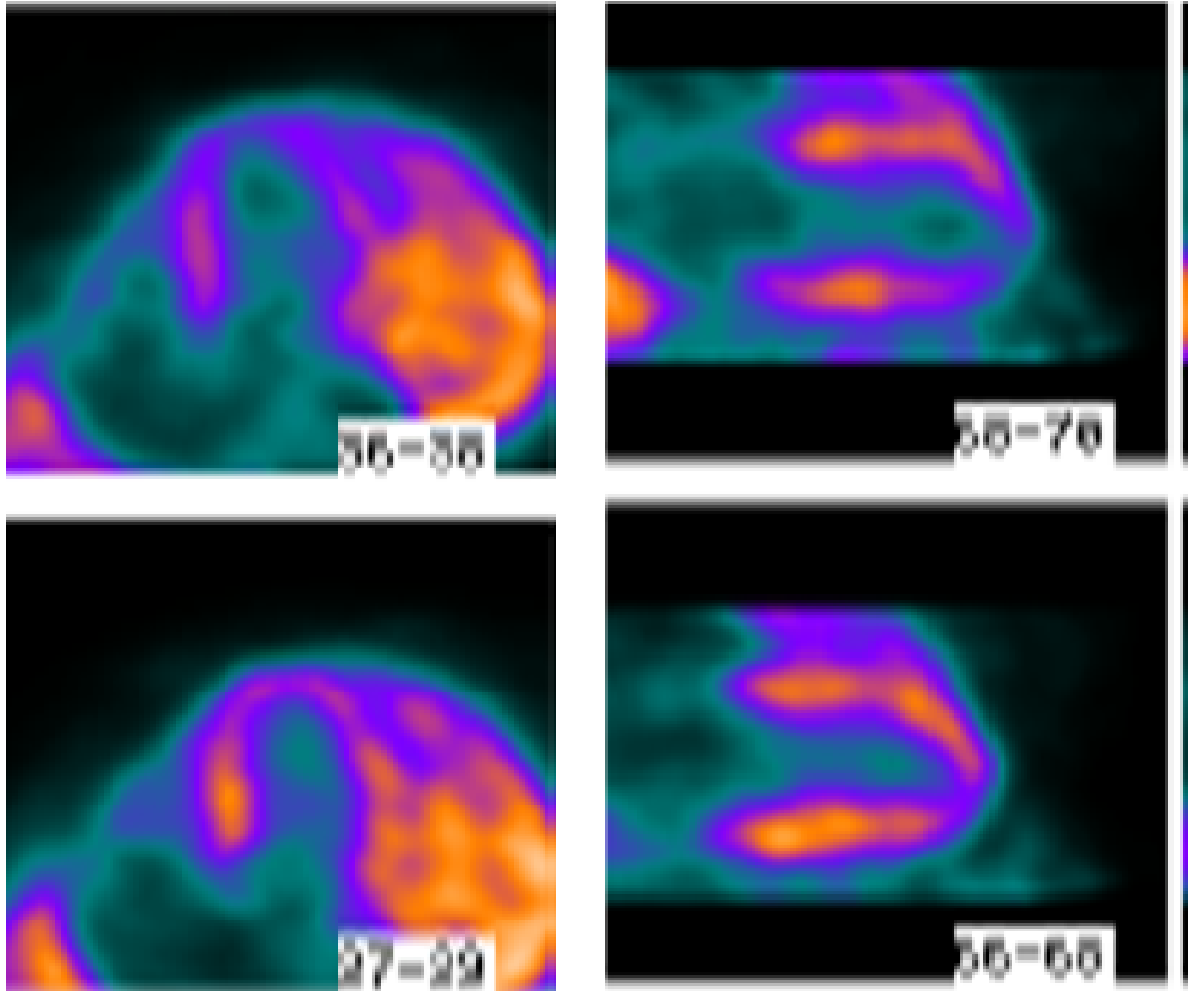


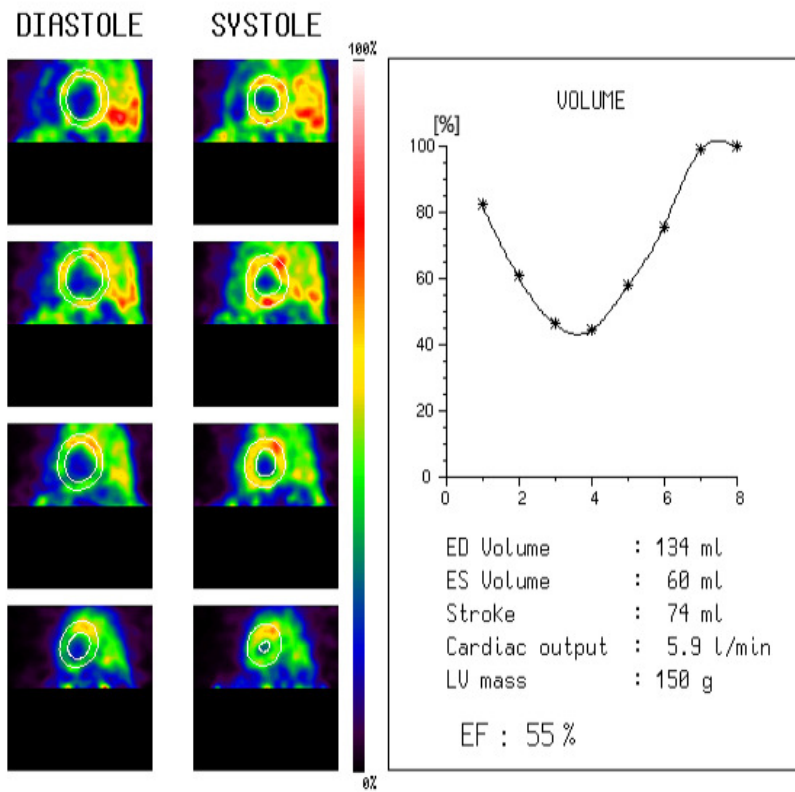
Fig 4A; Above: Nitroglycerin stimulated perfusion brain images for a 60 year-old cardiac patient showing minor temporal deficits in a coronal section and an example of axial isocontour analysis. Her Sn was 0.776 consistent with mild cognitive impairment similar to 258 MCI patients with MoCA 24.2+2.73 and CMi (58.4+5.8)%: her CMi was 50.6%, borderline low.

4b.

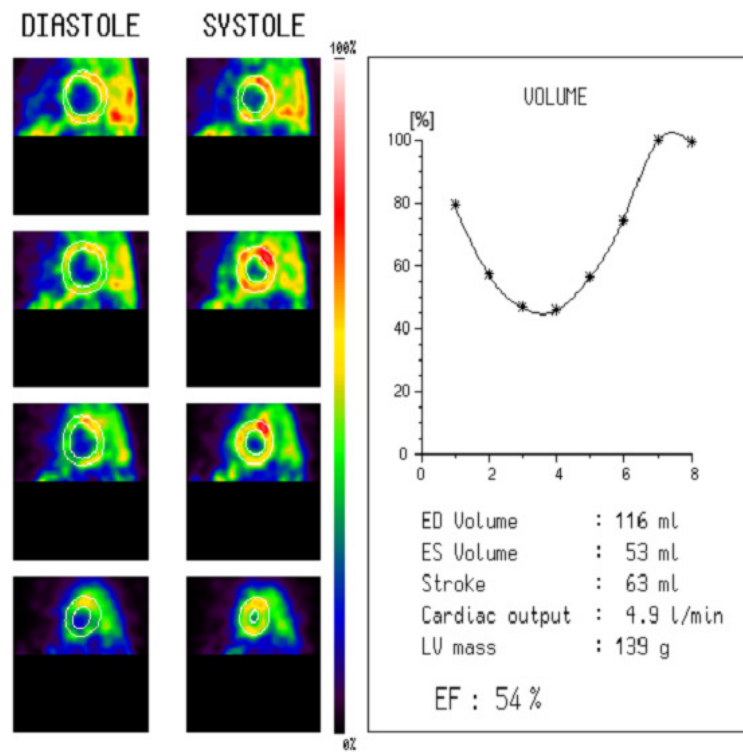
Fig 4b: N-13 ammonia Lexiscan cardiac stress and rest images for a 54 year-old type 2 diabetic woman post gastric bypass surgery who smokes cigarettes and has mild cognitive impairment (MoCA 23/30) as well as bipedal edema. Apical ischemia is evident in the vertical long axis images (upper right, stress displayed above the rest image) as well as significant pulmonary uptake consistent with CHF. Although her normal LVEF does not indicate systolic dysfunction, she does not increase LVEF with stress, suggesting compromised coronary flow reserve. Patients with high BMI are well suited for attenuation corrected PET imaging.



