Slides

Pharmacology/Toxicology and Clinical Pharmacology of [^{18}F]FDG

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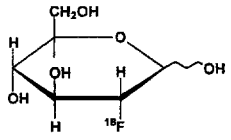
Approach Taken

- Peer-reviewed publications written in English
- Materials reviewed previously as part of [^{18}F]FDG NDA for epilepsy
- Solicited materials from PET community

Aspects of [^{18} F]FDG covered

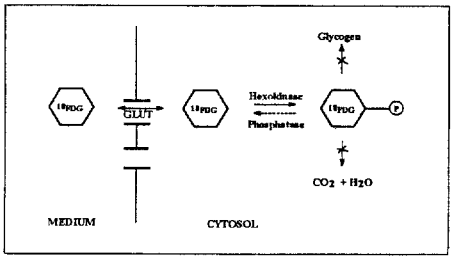
- The Characteristics of [^{18} F] FDG & uptake / trapping mechanism
- Theoretical considerations
- Myocardial & oncological considerations
- Dosimetry Information
- Metabolism & Biodistribution
- Toxicology

Characteristics of [^{18}F]FDG



- Glucose analog
- Concentrates in cells dependent on glucose as primary energy source or pathophysiologically
- Shares similar kinetics of transportation and phosphorylation with glucose
- Subtle differences in the way the body handles the two hexoses

Schema of [^{18}FDG] Uptake Mechanism



Theoretical Considerations

- Balance GLUT, HEX and PT
- To allow for glucose quantification, the kinetic differences between glucose and [^{18}F]FDG transport and phosphorylation are reflected in a ratio called "Lumped constant"

Region of decrease/absent uptake reflects absence of glucose metabolism

Myocardial Considerations

- Fatty acids are preferred source of energy
- Contributive use of glucose increases during hypoxic conditions because of glucose requirement for less energy
- Therefore, increased uptake of glucose analogs such as [^{18}F]FDG

Myocardial considerations

- Perfusion-metabolic match: there is a simultaneous reduction in both FDG uptake and flow
- Perfusion-metabolic mismatch: there is enhanced FDG uptake and reduced blood flow
- Factors affecting uptake process include fasting, insulin level and diabetes

Oncological Considerations

- Tumors have high glycolytic activity
- High hexokinase activity
- Increased GLUT expression
- Decreased phosphatase activity
- Increased [^{18}F]FDG uptake in tumor cells

Dosimetry Information

- 1 ml vial contains 6.8-35.7 mCi (251-1,321 MBq)
- Physical half-life of 109.8 minutes
- Positron emission decay with 511 keV photons

Patient hydration and voiding reduces exposure to the bladder which is the critical organ.

Metabolism & Biodistribution

- Metabolized through phosphorylated intermediates to 2-fluoro-2deoxy-D-mannose (FDM)
- FDG and FDM are rapidly cleared from blood and brain, less rapidly from heart
- Variable levels of FDG & FDG-6-P in tumors
- Excreted unchanged in urine
- 2-chloro-2-deoxy-D-glucose (CDG) handled similarly

Toxicology

- No significant FDG toxicity found in studies conducted in dogs & mice
- Apparent LD_{50} of 200 mg/kg in mice
- 2-DG (50mg/kg, 50,000X MHD) caused hypoglycemic effect similar to that produced by insulin
- Extent of effect of FDG on metabolism in compromised myocardium is not known

Preliminary summary

Pharmacology, toxicology and clinical pharmacology assessment supports use of [^{18}F]FDG for oncology and myocardial indications

F-18 FDG PET in Oncology: Safety and Effectiveness Review

Florence Houn MD MPH

June, 1999

F-18 FDG Team

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F-18 FDG Oncology S&E Preliminary Review Conclusions

- Effectiveness
  - To identify areas of abnormal glucose metabolism for evaluating malignancy in patients with abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer
- Safety
  - IV doses from 200-740 MBq
  - Fasting at least 4 hrs

F-18 FDG Oncology Review

- Guidances on Clinical Effectiveness/Medical Imaging
- Intended Use of F-18 FDG Oncology
- Pathology Standard
- Search Methodology
- Selection Criteria
- Review of Findings
- Conclusions

F-18 FDG Oncology Review

Guidance on Clinical Effectiveness-Use of Published Literature Alone

- Multiple studies/adequate design/consistent findings
- Detailed protocol
- Objective and appropriate endpoints
- Consistent conclusions of efficacy
- Conduct of studies with documented operating procedures
- Examples: secretin, bleomycin and talc, doxycycline

F-18 FDG Oncology Review

Adequate/Well-Controlled (Med. Imaging Guidance)

- Selection of subjects=Target population
- Readers: independent, masked, randomized, separate
- Standards of truth
- Endpoints
- Analysis plans
- Safety: toxicity and radiation assessment

F-18 FDG Oncology Review

Intended Use: evaluating malignancy (diagnostic population)

- Preliminary review for major uses
- "Developing Medical Imaging Drugs and Biologics" draft guidance
  - "Functional, Physiological, or Biochemical Assessment"
    - Validated to a standard of truth
    - Spectrum of disease and normality tested
    - Pharmacological basis of "functional claim"

F-18 FDG Oncology PET Pathology Standard

- All studies compared to pathology
- Sensitivity and specificity

F-18 FDG Oncology Review Literature Search Methodology

- Criteria for Search
  - January 1, 1990 to July 1, 1998
  - Human clinical trials
  - English
  - On-line databases: Medline, Cancerlit, Derwent Drug File, Biosis Preview, International Pharmacology Abstracts, and Embase
  - PET community suggested articles
  - References cited in above articles

F-18 FDG Oncology Review Literature Search Methodology

- Selection Criteria
  - Prospective
  - F-18 FDG PET results compared to pathology
  - Clinical performance hypothesis
  - Well-described study population
  - More than 50 evaluable patients
  - Larger data set reviewed when multiple papers were produced from same data set

F-18 FDG Oncology Published Literature

- Adequate/Well-Controlled Clinical Trials (2)
  - Prospective enrollment
  - Study population similar to target population for clinical use
  - Pathology
  - Multi-centered studies or with at least 50 evaluable patients
  - Details about interpretive criteria and masking
- Other Supportive Studies (14)
  - Prospective
  - Study population similar to target population for clinical use
  - Pathology
  - Ancillary hypotheses (retrospectively determined SUV)/no masking

F-18 FDG Oncology Adequate/Well-Controlled Studies

- Carr R. Blood 1998;91:3340-46.
- Lowe V., J Clin Oncol 1998;16:1075-84.

F-18 FDG Oncology Supportive Studies

- Avril N. J Clin Oncol 1996;14:1848-57.
- Bury T. Eur Respir J 1997;10:2529-34.
- Delbeke, Arch Surg 1998;133:510-16
- Dietlein M. Eur J Nucl Med 1997;24:1342-48.
- Friess H. Gut 1995;36:771-777.
- Gupta N. J Nucl Med 1996;37:943-48.
- Holder Jr. W. Annals of Surg 1998;227:764-771.

F-18 FDG Oncology Supportive Studies

- Lowe VJ. J Nucl Med 1994;35:1771-76.
- Moog F. J Cliln Oncol 1998;16:603-9.
- Schiepers C. Curo J of Surgical Oncol 1995;21:517-22.
- Utech C. Eur J Nucl Med 1996;23:1588-93.
- Valk PE. Ann Thorac Surg 1995;60:1573-82.
- Vansteenkiste JF. J Clin Oncol 1998;16:2124-49.

F-18 FDG Oncology Review

Adequate /Well-Controlled: Carr (1998)

- Objective: F-18 FDG diff. benign vs malignant marrow lesions identified by routine staging after dx
- Sample size: 50 pts.
- Design: Prospective; compared pathology /PET; routine lymphoma staging: thor/ab CT, unilat iliac crest asp/trephine bx
- Image Protocol: Visual interpretation by 3 indep. nucl meds; Kappa=0.64; masked path.
- Dose: >6hrs fasting; 350 MBq IV, emission scan after 35-45 minutes
- Sensitivity 13/16 (81%) Specificity 26/34 (76%) using unilat Bone Marrow

F-18 FDG Oncology Review

Adequate /Well-Controlled: Carr (1998)

- Strengths
  - 3 independent readers
  - Criteria given for PET reading
  - Tracked agreement
  - Masked pathologists
  - Histology protocol given
- Weaknesses
  - 50 patients only
  - Unilateral iliac crest aspirates
  - Need to develop non-biased method for discrepancy resolution-
  - ? Readers masked
  - Combined HD and non-HD patients

F-18 FDG Oncology Review

Adequate/Well-Controlled: Lowe (1998)

- Objective: Sens/Spec of PET with SPN seen of CT or CXR
- Sample Size: 89 pts. Multi-centered trial
- Inclusion Criteria: Lesion <4cm>0.7cm and considered indeterminant
- Design: Compare PET vs. pathology and SUV

F-18 FDG Oncology :

Adequate and Well-Controlled: Lowe (1998)

- Image Protocol: masked, independent, 2 readers, film copies, disagreement resolved by consensus, Kappa= 0.95.
- Prospectively determined SUV >2.5 for malignancy
- CXR and CT scans read by non-site radiologists, masked
- SUV performed on ROI by masked reader
- Dose: Fast >4hrs; 370 MBq IV; emission scans after 55 -65 min.

F-18 FDG Oncology Review: Lowe (1998) Con't.

- Results
  - 60/89 SPN malignant; 29 benign
  - 50/60=NSCLC; melanoma, HD, small cell, carcinoid, neural, colon metastasis
  - 7/29=granuloma; fungal, debris, inflammation, fibrosis, hemangioma, metaplasia
  - Visual sens 98% (59/60); spec 69%(20/29)
  - SUV sens 92% (55/60); spec 90% (26/29)

F-18 FDG Oncology Review Lowe (1998) Con't.

- Strengths
  - Inclusion criteria
  - Pathology standard
  - Images read by 2 readers, independently, masked to CT/CXR
  - Interobserver differences in PET tracked/analyzed
  - Sensitivity and specificity

F-18 FDG Review Lowe (1998) Con't.

