ORIGINAL CONTRIBUTION

Detection of myocardial viability following ischemia/infarction: A comparison of 99mTc-MIBI and 18F-FDG

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This paper reviews current methods for evaluating myocardial viability following a vascular insult. Specifically, this article compares two radiopharmaceuticals, 99mTc-MIBI and 18F-FDG, and the techniques used to obtain images from them. A Medline CD ROM literature search for articles was conducted. The resulting papers were analyzed for both scientific methods and conclusions. It was found that 99mTc-MIBI does not estimate the extent of viable myocardium as well as 18F-FDG, the currently accepted standard for evaluating myocardial viability. However, in two of the three articles, improper statistical methods and procedural irregularities decreased the plausibility of conclusions reached in those papers.

Radiographic assessment is steadily becoming a more powerful tool that allows clinicians to predict outcomes of cardiovascular reperfusion procedures. Currently, there are a number of different radiopharmaceutical agents and a variety of imaging techniques available to the cardiologist. This paper compares two radiopharmaceuticals, the different techniques used to obtain images from them and attempts to answer the question: Is there a significant difference in the detection of myocardial viability following myocardial ischemia/infarction between technetium-99m-methoxy-isobutyl-isonitrile(99mTc-MIBI) on SPECT and fluorine-18-fluorodeoxy glucose (18F-FDG) on PET?

Myocardial viability is defined by the ability of myocardial cells to regain their former contractile strength following an insult (such as a myocardial infarction)(1). In the pathology of coronary artery disease (CAD), myocardium supplied by the diseased arteries may become chronically ischemic, show reduced contractility and/or dyskinesis on wall motion studies. In many cases, these areas of asynergy, termed "hibernating myocardium", show improvement after revascularization as the contractility returns to normal. Functional recovery of chronically dysfunctioning myocardium implies the presence of ischemic but viable myocytes within the area of abnormal wall motion (2).

18F-FDG is a glucose analog that is used to assess physiologic glucose metabolism (and thus indirectly cell viability). Although it is taken into the cell by the same transport carriers used by glucose, 18F-FDG is not metabolized by the cell and thus accumulates there according to glucose demand (2). This highlights the cell's active glucose uptake and its viability. Despite its high costs (see Table 1), it has been accepted throughout the literature that myocardial viability assessment is best accomplished with 18F-FDG PET scanning (3,4,5).

99mTc is a metastable radioactive isotope made from an onsite molybdenum generator and is used as a molecular tag for MIBI, a compound known to have an affinity for healthy myocardial tissue. As a cardiac imaging agent, 99mTc-MIBI has been found to be effective for assessment of transient ischemia, estimating salvaged myocardium following thrombolytic therapy, and for assessment of areas at risk for coronary artery disease (6). Until recently, its role in evaluating myocardial viability had not been fully investigated. As 99mTc-MIBI is a more commonly used radiopharmaceutical than 18F-FDG (and

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Table 1: Summary of radiopharmaceutical characteristics

	18F-FDG	99mTc-MIBI
Emission	electron (ß+ decay)(9)	gamma ray(9)
Half-life	1.16 hrs(9)	6 hrs(9)
Cost / scan	$1000*(10)	$20011
Equipment Costs	$4 million/ scanner, $4 million/ source (cyclotron) (10)	~$300,000/ scanner(11)

*enough for five jobs, provided all of it can be used before the product decays

less expensive), it would be of benefit to elucidate if it is as effective as 18F-FDG in evaluating myocardial viability. Clinically, this is important in the management of patients with CAD. If effective,these scans could be used as a screening test to determine which CAD patients might be good candidates for revascularization.

In the study by Altehoefer et al., patients with coronary artery disease who underwent 99mTc-MIBI scans were evaluated by 18F-FDG to assess the viability of myocardial tissue in perfusion defects detected by the MIBI scan. This study designated that 18F-FDG as a gold standard and used patients with angiographically-proven CAD and resting wall motion abnormalities. Exclusion criteria are given in Table 2.