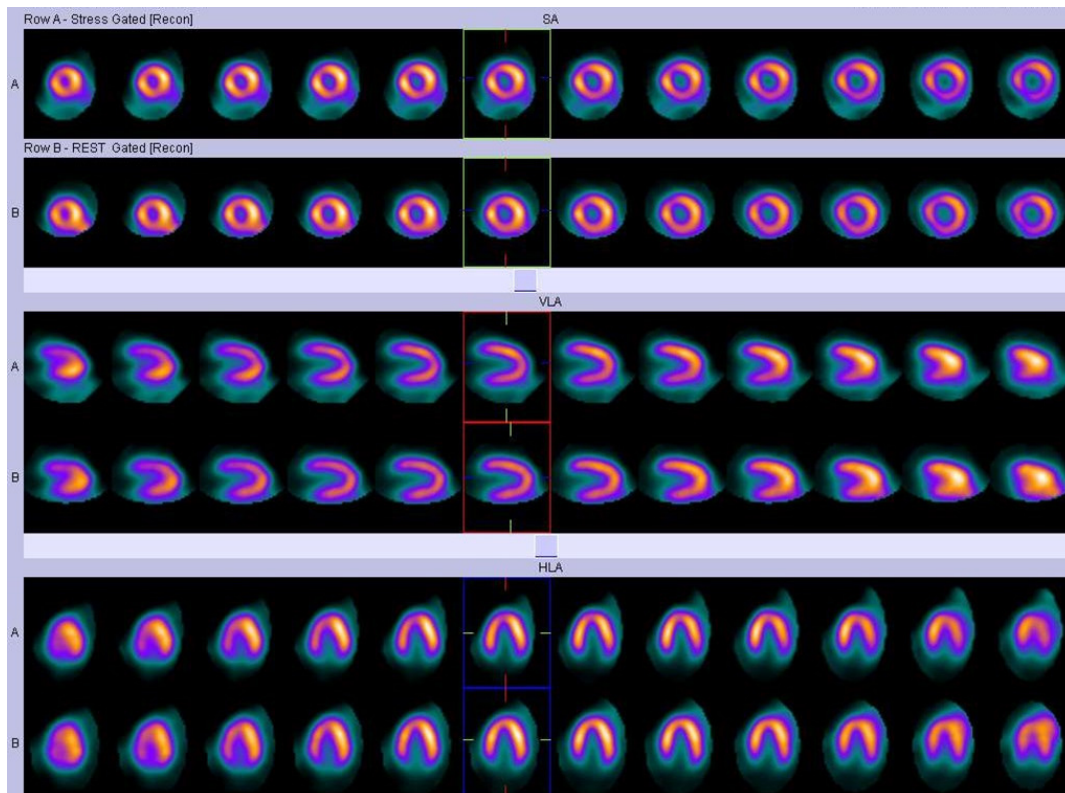
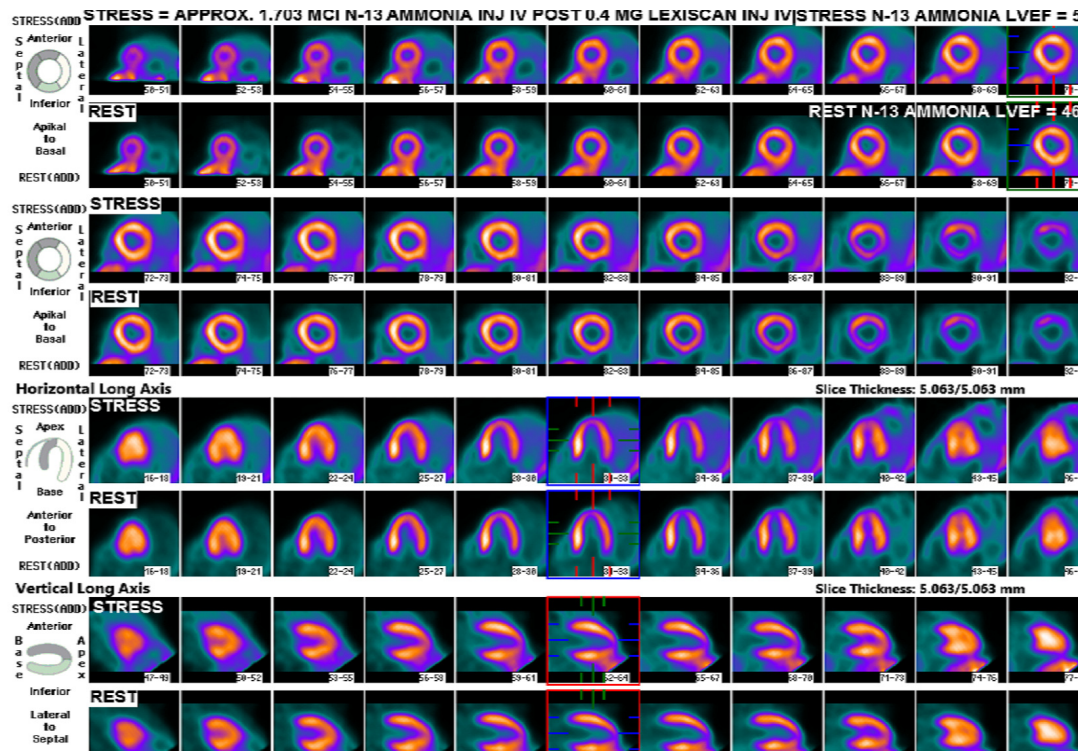
Stress