- Strengths Con't.
  - Dispute resolution described
  - Tracked readers' performances (Kappa)
  - Information on CXR/CT readings controlled
  - Multi-centered trial
  - Number of patients
  - Detailed patient information

F-18 FDG Oncology Review Lowe (1998) Con't.

- Weaknesses
  - Twice as many malignant lesions as benign
  - No information on pathology reading protocol
  - Sampling variations for TTNA vs. open-lung biopsy

F-18 FDG PET Oncology: Supportive Studies

Study	Goal	Patients	Design	Image Protocol	Dose	S/E
Avril (1996)	Benign vs Malignant Breast lesions	53 women before surgery; tumor>1cm	Pathology, Readings, SUV	[illegible] 2 readers; masked	270-290 MBq after >4 hrs fast	Visual Sens 83% and Spec 84%
Bury (1997)	Staging Accuracy of NSCLC	109 pts dx'd w/NSCLC; bone scan chest/abd CT	Pathology, Readings	PET readings not masked to CT/BS	200-300MBq after 7 fasting time	Metastatic Sens 100% Spec 94%
Delbeke (1998)	Benign vs Malignant Hepatic lesions on CT	87 pts with abnormal imaging	Pathology, Readings	Masked, visual interpre., CT used for localization	370 MBq after 4 hours	Sens 90% and Spec 96%

F-18 FDG Oncology Supportive Studies

Study	Goal	Patients	Design	Image Protocol	Dose	S/E
Dietlein (1997)	Thyroid metastases; PET vs I-131 WBI	58 patients with thyroid Ca	Pathology, PET readings	2 readers, masked, consensus	370 MBq after >12 hrs fasting	Met Sens 50% and Spec 97%
Friess (1995	Pancreatic Ca vs Pancreatitis	80 patients prior to surgery	Pathology, PET readings	Masked, 2 ind. Readers, ROI circled, ?CT proto.	250-350 MBq after >6 hrs fast; 10mg Lasix	Cancer Sens 94% Spec 88%
Gupta (1996)	SPN-malignant vs benign	61 pts w/indeterm. pulm. nodule	Pathology, PET readings	2 readers, not masked to CT/xray, SUV [illegible]	370 MBq after ~4hrs fasting	Visual Sens 93% Spec 88%

F-18 FDG Oncology Supportive Studies

Study	Goal	Patients	Design	Image Protocol	Dose	S/E
Holder (1998)	Detect metastatic melanoma	76 pts with dx melanoma	Pathology, PET reading	3 readers, not masked to CT, not all pts had bilat BMB	444-740 MBq after >4hrs fast, 10mg Val. Lasix	Met. Sens 94% Spec 83%
Lowe (1994)	Malignant vs Benign Lung lesions	88 pts w/abnormal findings	Pathology, PET reading, SUV	2 readers, not masked to CT, drew ROI masked w/o	370 MBq after >4hrs fasting	Visual read by consensus 98%
Moog (1998)	HD/NHD Lymphoma BM involvement	78 pts w/dx of lymphoma	Bil BMB Pathology, PET reading	2 readers, [illegible] consensus	250-350 MBq after >8hrs fasting	Vis vs. BMB Sens 64% and Spec 85%

F-18 FDG Oncology Supportive Studies

Study	Goal	Patients	Design	Image Protocol	Dose	S/E
Saxon (1996)	Lung lesions Ca vs Benign	107 pts w/abnormal CXR/CT	Pathology, PET reading	Two readers masked to CT	370 MBq after ?length fast	Sens 100% and Spec 52%
Schiepers (1995)	Metastatic colo-rectal Cancer PET vs CT	76 pts w/dx colo-rectal CA suspic. of recurr.	Pathology, PET reading	Masking not stated, ?readers	400-550 MBq after >6hrs fast, bladder flushing	Sens 94% Spec 100% vs. CT Sens 85% and Spec 98%
Utech (1996)	Axillary node staging w/ Breast CA	124 pts w/dx Breast CA	Pathology, PET reading	3 then 1 reader, masked to node info, knew CA	370 MBq after 4 hrs	Sens 100% Spec 75%

F-18 FDG Oncology Supportive Studies

Study	Goal	Patients	Design	Image Protocol	Dose	S/E
Valk (1995)	Staging of Lung CA and indeter. Lung lesions	99 pts (67 w/dx CA; 32 w/ inde.; 25 pts excluded	Pathology; PET reading	1-2 readers not masked to CT scans; Reread by 2 readers at end masked	0.143 mCi/kg after >4hrs fasting	Mediastinal sens 83% and Spec 94%
Vansteenkiste (1998)	PET and CT nodal staging of Lung CA	68 pts suspected or w/dx Lung ca	Pathology; PET reading	2 readers, not masked to CT	6.5 MBq/kg after >6 hrs fast	nodal stage PT+CT sens 87% vs. CT 59

F-18 FDG Oncology Review
Weaknesses of Literature

- Absence of statistical criteria for significance and power
- Less information protocols for imaging handling and reading criteria
- Absence of source data
- Bias (publication bias, subjectivity of readers scoring, patient selection)

F-18 FDG Oncology Review
Weaknesses of Literature cont'd

- No control of prior imaging interpretations
- Use of furosemide and serum glucose
- Variations in pathological sampling

F-18 FDG Oncology PET
Preliminary Review Conclusions

- Efficacy
  - To identify areas of abnormal glucose metabolism for evaluating malignancy in patients with an abnormality found by other testing modalities or with existing diagnosis of cancer (not for screening)
  - Consistent findings, diverse malignancies-generalized mechanisms for ↑ glc utilization
  - Sensitivity and specificity calculated

F-18 FDG Oncology S&E Preliminary Review Conclusions

- Safety (FDG/Radiation)
  - Small amount of FDG/glucose introduced
  - Know metabolism and excretion
  - Short physical half-life (110 minutes)
  - Acceptable radiation dosimetry
  - Acceptable risk of radiation
  - Unknown performance with hyperglycemia

F-18 FDG Oncology Review Preliminary Conclusions

- Effectiveness
  - To identify areas of abnormal glucose metabolism for evaluating malignancy in patients with abnormalities found by other testing modalities or in patients with existing diagnosis of cancer
- Safety:
  - Fasting at least 4 hours before injection
  - IV doses of 200-740 MBq studied

F-18 FDG Cardiac PET
Draft Clinical Review

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28 June 1999

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- A Sancho-Biopharm

Clinical Review
Preliminary Conclusions

Efficacy

To identify left ventricular myocardium with altered glucose metabolism and reversible loss of contractility, when used together with myocardial perfusion imaging

Clinical Review
Preliminary Conclusions

Safety

- Previous NDA: Doses up to 10.5 mCi studied
- Most Literature: Doses up to 10 mCi studied
- Possible safety concerns in patients with impaired glucose homeostasis (because of fasting and/or glucose loading)

F-18 FDG CARDIAC PET
Literature Search

- Search Criteria for all Uses
  - January 1, 1990 to July 1, 1998
  - Human clinical studies
  - English
  - Medline, Embase, Cochrane Controlled Trials Register, Cancerlit, Derwent Drug File, HSTAR, Biosis Previews, International Pharmacology Abstracts
  - Articles provided by PET community
  - References cited in above articles
  - Cardiac: References in ACC/AHA Guidelines, USPDI

Results of Literature Search

Database	Number of References
Medline	250
Embase	274
Derwent	38
Cochrane	33
Cancerlit	25
Biosis	9
HSTAR	3

Framework for Literature Review

Draft Guidance for Industry: "Developing Medical Imaging Drugs and Biologics"

- Federal Register Notice of Availability
  63 FR 55067
- Internet
  http://www.fda.gov/cder/guidance/index.htm

Framework for Literature Review

Consideration of Potential Claims:

- Structure delineation
- Functional, Physiological, or Biochemical Assessment
- Disease or Pathology Detection or Assessment
- Diagnostic or Therapeutic Patient Management
- Multiple Claims
- Other Claims

Framework for Literature Review

- Clinical usefulness of information
- Validity of information
- Studied in a defined clinical setting

Functional Consequences of Coronary Artery Disease

- Reversible myocardial dysfunction
  - Myocardial hibernation
  - Myocardial stunning
- Nonreversible myocardial dysfunction
  Myocardial infarction

Reversible Myocardial Dysfunction

- Myocardial hibernation
  Chronic, reversible left ventricular dysfunction due to coronary artery disease
- Myocardial stunning
  Prolonged, postischemic left ventricular dysfunction

Terminology

For purposes of this presentation:

- Hibernation = viability
- Radionuclide uptake = radionuclide localization = radionuclide accumulation

F-18 FDG PET Image Evaluation

- F-18 FDG is taken up into myocytes by the glucose transporter.
- After phosphorylation by hexokinase, F-18 FDG is not metabolized further.
- Phosphorylated F-18 FDG accumulates in the cell and generates a signal.

F-18 FDG PET Image Evaluation

- Flow-metabolism mismatch: increased accumulation of F-18 FDG compared to myocardial perfusion = hibernating tissue
- Flow-metabolism match: Concordant reductions in F-18 FDG accumulation and perfusion = scar tissue

Identification of Hibernating Myocardium in Principal Studies

- Performance of PET F-18 FDG is measured against a functional outcome: recovery or lack of recovery after revascularization
- Performance of PET F-18 FDG is not compared with that of a gold standard

Schema of Principal Studies

- Before revascularization
  - Identified asynergic myocardial segments and graded the severity of dysfunction
  - Assessed perfusion (in most studies)
  - Predicted viability with F-18 FDG PET
- Coronary revascularization

  CABG and/or angioplasty.