Analysis of SPECT images was assessed by three independent and experienced clinicians. They differentiated the left ventricle into 9 segments in 46 patients (n=414). Each segment was classified as: 1) normal; 2) only slightly reduced perfusion, or 3) a definite perfusion defect. A perfusion defect was accepted as the diagnosis only if two of the three clinicians agreed. PET images for the same SPECT slices were obtained and a "match" between the two scans was defined as: 1) markedly reduced; 2) very faint, or 3) lacking 18F-FDG uptake in the area of a perfusion defect detected on SPECT. A "complete mismatch" refers to a normal, increased, or only very slightly reduced 18F-FDG uptake in the area of a perfusion defect on SPECT scan (i.e. viability where there was a noted defect) (3). This method of qualitative analysis is only an acceptable method if there is blinding of the observers, that is, observers must not be able to connect two subjects between the diagnostic scans. No mention of blinding was made in their study. The authors of this paper use a very subjective method of classification (agreement of two observers) and do not adhere to any accepted criteria for diagnosis. Further, no kappa statistic was used to show that their results occurred due to a trend within the data set rather than by chance. Finally, there was no numerical value assigned to what was considered as normal on PET scanning, which strongly suggests a great deal of subjectivity in the diagnosis of the 18F-FDG uptake.

Table 2: Summary of studies comparing 99mTc-MIBI and 18F-FDG

Study	Altehoefer et al. (3)	Altehoefer et al.(5)	Sawada et al.(4)
# of patients	46	111	20
Inclusion criteria	angiographically proven CAD and resting wall motion abnormalities	angiographically proven CAD and resting wall motion abnormalities	documented myocardial infarct
Exclusion criteria	diabetics on oral Rx L. bundle branch block unstable angina acute MI	L. bundle branch block unstable angina acute MI	revascularization change in clinical status
Anti-anginal med.	stopped 12h prior	stopped 12h prior	?
Radiopharmaceutical used	259-370 MBq* 99mTc-MIBI 222-296 MBq 18F-FDG	260-370 MBq 99mTc-MIBI 200-300 MBq 18F-FDG	296 MBq 99mTc-MIBI 370 MBq 18F-FDG
# of segments/patient	9	13	9

* MBq= megabecquerel (1million disintegrations per second)

In this study when each of these segments were assessed qualitatively, eight other segments were viewed at the same time. If an observer saw a defect in one region, bias may cause the observer to score the surrounding areas as perfusion deficiencies as well. On this point, it is important to realize that each segment of the scan, contributing to the "statistical analysis" is a part of the entire "clinical" picture, and cannot be looked upon clinically as a distinct point of data.

Of the 414 segments analyzed, 167 were diagnosed as having a resting perfusion defect on SPECT testing. The patients were classified into three groups based on segmental uptake: (I) ≤30% of maximal uptake (severe perfusion defect; n1=41), (II) 31-50% uptake (moderate defects; n2=100), and (III) >50% uptake (mild defects; n3=26). Within Group I, there were no "complete mismatches" and those Group I segments presenting as a "match" had PET scan uptakes that were not statistically different from SPECT scanning (paired t-test; $p>0.05$). However, in Groups II and III, there is a significant difference (paired t-test; $p<0.01$) in the way the two methods "read" the viability of the tissue. Furthermore, the authors make the statement that the lack of 18F-FDG uptake in an area with a perfusion defect seems to be associated with the severity of perfusion reduction ($p<0.0001$) (3). In Groups II and III, there were 38 segments that were "complete mismatches". In all the Groups, 53% had a lack of glucose metabolism, 23% had complete preservation of glucose metabolism, and there was partially preserved metabolism in 24% of the segments. This led to the conclusion that 99mTc-MIBI uptake underestimates the extent of viable myocardium in patients with CAD, and that only moderate reduction of perfusion assessed with 99mTc-MIBI implies a greater likelihood of potential for viability than severe perfusion reduction (3).