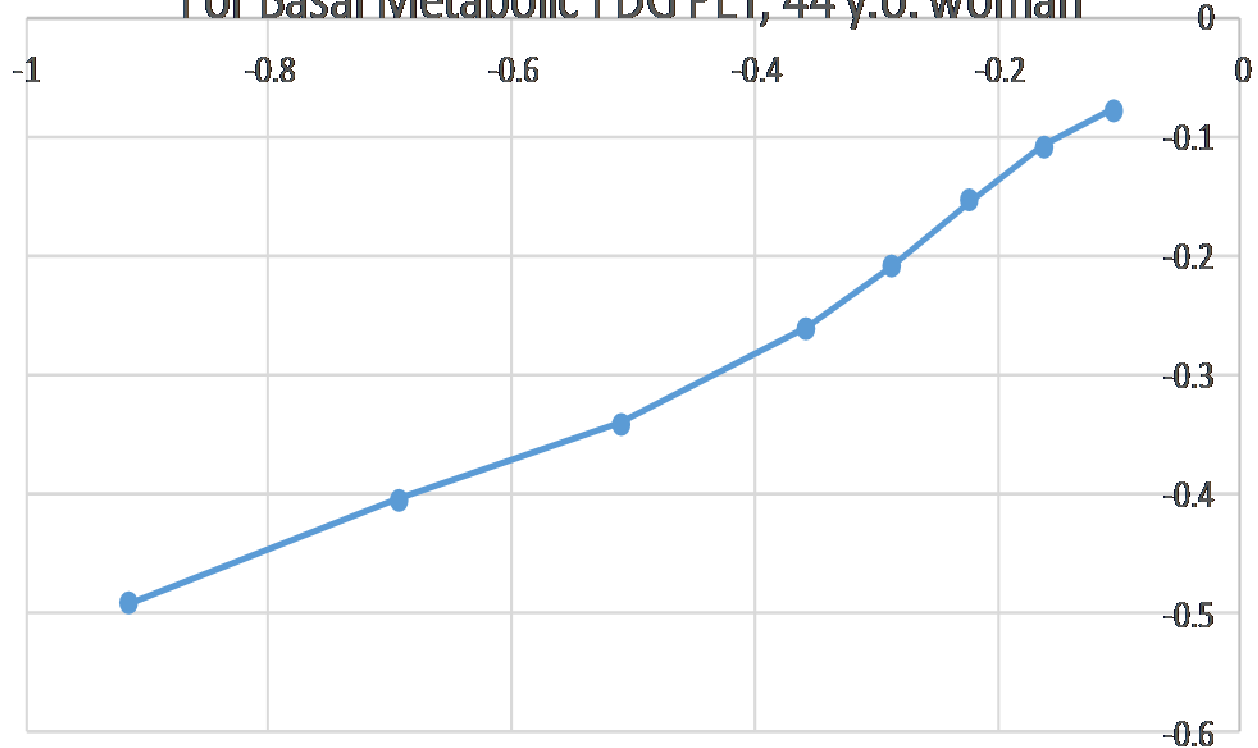
Rest



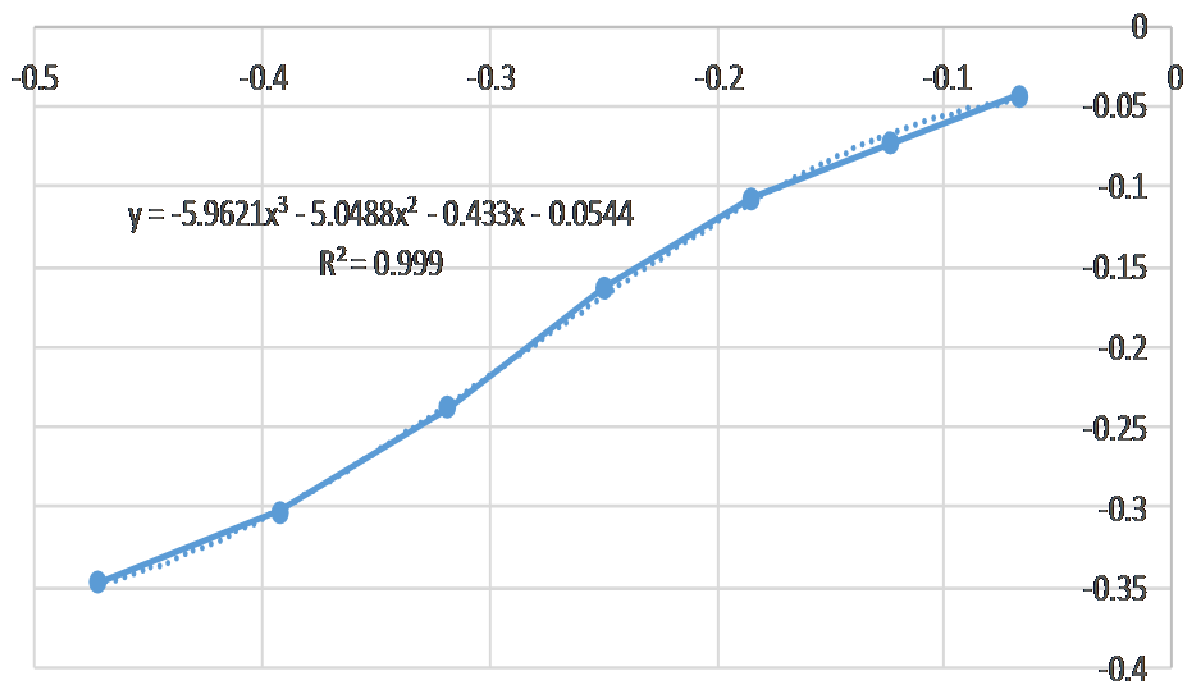
5.



LN(%Isocont/100) vs.LN[(IsocontAv)/(PK)]
For Basal Metabolic FDG PET; 44 y.o. woman



Ln(%Isocon/100) vs Ln[(IsoconAv)/(Pk)] for 45
y.o.woman w. Delayed Metabolic N-13 Amm.