Schema of Principal Studies

- After revascularization
  - Assessed success of revascularization (usually)
  - Assessed degree of wall-motion improvement
- Data analysis
  - Described patient and segment disposition
  - Calculated diagnostic performance measures (e.g., sensitivity, specificity, PPV, NPV)

Cautions: Data Analysis of Principal Studies

- Studies often had primary objectives other than the evaluation of the diagnostic performance of PET F-18 FDG
- Performance measures such as sensitivity, specificity, PPV, and NPV are derived from relatively small numbers of patients in each study

Cautions: Data Analysis of Principal Studies

- Segments were defined differently in each study
- Performance measures such as PPV and NPV are heavily influenced by prevalence

Framework for Literature Review

- Sufficient detail of study design, study population, doses used, endpoints, image acquisition, image interpretation, statistical analyses, etc.
- Adequate study design: Controls, gold standard, blinded image evaluation, sufficient accounting for patients and segments, etc.
- Study population sufficiently similar to the population for which F-18 FDG is intended

F-18 FDG Cardiac PET Primary Literature Selection

- Baer FM, Voth E, Deutsch HF, et al. J Am Coll Cardiol 1996;28:60-9.
- Gerber BL, Vanoverschelde JJ, Bol A, et al. Circulation 1996;94:651-9.

F-18 FDG Cardiac PET Primary Literature Selection

- Gropler RJ, Geltman EM, Sampathkumaran K, et al. J Am Coll Cardiol 1993;22:1587-97.
- Knuuti MJ, Saraste M, Nuutila P, et al. Am Heart J 1994;127:785-96.

F-18 FDG Cardiac PET Primary Literature Selection

- Lucignani G, Paolini G, Landoni C, et al. Eur J Nucl Med 1992;19:874-81.
- Maes AF, Borgers M, Flameng W, et al. J Am Coll Cardiol 1997;29:62-8.

F-18 FDG Cardiac PET Primary Literature Selection

- Marwick TH, MacIntyre WJ, Lafont A, et al. Circulation 1992;85:1347-53.
- Tamaki N, Yonekura Y, Yamashita K, et al. Am J Cardiol 1989;64:860-5.

F-18 FDG Cardiac PET Primary Literature Selection

- Tamaki N, Kawamoto M, Tadamura E, et al. Circulation 1995;91:1697-705.
- Tillisch J, Brunken R, Marshall R, et al. N Engl J Med 1986;314:884-8.

Baer et al Description of Study

- Objective: To assess the predictive value of myocardial viability diagnosed by dobutamine transesophageal echocardiography and F-18 FDG PET for left ventricular functional recovery
- Patients: Prospective, consecutive, CAD, chronic LV dysfunction
- Perfusion: Not assessed

Baer et al. Description of Study

- F-18 FDG PET: 10 mCi, quantitative image evaluation, 28 segments, viable if accumulation ≥50% of maximum
- Comparator: low-dose dobutamine TEE
- Revascularization: CABG or angioplasty, success evaluated with coronary arteriography
- Wall motion: transesophageal echocardiography, blinded image evaluation by two readers, four-point ordinal scale

Baer et al. Results of Study

- Patients: 42 included in analysis, 26 improved function
- Segments: 1176 possible, 405 akinetic or dyskinetic at rest, 371 successfully revascularized, 180 improved function
- Diagnostic performance: calculated both by segment and by patient

Baer et al. Results of Study

- F-18 FDG PET results, by segment
  - Prevalence: 49%
  - Sensitivity: 93% (88, 96)
  - Specificity: 66% (59, 72)
  - PPV: 72% (66, 78)
  - NPV: 91% (84, 95)

Baer et al. Results of Study

- F-18 FDG PET results, by patient
  - Prevalence: 62%
  - Sensitivity: 96% (80, 100)
  - Specificity: 69% (41, 89)
  - PPV: 83% (65, 94)
  - NPV: 92% (61, 100)

Baer et al.
Assessment of Study

- Strengths (not all inclusive)
  - Consecutive patients, prospective
  - Wall-motion assessment blinded
  - Multiple readers for wall-motion
  - By-patient analysis performed
  - Compared different diagnostic modalities

Baer et al.
Assessment of Study

- Limitations (not all inclusive)
  - Small sample size (but one of the three largest)
  - Perfusion not assessed
  - Number of PET readers not specified
  - Wall-motion assessment based only on systolic wall thickening (not on wall movement)
  - Global LV function and clinical outcomes not assessed

Gerber et al.
Description of Study

- Objective: To delineate the flow and metabolic correlates of the reversibility of left ventricular ischemic dysfunction
- Patients: Consecutive, CAD, anterior wall LV dysfunction
- Perfusion: N-13 ammonia (dose not specified)
- Comparator: low-dose dobutamine 2-D echo

Gerber et al.
Description of Study

- F-18 FDG PET: Dose not specified; quantitative, operator-interactive image analysis; analysis limited to anterior-wall segments; match/mismatch pattern used to predict viability
- Revascularization: CABG or angioplasty; success evaluated by angiography
- Wall motion: 2-D echo; 3-point ordinal scale

Gerber et al.
Results of Study

- Patients: 39 included in analysis
- Segments: 39 (limited to anterior wall)
- Diagnostic performance: calculated by segment, assumed to be identical to by-patient analysis

Gerber et al.
Results of Study

- F-18 FDG PET results, by segment
  - Prevalence: 62%
  - Sensitivity: 75% (53, 90)
  - Specificity: 67% (38, 88)
  - PPV: 78% (56, 92)
  - NPV: 62.5% (35, 85)

Gerber et al.
Assessment of Study

- Strengths (not all inclusive)
  - Consecutive patients, prospective
  - All 39 patients included in analysis
  - By-segment analysis = by-patient analysis
  - Compared different diagnostic modalities
  - Wall-motion assessments included evaluation of wall excursion and of systolic wall thickening

Gerber et al.
Assessment of Study

- Limitations (not all inclusive)
  - Doses of F-18 FDG and N-13 ammonia not specified
  - Number of readers of 2-D echocardiograms or of PET images not specified
  - Not specified if readers of 2-D echocardiograms or PET images were blinded
  - Results may not apply to other regions of the left ventricle

Gropler et al.
Description of Study

- Objective: To determine whether prediction of recovery of LV mechanical function could be accomplished more effectively by PET with C-11 acetate than F-18 FDG
- Patients: CAD, LV dysfunction
- Perfusion: 0.25-0.40 mCi/kg C-11 acetate (early myocardial uptake)

Gropler et al.
Description of Study

- F-18 FDG PET: dose not specified, quantitative image evaluation, 8 segments, viable if F-18 FDG glucose normalized to flow > 2 SD above mean in controls
- Comparator: C-11 acetate PET
- Revascularization: CABG or angioplasty
- Wall motion: 2-D echo, contrast ventriculography, or radionuclide ventriculography, blinded image evaluation by two readers, 5-point ordinal scale

Gropler et al.
Results of Study

- Patients: 34 evaluated
- Segments: 272 possible, 141 dysfunctional, 116 included in analysis, 46 had improved function
- Diagnostic performance: calculated by segment

Gropler et al.
Results of Study

- By segment:
  - Prevalence: 40%
  - Sensitivity: 83% (68, 92)
  - Specificity: 50% (38, 62)
  - PPV: 52% (40, 64)
  - NPV: 81% (67, 92)

Gropler et al.
Assessment of Study

- Strengths (not all inclusive)
  - Wall-motion analysis performed by two, blinded readers
  - Alignment of segments across modalities well discussed
  - ROC analysis performed
  - Different diagnostic agents were compared

Gropler et al.
Assessment of Study

- Limitations (not all inclusive)
  - Dose of F-18 FDG not indicated
  - C-11 acetate used to assess perfusion
  - Number of PET readers not specified
  - Blinding of PET readers not specified
  - Only nominal assessment of success of revascularization (operative, cath-lab reports)
  - Global LV function and clinical outcomes not assessed

Knuuti et al.
Description of Study

- Objective: To assess the value of PET F-18 FDG in predicting cardiac wall motion recovery after revascularization
- Patients: Consecutive patients, previous MIs, wall motion abnormalities at rest
- Perfusion: SPECT with thallium-201 or Tc-99m MIBI

Knuuti et al.
Description of Study

- F-18 FDG PET: 7.0±1.5 mCi, semi-quantitative image evaluation, 8 segments, viable if F-18 FDG uptake was above the lower limit (mean-2SD) of normal segments
- Revascularization: CABG or angioplasty; success evaluated by surgical report
- Wall motion: 2-D echo, one blinded reader, four-point ordinal scale.

Knuuti et al.
Results of Study

- Patients: 48 included in analysis
- Segments: 384 possible, 106 abnormal wall motion, 90 successfully revascularized, 27 recovered function.
- Diagnostic performance: calculated by segment

Knuuti et al.
Results of Study

- By segment
  - Prevalence: 30%
  - Sensitivity: 100% (87, 100)
  - Specificity: 63% (50, 75)
  - PPV: 54% (39, 68)
  - NPV: 100% (91, 100)

Knuuti et al.
Results of Study

When an optimized threshold was identified by discriminant analysis, without consideration of perfusion:

- sensitivity = 85%
- specificity = 84%

Knuuti et al.
Assessment of Study

- Strengths (not all inclusive)
  - Largest sample size of the ten principal
  - Wall-motion analysis was performed blindly
  - Alignment of myocardial segments obtained by different imaging methods was described
  - Reproducibility of wall-motion analysis by the same reader was assessed and documented
  - Evaluated different potential thresholds of F-18 FDG localization

Knuuti et al.
Assessment of Study

- Limitations (not all inclusive)
  - Information to which readers were blinded was not specified
  - Number of readers of PET images not specified
  - Blinding of PET image evaluations not specified
  - No assessment of improvement in global LV function or of clinical outcomes.