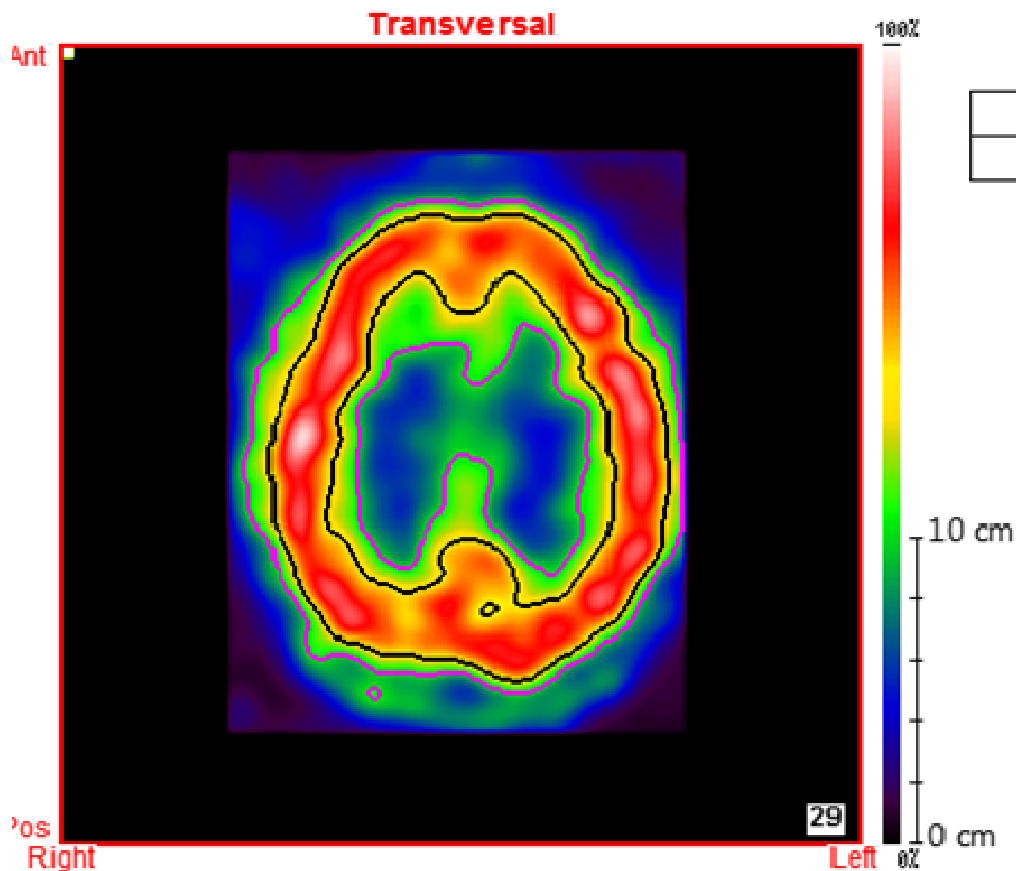
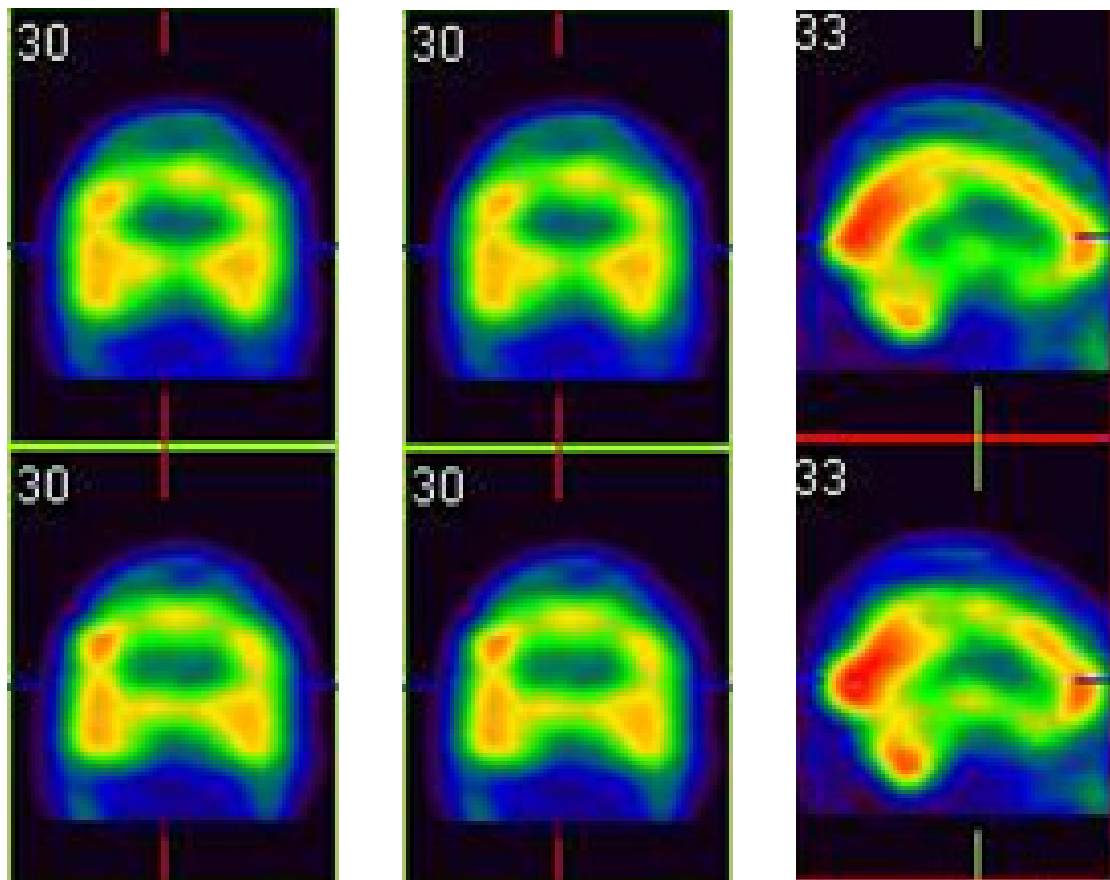
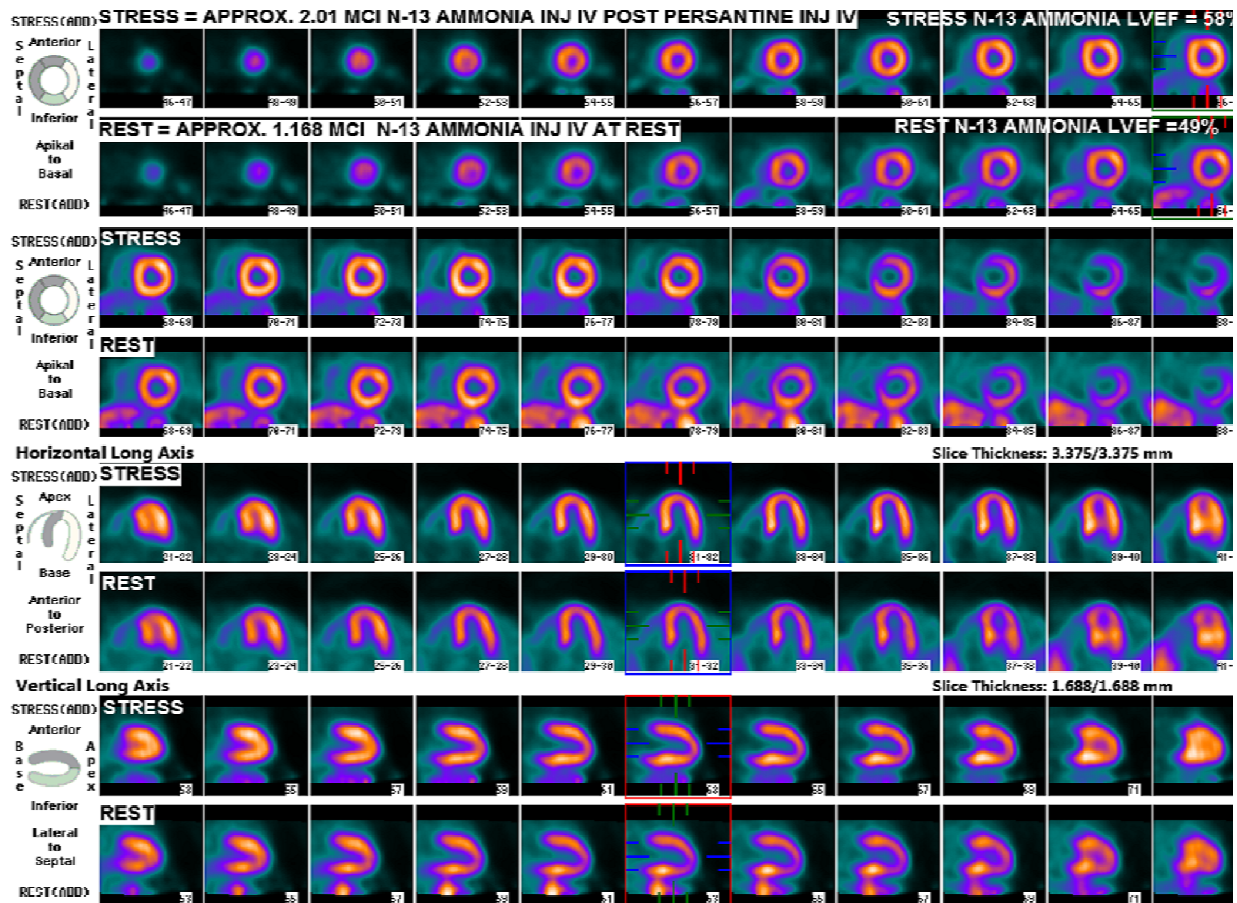