Lucignani et al.
Description of Study

- Objective: To identify hibernating myocardium with Tc-99m MIBI SPECT and F-18 FDG PET
- Patients: CAD, LV dysfunction
- Perfusion: SPECT with Tc-99m MIBI at rest and stress
- F-18 FDG PET: 6.8 mCi; visual analysis, 5 segments, viable if any degree of F-18 FDG uptake identified (on a three-point ordinal scale)

Lucignani et al.
Description of Study

- Revascularization: CABG, success verified by repeat coronary arteriography
- Wall motion: EKG-gated planar perfusion scintigraphy and first-pass radionuclide angiography with Tc-99m MIBI, five-point ordinal scale, number of readers not specified, blinding of readers not specified

Lucignani et al.
Results of Study

- Patients: 14 included in analysis
- Segments: 70 possible, 54 asynergic, 40 improved function
- Diagnostic performance: calculated by segment
- Additional analyses: two multiple logistic analyses performed

Lucignani et al.
Results of Study

- By segment
  - Prevalence: 74%
  - Sensitivity: 92.5% (80, 98)
  - Specificity: 80% (52, 96)
  - PPV: 95% (83, 99)
  - NPV: 80% (52, 96)

Lucignani et al.
Results of Study

- First multiple logistic analysis showed that highest probability of wall motion recovery was associated with high F-18 FDG uptake and absent perfusion at rest
- Second multiple logistic analysis (on F-18 FDG uptake data alone) showed that probability of wall motion recovery increased as F-18 FDG uptake increased

Lucignani et al.
Assessment of Study

- Strengths (not all inclusive)
  - Qualitative evaluation of F-18 FDG PET images and SPECT perfusion images may be possible
  - Multiple readers (n=3) used in evaluation of F-18 FDG PET and SPECT perfusion images
  - Evaluated stress hypoperfusion

Lucignani et al.
Assessment of Study

- Limitations (not all inclusive)
  - Small sample size
  - Not specified if readers of F-18 FDG PET and SPECT perfusion images were blinded to results of wall-motion analysis
  - Number of readers for wall-motion analysis not specified
  - Not specified if wall-motion analysis was blinded

Maes et al.
Description of Study

- Objective: To evaluate the ability of Tc-99m MIBI to assess viability, as compared to PET metabolism and perfusion studies
- Patients: Prospective, CAD, motion abnormalities of anterior wall
- Perfusion: 20 mCi N-13 ammonia
- F-18 FDG PET: 10 mCi; quantitative image evaluation, analysis limited to anterior wall, viable if ratio of metabolic index to flow index > 1.2

Maes et al.
Description of Study

- Revascularization: CABG
- Wall motion: Radionuclide angiography, regional ejection fractions were calculated to assess improvements in regional ventricular function

Maes et al.
Results of Study

- Patients: 23 included in analyses
- Segments: 23 segments included in analyses (limited to anterior wall)
- Diagnostic performance: calculated by segment, assumed to be identical to by-patient analysis

Maes et al.
Results of Study

- By segment
  - Prevalence: 52%
  - Sensitivity: 83% (52, 98)
  - Specificity: 91% (58, 100)
  - PPV: 91% (58, 100)
  - NPV: 83% (52, 98)

Maes et al.
Assessment of Study

- Strengths (not all inclusive)
  - Evaluated morphological correlates of reversible myocardial function (biopsies performed of anterior wall)
  - By-segment analysis = by-patient analysis
  - Compared diagnostic performance of different modalities (PET F-18 FDG vs Tc-99m MIBI)

Maes et al.
Assessment of Study

- Limitations (not all inclusive)
  - Small sample size
  - Number of readers for PET and SPECT scans not specified
  - Not specified if PET and SPECT scans read blindly
  - Results may not apply to other regions of the left ventricle

Marwick et al.
Description of Study

- Objective: To assess the metabolic response of hibernating tissue to revascularization, as assessed by PET imaging with F-18 FDG and Rb-82
- Patients: Previous MI
- Perfusion: 40-60 mCi Rb-82 at rest and stress
- F-18 FDG PET: 4-10 mCi, at rest and postexercise, two blinded readers, 13 segments, viable if F-18 FDG activity > 2 SD above reference normal segment

Marwick et al.
Description of Study

- Revascularization: CABG or angioplasty
- Wall motion: 2-D echocardiography, two blinded readers, six-point ordinal scale

Marwick et al.
Results of Study

- Patients: 16 included in analysis
- Segments: 208 possible, 85 with fixed perfusion defect and resting wall-motion abnormality, 35 had improved function
- Diagnostic performance: calculated by segment

Marwick et al.
Results of Study

- By segment
  - Prevalence: 41%
  - Sensitivity: 71% (54, 85)
  - Specificity: 76% (62, 87)
  - PPV: 68% (50, 80)
  - NPV: 79% (65, 89)

Marwick et al.
Assessment of Study

- Strengths (not all inclusive)
  - Blinded evaluation of 2-D echocardiograms, PET F-18 FDG scans, and PET Rb-82 scans
  - Images were analyzed by two blinded readers
  - Evaluated stress hypoperfusion and post-exercise F-18 FDG uptake
  - Used PET to evaluate perfusion and F-18 FDG uptake after perfusion

Marwick et al.
Assessment of Study

- Limitations (not all inclusive)
  - Small sample size
  - Did not specify to what information blinded readers were blinded.
  - By-patient analysis was not performed.
  - Changes in global ventricular function not assessed
  - Changes in angina not correlated with PET predictions

Tamaki N, Yonekura Y, et al.
Description of Study

- Objective: To determine the predictive value of PET for identifying improvement in hypoperfusion and wall motion abnormality after CABG
- Patients: Consecutive, CAD, fasting
- Perfusion: 10-20 mCi N-13 ammonia PET
- F-18 FDG PET: 2-7 mCi, 5 segments, three readers, viability assessed by visual evaluation of match/mismatch pattern

Tamaki N, Yonekura Y, et al.
Description of Study

- Revascularization: CABG, success assessed by evaluation of post-operative improvements in perfusion with N-13 ammonia
- Wall motion: Radionuclide ventriculography, images evaluated by three blinded readers,

Tamaki N, Yonekura Y, et al. Results of Study

- Patients: 22 included
- Segments: 110 possible, 46 asynergic, 23 function improved
- Diagnostic performance: calculated by segment

Tamaki N, Yonekura Y, et al. Results of Study

- By segment
  - Prevalence: 50% segments, 91% patients
  - Sensitivity: 78% (56, 92)
  - Specificity: 78% (56, 92)
  - PPV: 78% (56, 92)
  - NPV: 78% (56, 92)

Tamaki N, Yonekura Y, et al. Assessment of Study

- Strengths (not all inclusive)
  - Wall-motion analysis performed by multiple, blinded readers
  - Success of revascularization assessed quantitatively with N-13 ammonia PET
  - Alignment of segments before and after revascularization, and as obtained by different modalities was discussed.

Tamaki N, Yonekura Y, et al. Assessment of Study

- Limitations (not all inclusive)
  - Small sample size
  - Little information provided about study subjects
  - Not specified if visual PET analyses were blinded

Tamaki N, Kawamoto M, et al. Description of Study

- Objective: To compare the value of resting perfusion studies with PET, exercise perfusion studies with PET, and metabolic studies with PET for predicting improvement in wall motion after revascularization
- Patients: Consecutive, chronic MI, fasting
- Perfusion: 11-16 mCi N-13 ammonia PET at rest and stress

Tamaki N, Kawamoto M, et al. Description of Study

- F-18 FDG PET: 2-8 mCi F-18 FDG, quantitative image evaluation, 5 segments, viability predicted by match/mismatch pattern
- Revascularization: CABG, success evaluated by angiography
- Wall motion: contrast or radionuclide angiography, three blinded readers, five-point ordinal scale

Tamaki N, Kawamoto M, et al. Results of Study

- Patients: 43 with successful revascularization included
- Segments: 215 possible, 130 asynergic, 51 functional improvement
- Diagnostic performance: calculated by segment

Tamaki N, Kawamoto M, et al. Results of Study

- By segment
  - Prevalence: 39%
  - Sensitivity: 88% (76, 96)
  - Specificity: 82% (72, 90)
  - PPV: 76% (63, 86)
  - NPV: 92% (82, 97)

Tamaki N, Kawamoto M, et al. Assessment of Study

- Strengths (not all inclusive)
  - Second largest sample size among ten principal studies
  - Wall-motion analyses were performed blindly by multiple readers
  - Compared diagnostic performance of different agents
  - Rigorous assessment of the success of coronary revascularization

Tamaki N, Kawamoto M, et al. Assessment of Study

- Limitations (not all inclusive)
  - Information to which readers were blinded was not specified
  - Number of readers of PET images not specified
  - Not specified if PET images read blindly
  - By-patient analyses were not performed
  - Changes in global ventricular function and clinical outcomes were not assessed

Tillisch et al. Description of Study

- Objective: To determine if F-18 FDG uptake in segments with abnormal motion indicates viability, and if uptake predicts functional recovery
- Patients: Consecutive, resting regional wall-motion abnormalities, undergoing CABG, glucose load
- Perfusion: 15-20 mCi N-13 ammonia

Tillisch et al. Description of Study

- F-18 FDG PET: 10 mCi, 12 sectors, quantitative image analysis, viability assessed by match/mismatch pattern
- Revascularization: CABG, success evaluated by review of operative report and preoperative coronary angiogram
- Wall-motion: radionuclide or contrast ventriculography, three blinded readers, seven segments, five-point ordinal scale

Tillisch et al.
Results of Study

- Patients: 17 included
- Segments: 119 possible, 67 asynergic with successful revascularization
- Diagnostic performance: calculated by segment

Tillisch et al.
Results of Study

- By segment
  - Prevalence: 55%
  - Sensitivity: 95% (82, 99)
  - Specificity: 80% (61, 92)
  - PPV: 85% (70, 94)
  - NPV: 92% (75, 99)

Tillisch et al.
Assessment of Study

- Strengths (not all inclusive)
  - Wall-motion assessments performed by blinded readers
  - Wall-motion assessments performed by multiple readers
  - Consecutive patients enrolled
  - Success of revascularization assessed
  - Alignment of myocardial segments described

Tillisch et al.
Assessment of Study

- Limitations (not all inclusive)
  - Small sample size
  - Number of readers of PET images not specified
  - Did not specify whether PET readers were blinded
  - Few patient characteristics described
  - By-patient analysis not included
  - Changes in global LV function not correlated with PET findings

Secondary Published Literature

- Provide supportive evidence of clinical usefulness of PET imaging with F-18 FDG
- Provide support that cardiac PET imaging with F-18 FDG influences clinical decision making appropriately

Secondary Published Literature

- Provide support that regional LV functional recovery is associated with global LV functional recovery
- Provide support that regional LV functional recovery is associated with improvements in symptoms, increases in exercise tolerance, or prolongation of survival

Safety of Cardiac F-18 FDG PET

- Approved in 1994 for identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures (doses 5-10 mCi)
- No additional safety concerns raised by safety studies performed by Edward Silberstein and Janet Ryan, and by Edward Silberstein and the Pharmacopeia Committee of SNC

Safety of Cardiac F-18 FDG PET

- None of the reviewed articles included any information about safety of F-18 FDG PET in cardiac patients (doses <10 mCi)
- Ingestion of glucose load, or fasting, may raise safety concerns in patients with impaired glucose homeostasis.

F-18 FDG Cardiac PET Preliminary Conclusions

The literature supports the use of PET F-18 FDG in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, to identify left ventricular myocardium with altered glucose metabolism and reversible loss of contractility.

F-18 FDG Cardiac PET Preliminary Conclusions

However, the reversal of contractile dysfunction assumes success of subsequent coronary revascularization, which may limit the usefulness of F-18 FDG PET imaging.

The likelihood of successful revascularization should be considered carefully by the health care provider before imaging with F-18 FDG is performed.

F-18 FDG Cardiac PET Preliminary Conclusions

The use of F-18 FDG PET for cardiac evaluation generally appears to be safe.

However, patients with impaired glucose homeostasis may require special precautions if they undergo fasting and/or glucose loading prior to drug administration.

O-15 WATER PET in CEREBRAL PERFUSION:

SAFETY and EFFICACY REVIEW

Patricia Y. Love, M.D., M.B.A.

June 29, 1999

1

O-15 WATER TEAM

- Maboob Sobhan, Ph.D. - Statistics
- Nakissa Sadrieh, Ph.D. - Pharm/Tox
- Alfredo Sancho, Ph.D. - Biopharm
- Patricia Love, M.D. - Medical

2

PRESENTATION FORMAT

- Focus: O- 15 water by injection

3

USE of LITERATURE

- Guidances for Industry
  - Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic Products
  - Developing Medical Imaging Drugs and Biologics (DRAFT)

4

PROVIDING EVIDENCE OF CLINICAL EFFECTIVENESS

- Multiple studies, different investigators
- Prospective statistical plan, full accounting of patients
- High level of detail in report, analytic plan
- Clear and appropriate endpoints
- Robust, consistent conclusion on basis of primary analysis

5

POTENTIAL KEY STUDIES

- Blinded image interpretation
- Adequate standard of truth
- Appropriate control groups/imaging modalities
- Sample size ≥50 patients; or ≥40 special population patients w clinical outcomes

6

INDICATION OPTIONS

- FUNCTIONAL ASSESSMENT
- DISEASE /PATHOLOGY DETECTION OR ASSESSMENT
- DIAGNOSTIC OR THERAPEUTIC PATIENT MANAGEMENT

7

INDICATION OPTIONS

- FUNCTIONAL -
  - Function, physiology, or biochemical assessment of tissue, organ or system
  - Determine if measured parameter is normal/abnormal
  - CBF listed as example in draft guidance
  - CBF assessment is an accepted indication for approved radiopharmaceuticals

8

INDICATION OPTIONS (Cont'd)

- Disease or Pathology Detection or Assessment
  - Specifically documented

9

INDICATION OPTIONS (Cont'd)

- DIAGNOSTIC / THERAPEUTIC MANAGEMENT
  - Explicit statement of the value of the imaging information
  - Explicit study to test the hypothesis

10

O15-WATER LITERATURE SOURCES

- USP
- ICP
  - Criteria: Medline, English, 1983 to 1999

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AVAILABLE LITERATURE

• Did not use O15-water	7
Non clinical studies	7
Duplicates/abstracts	3
Cardiac	1
Case reports/summaries	23
Cerebral (<39 patients)	36
Pediatric (15, 49 patients)	2
Cerebral (50, 87, 117 patients)	3
TOTAL	82

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CEREBRAL PERFUSION MODELS

- ISCHEMIC MODEL
  - Stroke, Aneurysm, AVM, Epilepsy, Meningiomas
- MAPPING MODELS
  - Sickle cell anemia, Epilepsy, Presurgical localization
  - Most used O-15 water w other PET drugs or imaging modalities. Focus on O-15 water only.

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O- 15 Water Preliminary Assessment

- Effectiveness
  - To measure cerebral perfusion in patients with cerebral vascular abnormalities associated with ischemia, hemodynamic abnormalities, occlusion and other vascular disorders
  - IV doses from 10 to 15 mCi (average)
  - Bolus and equilibrium methods

14

CRITICAL STUDIES

- Grubb, R., et. al., Importance of Hemodynamic Factors in the Prognosis of Symptomatic Carotid Occlusion, JAMA, 1998; 280 (12), 1055-60. *{Ischemic}*
- Powars, D., et., al., Cerebral Vasculopathy in Sickle Cell Anemia: Diagnostic Contributions of Positron Emission Tomography, Blood, 1999; 93(1), 71-79. *{Ischemic, Mapping, Pediatric Study}*

15

ISCHEMIC MODELS

- 55 Articles
- GRUBB, R., et. al., 1998
  - Derdeyn, C., et. al., 1998
  - Kuwabara, Y., et. al., 1997
  - Powers, W., et. al., 1989
  - Marchal, G., et. al., 1993

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GRUBB, et. al.

- Prospective design, multicenter
- Blinded image interpretation
- Sample size > 50 [87 patients + small control group]
- Clear protocol, identified amendments, full accounting of all patients
- Clear endpoints
- Clear statistical plan

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GRUBB, et. al. (Cont'd)

- O-15 Water use in OEF in patients with
- TIA and occlusion of carotid(s) on IC angio
- CT to define infarct zone: Controls - MRI brain, US carotids
- All criteria met within 120 days
- 6 month follow-up
- Protocol modified to allow MRA & US to detect occlusion
- Eliminate the 120 day requirement

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GRUBB, et. al. (Cont'd)

- Blinded Hemodynamics of MCA
  - Stage 0 = Normal CBF, Normal OEF
  - Stage I = ↑ CBF volume, Normal OEF
  - Stage II = ↑ CBF volume, ↑ OEF ratio

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GRUBB, et. al. (Cont'd)

- Endpoints
  - Subsequent ischemic stroke any territory (symptoms > 24 hours)
  - Ispilateral stoke and death

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GRUBB, et. al. (Cont'd)

- DEMOGRAPHICS
  - 419 → 105 enrolled (87 patients, 18 controls) → 99 completed (81 patients, 18 controls)
  - Patients 58 M, 23 F, 65 yr mean age
  - Controls 10 M, 8 F, 45 yr mean age
  - IC Angio - 75 (93%); MRA - 4 (5%); US 2 (2%)
  - Per protocol 120 days = 60 (74)%; > 120 d < 1yr = 12 (15%); > 1 yr = 9 (11%)

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GRUBB, et. al. (Cont'd)

- RESULTS
  - Stage 0/I - 42/81 (52%) → Stroke 3/42 (7%)
  - Stage II - 39/81 (48%) → Stroke 12/39 (31%)
  - 120 day entry: p = 0.008 (all); p = 0.02 (ipsi)
  - Any entry: p = 0.005 (all); p = 0.004 (ipsi)
  - Age adjusted independent risk: Ipsi - 7.3 [1.6 -33.4]; All 6 [1.7 - 21.6]

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GRUBB, et. al. (Cont'd)

- Assessment
  - Key study: prospective, blinded, statistical plan, amendments, accounting of patients, method adequate to quantify relative risk
  - Weakness: Normal range data - would be stronger with ↑ sample, or other data; absence of gender, racial or ethnic demographic analysis
  - Proposes clinical use of CBF measurements

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Ischemic Model Supportive Studies

- Derdeyn, C., et. al., 1998
- Kuwabara, Y., et. al., 1997
- Powers, W., et. al., 1989
- Marchal, G., et. al., 1993

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Ischemic Model Support

- Derdeyn, C., et. al., Increased Oxygen Extraction Fraction is Associated with Prior Ischemic Events in Patients with Carotid Occlusion, Stroke, 1998; 29, 754-758.

25

Ischemic Model Support

- Derdeyn, et. al. 1998
  - Same investigators & protocol as Grubb; analyzed baseline factors
  - Research study recommendation: consider that asymptomatic patients are less apt to have ↑ OEF
  - Strength: Prospective, blinded, endpoints clear, N = 117 patients, IC angiography, consistency of conclusions, use of CBF
  - Weakness: Lack of independence, same controls, less detail, clinical utility not confirmed

26

Ischemic Model Support

- Kuwabara, Y., et. al., Response to Hypercapnia in Moyamoya Disease: Cerebrovascular Response to Hypercapnia in Pediatric and Adult Patients with Moyamoya Disease, Stroke, 1997; 28, 701-707.
  - (Special population)

27

Kuwabara, et. al. (Cont'd)

- 20 (13 adult, 7 pediatric) patient subset of a larger study, Moyamoya, TIA symptoms
- Measured OEF steady state, descriptive
- Strength: prospective, homogeneous uncommon disorder
- Weakness: Blinded? selection bias? statistical hypothesis? small sample size

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Ischemic Model Support

- Powers W., et. al., Influence of Cerebral Hemodynamics on Stroke Risk: One Year Follow-up of 30 Medically Treated Patients, Ann Neurology 1989; 25, 325-330.

29

Powers, W., et. al., 1989

- Prospectively designed, retrospective analysis
- 47 subjects (30 stroke patients, 17 abnormal controls for ROI)
- Either >75% carotid occlusion, TIA or completed stroke
- 1 year of follow-up data in medical record
- Had repeat PET images? Blinded?