Fig. 5: A 45 year-old woman complains of decreasing ability to complete her work in a timely manner and is concerned she may eventually have to pursue disability application: she has history of Asperger's syndrome, reportedly associated with early coronary ischemia, and has a son with autism but also complains of chronic fatigue. Her N-13 ammonia PET is compared to Myoview SPECT above. Although the myocardial lateral wall may appear relatively hypoperfused with N-13 ammonia, this effect is reduced with modern gated studies, and further reduced if rest and stress heart rates are relatively similar. In this case we felt that septal prominence was more than usual and consistent with asymmetric septal hypertrophy more evident on PET than SPECT. Minor cardiomyopathy was confirmed by borderline low rest LVEF 46% and stress LVEF 50%. In retrospect, additional history suggested possible excess alcohol intake which could contribute to cardiomyopathy.

This patient's combined N-13 ammonia PET used initial acetazolamide 500 mg, given shortly before the stress and rest cardiac studies which were completed within the 15 minutes required to develop the full acetazolamide effect of stimulating cerebral perfusion. This protocol compares early Acetazolamide-stimulated brain PET as a measure of brain perfusion with delayed N-13 ammonia PET as a measure of brain metabolism. Control studies with FDG (with CMi 50.7% vs. CMi 51.7% with delayed N-13 ammonia, and stimulated HMPAO SPECT with CPi 52.25% vs 47.25% for early, stimulated N-13 ammonia (image above, right, emphasizes cortical perfusion), and with Sn 0.882 \pm 0.069 for FDG and HMPAO SPECT vs. 0.856 \pm 0.039 for N-13 ammonia basal and stimulated brain PET, suggest that this approach, which avoids separate basal injections, is promising. We have used a similar protocol with ECD SPECT (Cf. Fig 6A), for which there is excellent evidence that images from about 60 to 180 sec are a measure of perfusion, while later images, apart from the tendency to occipital increased ECD uptake, closely approximate FDG brain metabolism.

6.



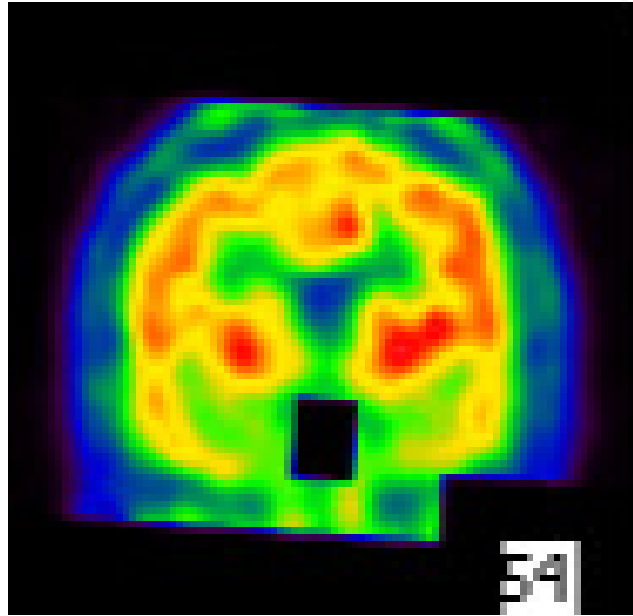


Fig. 6: A 56 year-old woman with history of traumatic brain injury in childhood has fatigue and memory loss and is considering disability evaluation since she is unable to multitask at work. Her symptoms were reminiscent of coronary microangiopathy and she has insulin resistance; however, her N-13 ammonia PET cardiac study (above, right), which used dipyridamole stress, was normal, including coronary flow reserve index 2.85 ± 0.2 (normal approx. 3.0 ± 0.5).

Dipyridamole crosses the blood brain barrier and can be used for simultaneous cardiac and cerebral perfusion stimulation which revealed bilateral mesial temporal deficits, more clearly seen on N-13 ammonia PET (above, right) than her prior ECD SPECT shown above, left. Rebinning of list mode studies allows PET similar to an ECD SPECT with dynamic SPECT at 7 sec per frame and 16 acquisitions on dual head SPECT (32 views) but at higher resolution for PET. The delayed N-13 ammonia SPECT is similar to FDG basal brain PET in cases so far investigated (cf. Fig. 5).

Conclusions:

Both Brain and Heart PET are possible with a single 15 to 20 mCi N-13 dose, since 1 mCi is sufficient for gated list mode studies using the high sensitivity, 3D mode.

Current Protocols effectively extend N-13 ammonia use to suburbs of most cities; moreover, a new, small N-13 cyclotron with very modest site requirements can further extend N-13 ammonia use to most specialty clinics.

Late (> 7 to 10 min) N-13 ammonia brain and heart images = FDG metabolism: well known as reverified with our modified fractal analysis = histogram analysis, much simpler than most statistical parametric image comparisons and we believe robust enough for individual patient comparisons.

Further work is needed to show if stimulated early (near 1 to 3 min) N-13 ammonia brain images, similar to early ECD SPECT brain images = nearly true brain perfusion, but early N-13 ammonia stress heart activity, best found in list mode, is well established as a measure of cardiac perfusion, and appropriate, with delayed rest activity, to measure a coronary flow reserve index.