30

Powers, W. (Cont'd)

- Null hypothesis = If hemodynamic abnormality, 1 yr. stroke rate ≥ than in EC/IC Bypass trial
- Result: 21 pts, vs 417 historic control; rate 0.048 vs 0.127; p ≥0.2
- Strength: prospective statistical plan
- Weakness: retrospective analysis - ? Selection bias, EC/IC historic control not described, actual results not fully presented
- Conceptual use of CBF measurement

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Ischemic Model Support

- Marchal, G., et. al. PET Imaging of Cerebral Perfusion and Oxygen Consumption in Acute Ischaemic Stroke: Relation to Outcome, Lancet 1993; 341, 925-27.
  - Prospective OEF in 18 Pts MCA < 18 hrs.
  - Correlated image patterns and course
  - Pattern I - ↓↓ Perfusion & OEF
  - Pattern II - ↓Perfusion & OEF / ↓ OEF
  - Pattern III - ↑ Perfusion ± ↓ OEF

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Marchal (Cont'd) - Support

- Results:
  - Pattern I - poor course
  - Pattern II - mixed (1 death, 2 interm, 2 good)
  - Pattern III - good recovery
  - $p < 0.005$
- Strength: prospective
- Weakness: image bias?, sample size, statistical plan

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ISCHEMIC ASSESSMENT

- 1 Key Study - GRUBB
- 4 Supportive
  - 1 efficacy - Derdeyn
  - 3 concept - Kuwabara, Powers, Marchal

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MAPPING MODELS

- Total of 15 articles identified
  - 1 in ischemic model (SS), 1 in seizures
  - 13 Localization of normal sites
    - 3: Duplicate/summaries
    - 1: Abstract of 10 patients
    - 3: Reported 10 - 15 patients
    - 6: Reported < 8 patients

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MAPPING MODELS

- POWARS, D., et. al. , 1999
  - Breier, J., et. al., 1997
  - Viñas, F., et. al., 1997
  - Duncan, C., et. al., 1997

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MAPPING MODELS

- Powars, D., Cerebral Vasculopathy in Sickle Cell Anemia: Diagnostic Contributions of Positron Emission Tomography, Blood, 1999; 93(1), 71-79.
- Ischemic, Mapping, Pediatric Study

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POWARS, D. , 1999

- Prospective; 49 Sickle Cell Pediatric Stoke
- Evaluated added benefit of O-15 Water, F-18 FDG and MRI on Detection of Cerebral Vasculopathy
- Standard of truth? - MRI ± Intelligence Testing
- O15- water max dose: 70 mCi
  - (?equilibrium or repeated small doses)
- Statistics: x^2 & multiple comparisons analysis of variance with Bonferoni adjustment

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POWARS, D., et. al. (Cont'd)

- Neurologic defect groups
  - Category I - Overt CVA
  - Category II - Soft signs / previous hypoxic illness
  - Category III - No signs, no hypoxic event

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POWARS, D., et. al., (Cont'd)

- Demographics:
  - 49 patients (29 M, 23 F)
  - Age of neurologic defect onset
    1.8 to 16.3 years

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POWARS, D., et. al., (Cont'd)

- Strengths: Prospective, blinded, pediatrics, statistics described
- Weakness:
  - ? Standard of truth, incomplete correlation to IQ scores
  - How to use strongly suggested; not confirmed
- Key for CBF measurements in patients ± other modalities

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Mapping Concept Support

- Breier, J., et. al., Effects of Duration of Epilepsy on the Uncoupling of Metabolism and Blood Flow in Complex Partial Seizures, Neurology, 1997; 48, 1047-1053.

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Breier, et. al., 1997

- Prospective, N = 50 (34 consecutive complex partial seizure patients, 16 controls)
- EEG (24 hr), MRI, SPECT, Neuropsychiatric tests (FSIQ)
- O-15 water and F-18 FDG
- Endpoints ?, Statistics ±
- Observational asymmetry index = [(R-L)/R+L)*2] vs. Time seizure onset

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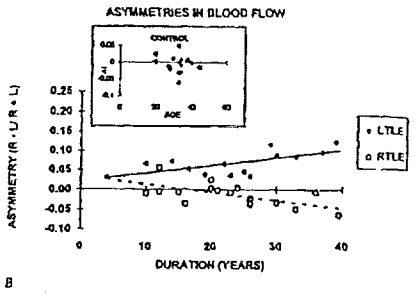
Breier, et. al. (Cont'd)

- Results:
- Correlation of duration and asymmetry; $p < 0.0001$
- F-18 FDG correlation slightly better than O15- water
- IQ results not presented

45



Cerebral Perfusion with O15-water
Breier 1997; 48, 1047-1053

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Breier, et. al. (Cont'd)

- **Strengths: Prospective, N=50, several modality comparison, description of test factor**
- **Weakness: Lacks clear endpoints, statistical hypothesis, IQ not presented, clinical setting not confirmed**
- **Supportive of CBF measurements**

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Mapping Concept Support

- Viñas, F., et. al, [^{15}O-Water PET and Intraoperative Brain Mapping: A Comparison in the Localization of Eloquent Cortex, Neurologic Research, 1997; 19, 601-607
  - 18 patients, no controls
  - Pre- & intra- operative brain surgery electrical brain mapping
  - O-15 water PET - 5 task sets, each imaged x 2, 10 minutes delay
  - Tasks = resting, finger-thumb, listening, listening and repeat, visual R/L half field

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Viñas, et. al. - (Cont'd)

- Results: 18 patients (6 M, 12 F); mean age 36.3 yr (8-74 yr)
- 15 language, 5 motor localization
- Motor co-registration - PET and MRI concordant in gray matter, not white
- Language - all concordant
- Examples - 2 patients recovered fully

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Viñas, et. al. (Cont'd)

- Strength: used clinical outcome
- Weakness: small study, statistical plan? selection bias? image bias? expected difference in clinical outcomes? few outcomes described, reproducibility?
- Supportive of concept that CBF measurements correlate with brain function

50

Mapping Concept Support

- Duncan, et. al., Use of Positron Emission Tomography for Presurgical Localization of Eloquent Brain Areas in Children with Seizures, Pediatric Neurosurgery, 1997, 26, 144-156
  - Prospectively (?) designed retrospective series: 16 pediatric seizure patients
  - Hypothesis - PET optimizes presurgical evaluation
  - ?Statistical plan to assess the hypothesis; ?Blinded
  - O15 water 25 - 50 mCi; Co-registered w MRI
  - Task imaging - language, visual

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Duncan, et. al. - (Cont'd)

- Results:
  - 15/16 O15 water PET images coregistered with MRI
  - Outcomes - changed surgical plan (12), or changed Tx plan (3)
- Strength: Pediatric population, clinical outcomes
- Weakness: Image/selection bias, statistical plan? expected outcomes, reproducibility? variability?

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PRELIMINARY ASSESSMENT

- Ischemic model demonstrates O-15 Water measurements of abnormal perfusion can occur and identifies clinical utility
  - Grubb + supportive
- Sickle Cell anemia study (both an ischemic model and functional model) further supports use of these measurements to identify other types of abnormally functioning areas
  - Powars , D.

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PRELIMINARY ASSESSMENT (Cont'd)

- Use in normal brain function
  - Intuitively appealing; neuroanatomy of brain known; but –
  - All articles are small (all < 15 patients; not systematically studied)
  - Mostly research studies of developing techniques or treatments
  - Reproducibility / variability of normal measurements not included in articles

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SAFETY

- AE not in articles / recent publication on safety of radiopharmaceuticals
- O-15 water does not have ligand
- Behaves as stable water, < 1% TBW
- Not expected to have tonicity effect, or nitrogen balance effect
- Excipients / impurities = mfr issue
- Radioactive dose; ↓ 15 minutes (≅7 $T_{1/2}$)
- Radiation dosimetry - Peds+, Adult ±

55

O-15 WATER PRELIMENARY EFFECTIVNENESS

- To measure cerebral blood perfusion in patients with cerebral vascular abnormalities associated with ischemia, hemodynamic abnormalities, occlusion, and other vascular disorders.

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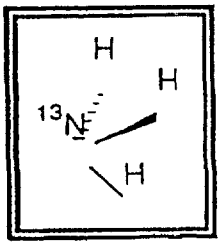
Pharmacology/Toxicology & Pharmacokinetics of N 13 Ammonia

David G. Udo, Ph.D.
Adebayo A. Laniyonu, Ph.D.

MIDAC June 28 - 29, 1999

Structure

- Measurement of myocardial blood flow with PET in patients with known or suspected coronary artery disease

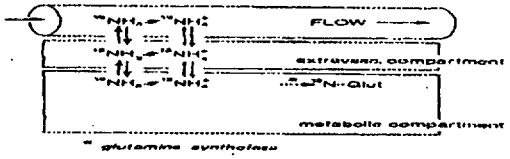


Aspects of N 13 Ammonia

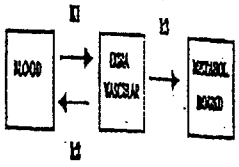
- The concept of blood flow measurement
- Pharmacokinetics
- Metabolism
- Safety, pharmacokinetics and metabolism
- Summary

Blood Flow Measurement

From Schelbert et al. (1981) Circulation 63, (6), 1268



Three Compartmental Kinetics of N 13 Ammonia



- K1 = E*F
- E > 0.9 even at high flow rates
- K1 ≈ F
- E = Extraction fraction
- F = blood flow rate

Determination of K1

$$\frac{dC_E(t)}{dt} = K_1C_a(t) - k_2C_E(t) - k_3C_E(t) - \lambda C_E(t)$$

C_E: Conc. of N-13 ammonia in myocardial tissue

C_a: Conc. of N-13 ammonia in the arterial blood

K_1: Rate of N-13 ammonia uptake from blood into myocardial extravascular space

k_2: Rate of passage of N-13 ammonia back to coronary capillary

k_3: Rate of N-13 label trapping in the myocardial cell in the form of N-13 glutamine.

λ: N-13 ammonia decay rate constant

t: Time

Pharmacokinetics

- Recommended i.v dose of RA: 10-20mCi
- Mass Dose: 0.05-0.1 μmole (0.80-1.60 μg)
- $T_{1/2}$ of Physical decay: 9.96 min
- $T_{1/2}$ in blood: 3 min
- $T_{1/2}$ in myocardium: 2 min
- $T_{1/2}$ in brain: 3 sec

Metabolism

- N 13 Urea (major metabolite)
- Neutral amino acids
- Traces of acidic amino acids (glutamate and aspartate)

Pharmacokinetics and Safety

- Mass Dose 0.8-1.6 μg
- Normal range of ammonia 12-55 μg/dL
- Ammonia in a 70 kg person 720-3300 μg

No significant change in the amount of ammonia

Metabolism and Safety

- Urea is readily eliminated in urine
- Amino acids are normal component of body tissues

There appears to be no adverse health effects from metabolic products

Absorbed Radiation Dose (rem/mCi) - derived from ICRP[1] data

Organ	Adult	5 year old	1 year old
[2]Bladder wall	0.030	0.089	0.17
Heart	0.0078	0.023	0.041
Kidneys	0.017	0.048	0.089
Red Marrow	0.0063	0.020	0.037
Ovaries	0.0063	0.021	0.041
Testes	0.0067	0.018	0.035

[1]International Committee for Radiation Protection
[2]Urinary bladder

Summary

- Due to high extraction of N 13 Ammonia from coronary capillaries into myocardial extravascular space, the value of K1 obtained via 3-compartmental equation can yield a reasonable estimate of myocardial blood flow.
- N 13 Ammonia is efficiently eliminated from the body.

Summary

- Dosimetry table has been developed allowing physicians to determine, for patients of various age groups, N 13 Ammonia doses resulting in acceptable organ absorbed radiation doses.
- Pharmacology, toxicology and pharmacokinetics of N 13 Ammonia support its use for myocardial indications.

N-13 Ammonia PET: Safety and Effectiveness Review

Florence Houn MD MPH
Sonia Castillo PhD

June, 1999

N-13 Ammonia Team

- Sonia Castillo- Stat
- Kaye Cho- PM
- Flo Houn- Medical
- David Hussong- Micro
- Ravi Kasliwal- Chem
- Adebayo Laniyonu- Pharm/Tox
- David Udo- Biopharm

N-13 Ammonia S&E Review Preliminary Conclusions

- Effectiveness
  - To assess myocardial perfusion in the evaluation of CAD in patients with known or suspected CAD (stress and rest administration)
- Safety
  - Single doses up to 25 mCi studied
  - 2 IV doses up to 20 mCi each studied

N-13 Ammonia S&E Review

- Guidances on Clinical Effectiveness/Medical Imaging
- Intended Use of N-13 Ammonia
- External Standards
- Search Methodology
- Selection Criteria
- Review of Findings
- Conclusions

N-13 Ammonia S&E Review

Guidance on Clinical Effectiveness-Use of Published Literature Alone

- Multiple studies/adequate design/consistent findings
- Detailed protocol
- Objective and appropriate endpoints
- Consistent conclusions of efficacy
- Conduct of studies with documented operating procedures
- Examples: secretin, bleomycin and talc, doxycycline

N-13 Ammonia S&E Review

Adequate/Well-Controlled (Med. Imaging Guidance)

- Selection of subjects=Target population
- Readers: independent, masked, randomized, separate
- Standards of truth
- Endpoints
- Analysis plans
- Safety: toxicity and radiation assessment

N-13 Ammonia S&E Review

Intended Use: To assess Myocardial Perfusion (MP)

- Preliminary review for major uses
- "Developing Medical Imaging Drugs and Biologics" draft guidance
  - "Functional, Physiological, or Biochemical Assessment"
    - Validated to a standard of truth
    - Spectrum of disease and normality tested
    - Pharmacological basis of "functional claim"

N-13 Ammonia PET External Standards for MP

- Vessel Anatomy, CAD, and blood flow
  - Coronary Angiography
  - Rubidium-82
- Coronary microperfusion
  - Functional Aspects
    - Wall Motion
    - Functional Capactity (stress testing)
    - Clinical outcomes (survival)

N-13 Ammonia PET Literature Search Methodology

- Criteria for Search
  - January 1, 1990 to July 1, 1998
  - Human clinical trials
  - English
  - On-line databases: Medline, Cancerlit, Derwent Drug File, Biosis Preview, International Pharmacology Abstracts, and Embase
  - PET community suggested articles
  - References cited in above articles

N-13 Ammonia PET Literature Search Methodology

- Selection Criteria
  - N-13 ammonia PET results compared to appropriate clinical standard of truth
  - Relevant study question to MBP
  - Well-described study population
  - Procedures to reduce bias

N-13 Ammonia S&E Review Published Literature

- Adequate/Well-Controlled Clinical Trials (2)
  - Prospective enrollment - study hypothesis related to intended use
  - Study population similar to target population for clinical use
- Other Controlled Published Studies (3)
  - Various study hypotheses
  - Retrospectively selected patients; normal volunteers assumed CAD-free
- Other Published Studies (9)
  - Wide variety of study hypotheses
- MBF Quantification Algorithm (3)

N-13 Ammonia S&E Review Adequate/Well-Controlled Studies

- Gould LK, Goldstein RA, Mullani NA, et al. J Am Coll Cardiol 1986;7:775-89.
- Demer LL, Gould LK, Goldstein RA, et al. Circulation 1989;79:825-35.

N-13 Ammonia S&E Review
Other Controlled Studies

- Schelbert HR, Wisenberg G, Phelps M et al Am J Cardiol 1982;49:1197-1207.
- Di Carli M, Sherman T, Khanna S et al. J Am Coll Cardiol 1994;23:860-68.
- Gewirtz H, Fischman AJ, Abraham S et al. J Am Coll Cardiol 1994;23:851-59.

N-13 Ammonia S&E Review
Other Supportive Studies

- Beansland RSB, Muzik O, Melon P, et al. J Am Coll Cardio 1995;26:1465-75.
- Czernin J, Barnard RJ, Sun KT, et al. Circulation 1995;92:197-204.
- Di Carli MF, Davidson M, Little R, et al. Am J Cardiol 1994;73:527-33.
- Gould LK, Martucci JP, Goldberg DI, et al. Circulation 1994;89:1530-38.
- Gould LK, Ornish D, Scherwitz L, et al. JAMA 1995;274:894-901.

N-13 Ammonia S&E Review
Other Supportive Studies

- Haas F, Haehnel CJ, Picker W, et al. J Am Coll Cardiol 1997;30:1693-1700.
- Laubenbacher C, Rothley J, Sitomer J, et al. J Nucl Med 1993;34:968-978.
- Sambucetti G, Parodi O, Giorgetti A, et al. J Am Coll Cardiol 1995;26:615-23.
- Soufer R, Dey HM, Lawson AJ, et al. J Nucl Med 1995;36:180-87.

N-13 Ammonia S&E Review
MP Quantification Algorithm

- Krivokapick J, Smith GT, Huang SC, et al. Circulation 1989;80:1328-37.
- Hutchins GD, Schwaiger M, Rosenspire KC, et al. J Am Col Cardiol 1990;15:1032-42.
- Gerwitz H, Skopicki HA, Abraham SA, et al. Cardiology 1997:88:62-70.

N-13 Ammonia S&E Review
Adequate /Well-Controlled: Gould (1986)/Demer (1989)

- Objective: Feasibility study for diagnosing CAD with Rb/NH3 using rest/stress testing (DP)
- Sample size: 23/50 patients received NH3
- Design: Prospective; compared angio and PET
- Image Protocol: Masked, Reread x 3
- Dose: 2 IV 10-20 mCi N-13 ammonia or 30-50 mCi Rubidium
- Significant CFR defined <3.0 on angio; % isocount reduction assumed proportional to % decrease CFR
- Sensitivity 21/22 (95%) Specificity 9/9 (100%)

N-13 Ammonia S&E Review
Adequate/Well-Controlled: Demer (1989)

- Objective: Accuracy of N-13 NH3 in evaluating CAD using rest/stress testing compared to coronary angiography
- Sample Size: 111/193 pts received N-13 NH3 (n=174 analyzed)
- Indusion Criteria: All patients undergoing cath (population suspect for disease but some do not have it).
- Design: Compare stenosis flow reserve (SFR-automated) vs. PET defect scores

N-13 Ammonia S&E Review:
Adequate/Well-Controlled: Demer (1989)

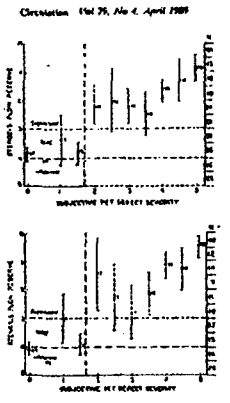
- Scales: SFR 0-5 (5=nl;<3=signif. CAD) PET defect scores 0-5 (5=severe perfusion defect;>2 signif. CAD, SFR<3)
- Image Protocol: masked, independent, reread x 2, rest/stress read side by side
- Scores for PET averaged, interobs. variation defined and tracked, dispute resolution described
- Dose: 2 IV 10-20 mCi NH3 / 30-50 mCi Rb

N-13 Ammonia Review: Demer (1989) Con't.

- Results
  - Spearman Correlation Coefficient 0.77 (±0.06) for patients' scores of most severe PET/SFR scores
  - Rb/NH3: For N=193, 2 false positives (1 Rb/1NH3); 7 false neg (2 Rb/5 NH3)

N-13 Ammonia S&E Review Demer (1989) Con't.

- Results Continued
  - Figure 3
  - FDA approach to calculating sensitivity and specificity



N-13 Ammonia S&E Review

Demer (1989) 2x2 Table (Patients)

	SFR < 3	SFR ≥ 3	Totals
PET Score ≥ 2	94	12	106
PET Score < 2	2	66	68
Totals	96	78	174

N-13 Ammonia S&E Review

Demer (1989) 2x2 Table (Vessels)

	SFR < 3	SFR ≥ 3	Totals
PET Score ≥ 2	133	28	161
PET Score < 2	2	80	82
Totals	135	108	243

N-13 Ammonia S&E Review
Demer (1989) Sensitivity/Specificity

- Patients
  - Sens=98% (95% CI: 92.1-99.7%)
  - Sp=85% (95% CI: 74.7-91.7%)
- Vessels
  - Sens=99% (95% CI: 94.9-99.9%)
  - Sp=74% (95% CI: 64.5-81.7%)

N-13 Ammonia S&E Review
Demer (1989)

- Strengths
  - Inclusion criteria
  - Images read by 2 readers, independently, masked
  - Interobserver differences in PET tracked/analyzed
  - Graphical data to calculate sens/sp

N-13 Ammonia S&E Review
Demer (1989) Con't.

- Strengths Continued
  - Dispute resolution
  - Detailed information on readers' performances
  - Detailed information on reader variability
  - Large number of patients

N-13 Ammonia S&E Review
Demer (1989) Con't.

- Weaknesses
  - Rubidium/NH3
  - Age/Sex distribution
  - 19 patients excluded from analysis "because they had undergone revascularization during acute infarction causing residual stenosis severity that would not be comparable to the severity of the fixed perfusion defect" vs ITT

N-13 Ammonia S&E Review
Other Controlled Studies

- **Schelbert (1982)**
- Objective: Correlate angio and N-13 ammonia PET.
- Sample Size: N=32 CAD/ N=13 normal volunteers.
- Design: PET compared to angio. 11CAD pts stress-thall.
- Image Protocol: 2 readers (consensus), masked, agreement tracked
- Dose: 2 IV doses of 0.22±0.09 mCi
- Results: **Sens (>50% stenosis) was 97% (31/32 patients). Sp assumed as 100% (13/13).** Thallium identified 11/19 stenosed vessels versus 17 PET+/19 stenoses vessels.

N-13 Ammonia S&E Review
Other Controlled Studies

- **Di Carli (1994)**
- Objective: Relationship of collateral flow, wall motion, and viability (defined by metabolism of 18-FDG).
- Sample Size: N=42 cons. patients (78 vessels) w/ CAD (angio) and LV dysfunction
- Design: Comparison
- Image Protocol: PET semiquant.,2 observers (consensus)
- Dose: 20 mCi
- Results: 58% w/angio collaterals had ↓ N-13 flow; 50% w/no angio collaterals had N-13 flow.

N-13 Ammonia S&E Review
Other Controlled Studies

- **Gerwitz (1994)**
- Objective: Determine minimum level of MP.
- Sample Size: N=26 pts with chronic MI referred for thall and PET.
- Design: Comparison of wall motion and PET FDG/NH3
- Image Protocol: Quantified PET readings; Visual analysis for Ventriculography, echocardiograms
- Dose: 25 mCi NH3/7.5 mCi FDG
- Results: Perfusion correlates with wall motion. Results demonstrate biologic consistency.

N-13 Ammonia Review: Other Published Studies

Study	Obj.	Sample Size	Design	Image Protocol	Dose	Safety/ Efficacy
Beanlands (1995)	To study MBF reserve and angio	N=5 vol. N=7 vol. mid-aged N=15 CAD on angio	Correlation of results	Quantit.	2 IV doses of 20 mCi	R=0.75 (min lumen diameter) R= -0.56 (%area sten)
Czernin (1995)	To study MP response to conditioning	N=13 vol. 4/13 CAD N=8 nr/nc Controls	Intervention; Assess exercise Capacity	Semiquant.	2 IV doses of 10-15 mCi	Improved flow and cardiac endpts.
Di Carli (1994)	To predict survival using PET/angio	N=93 consec. pts. w/severe LVdysfun.	Survival; F/U avg 13.6 mons (2-31mons)	Semiquant. 2 obs. Masked Independ.	20 mCi	Supports microperfu sion use of PET.

N-13 Ammonia Review: Other Published Studies

Study	Obj.	Sample Size	Design	Image Protocol	Dose	Safety/ Efficacy
Gould (1994)	To assess perfusion after chol program	N=15 CAD	Rand. to 3 programs; control-Rx-control sequential trial.	Quanti.	2 IV doses of 18 mCi	PET correl. w/lower chol/better exercise capacity
Gould (1995)	To assess CAD with angio and PET pre/post risk modif.	N=20 active N=15 usual care	Rand. Controlled trial	Quanti. at initial and 5 yrs	18 mCi NH3 or 40-50 mCi Rb	Correlation of PET and angio results
Hesse (1997)	To assess PET's correl. w/ outcomes CABG decisions	N=76 pts w/3VD	Survival study; use of PET data on outcomes	Semi-quant.	740 MBq (20 mCi)	PET results affected CABG selection— survival > angio

N-13 Ammonia Review: Other Published Studies

Study	Objective	Sample Size	Design	Image Protocol	Dose	Safety/ Efficacy
Lauben-bacher (1993)	To evaluate automated analysis for 3-D MBF	N=29 CAD (angio) N=23 controls	Compare angio-PET; ROC	2 readers masked vs. Quanti. Vari. Eval.	2 IV doses of 740 MBq (20 mCi)	Agreement of software and observers
Sambuceti (1995)	To study MP in collaterals	N=19 pts w/CAD N=13 nl	Compare angio and PET	Quanti.	2 IV doses of 0.2 mCi/kg	Angio and PET results give diff collat. info
Soufer (1995)	To study reverse redist. in Thallium	N=32 pts with CAD and RR	Compare PET/wall motion/thal -F/U14mon	Quanti.	15 mCi	Contributes info on PET/wall-motion/ micro-perf

N-13 Ammonia S&E Review Weaknesses of Literature

- Absence of statistical criteria for significance and power
- Small numbers of subjects
- Absence of source data
- Bias (publication bias, subjectivity of readers scoring, patient selection)

N-13 Ammonia PET Review Preliminary Conclusions

- Efficacy
  - Intended Use: To assess myocardial perfusion
  - Consistent findings, diverse populations
  - Sensitivity and specificity calculated
  - Blood flow and microperfusion

N-13 Ammonia S&E Review Conclusions

- Safety (Ammonia/Radiation)
  - Small amount of NH3 introduced
  - Know metabolism and excretion
  - Short physical half-life (10 minutes)
  - Acceptable radiation dosimetry
  - Acceptable risk of radiation

N-13 Ammonia S&E Review Conclusions

- Effectiveness:
  - To assess myocardial perfusion in the evaluation of CAD for patients with known or suspected CAD (stress/rest administration)
- Safety:
  - Single doses of up to 25 mCi studied
  - 2 IV doses up to 20 mCi each studied

Pharmacology/Toxicology and Clinical Pharmacokinetic Review of ^{15}O-Water

- MIDAC, June 28-29, 1999 -

Nakissa Sadrieh Ph.D.
Alfredo R. Sancho, Ph.D.

Outline

- Characteristics of ^{15}O-water
- Dosimetry
- Literature example

Characteristics of ^{15}O-H_2O

- Decay half-life= 122.5 seconds (2.1 minutes).
- Emits 1.74 meV positrons.
- Diluted in 0.9% NaCl prior to injection.

Characteristics of ^{15}O-H_2O

- Naturally occurring body constituent.
- Biologically inert
- No side effects.
- Kinetics not affected by metabolism.
- Diffusible radioactive drug.
- Crosses BBB
- High extraction within tissue (>95% in primates, Huang et al., 1983, JCBBM 3:2, 141-53).

Dosimetry

- Cumulated administered dose of ^{15}O-water is absorbed internally.
- Dosimetry is based on a study in newborn infants (Powers et al., JNM 29:1961-1970, 1988) and an ICRP extrapolation to adults.
- Critical organs are: lungs, spleen, gonads
- Absorbed dose: 32-46 mrem/mCi
- Effective whole-body dose: 80-100 mrem/mCi
- Average individual study dose range: 10-15 mCi

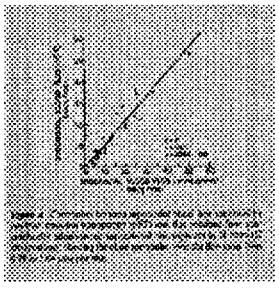
Pharmacology/Toxicology Studies

- Toxicology studies can be waived because:
  - characteristics
  - no ligand
  - radiation exposure
- Caveat
- Pharmacology and mechanism of action
- Additional physiologic mechanisms

Supportive Study (design)

- **Bergmann et al., JACC 4:3, 1989:639-52**
  - Myocardial blood flow was calculated and compared with measurements obtained with 15 μm microspheres in:
    - control dogs at rest
    - dogs with coronary artery occlusion or stenosis at rest or after dypiridamole
    - dogs with global low flow (propranolol).

Supportive Study (results)



- Correlation Coefficient=0.95

Flow models

- Heart model
  - high flow - low volume
- Brain model
  - low flow - high volume

Descriptive Formulas

- Blood Flow

$dC_T(t)/dt = F/V\ (C_a(t) - C_T(t)/\lambda)$

  - *C_T is the tissue tracer concentration (cts /gm)*
  - *F/V is the flow per unit of tissue volume (ml/gm/min)*
  - *C_a is the arterial concentration of tracer (cts/ml)*
  - *λ is the tissue/blood partition coefficient (ml/gm)*

Ref. Bergman S.R. et. al., JACC 14(3):639-652, 1989.

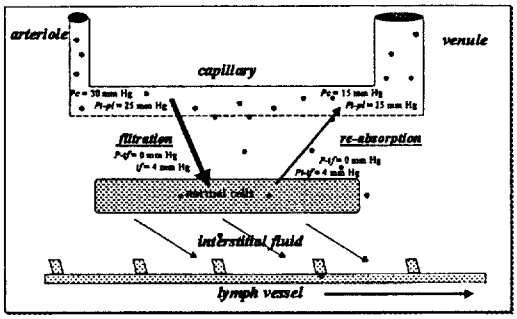
Additional Formulas

- Other formulas:
  - The concept of *high flow-low volume* and *low flow-high volume* criteria as a determining factor for cumulative radioactivity in organs. Ref. Powers W.J. et. al., JNM 29:1961-1970, 1988.
  - Variability in blood flow and blood volume between and within subjects. Ref. Coleman T.G. et. al., AJP 223(6):1371-1375, 1972.
  - Blood flow measurements using 15O-H2O after imaging agent has reached equilibrium. Ref. Bassingthwaighte J.B. et. al., Circ.Res. 77(6):1212-1221, 1995.

Descriptive Concepts

- Blood Flow
  - Amount of blood passing through a vessel within an organ-tissue during a discrete amount of time.
- Perfusion
  - The act of pouring over or through, especially the passage of fluid through the vessels of a specific organ.
- Other concepts:
  - Osmosis, Diffusion, Ultrafiltration, etc.

Local Regional Dynamics



Preliminary Assessment

- There are limited number of well controlled studies.
- Adults dosimetry is limited.
- PT/PK perspective: There is information to support the use of 15O-H2O in measuring cerebral perfusion.