In summary, this study concludes that SPECT may not be as effective as PET scanning with respect to detection of viable myocardium. However, because of the lack of a good study design (i.e. observer bias, subjective classification and lack of a Kappa test), the results of this study must by viewed with caution.

In the follow-up study by Altehoefer et al.(5), the relationship between 99mTc-MIBI uptake at rest and 18F-FDG uptake are assessed in patients with a similar set of characteristics as the first study (see Table 2). However, this study does not use a qualitative assessment and uses computers to focus on a more quantitative diagnosis. The use of computers makes this method more objective and thus eliminates the need for blinding.

This article defines normal for 99mTc-MIBI as >70% of maximum uptake within the region of interest (ROI). PET viability is defined as >70% of maximal uptake, while non-viability is defined as uptake <50% maximum uptake in ROI and "intermediate" segments were defined as 50-70% of maximal uptake. The study also expands in size from 46 subjects to 111. Finally, the number of segments used to section the left ventricle is raised from 9 to 13, allowing for better localization of any defect in the myocardium or the vasculature. In this study, segments were categorized according to their relative 99mTc-MIBI uptake and differentiated into PET viable, PET non-viable, or "intermediate" segments. The objective of this paper was to evaluate more precisely the relationship between the severity of a 99mTc-MIBI defect at rest and the frequency of myocardial scar or preserved myocardial viability according to PET criteria.

Of the 1443 segments examined, 713 (49%) displayed 99mTc-MIBI <70% of maximal uptake. In these same segments, the frequency of myocardial viability was loosely associated directly with the 99mTc-MIBI uptake values (regression analysis $r2=0.61$, $n=1443$, $p<0.001$). Chi-square analysis showed significant differences between the two methods.

However, the results of the chi-square test are elusive and it is unknown how they obtained their results. Moreover, the use of a chi-square is inappropriate in this case since both examination procedures were performed on the same individuals (the two trials included data which are not independent of each other). Because the results were gathered on an interval scale, a paired t-test would have been the most appropriate statistical test to use. This apparent discrepancy along with the inappropriate test decrease the validity of this study.

The comparison of 99mTc-MIBI and 18F-FDG uptake values shows that the predictive value of SPECT exams for scar tissue is greater than 80% when the MIBI uptake is ≤30%. However, at greater levels (up to 50% of peak activity) on SPECT/MIBI scans, 5-24% were PET-viable, indicating the myocardial viability is underestimated by 99mTc-MIBI scanning(5). Preserved 18F-FDG uptake was observed in one-third of the patients that were found to have a severely reduced 99mTc-MIBI uptake.

The conclusions are similar to those of the first paper reviewed (3). Because there is a great deal of uncertainty within the "intermediate" range of the data, many of the SPECT scans have a low positive predictive value (30.3%) and underestimate the viability of the myocardium. Altehoefer et al. (5) conclude that SPECT scanning, while highly predictive for scar tissue at low uptake levels, is inaccurate within a moderate (31-70% of peak) range of uptake (5). Because of procedural irregularities, the conclusions made by the authors must be met with skepticism.

Sawada et al. (4) attempted to use quantitative analysis techniques to determine the value of 99mTc-MIBI imaging in the detection of viable myocardium. Of the three papers, this was the only one to use a blinding protocol when the scans were read by a clinician. A 4 point grading system was used to determine the severity of reduction in 99mTc-MIBI uptake in the infarcted territory. Other study design specifications are given

in Table 2.

The results of this paper were similar to the others . Sawada et al. (4) and his group found that the SPECT imaging had limited accuracy for identification of myocardial viability. They concluded that clinical decisions with regards to tissue viability should not rely on assessment with 99mTc-MIBI scans. From this result, we can see that there is a statistically significant difference in the way these two methods evaluate myocardial viability.

Even though all of the articles achieved similar conclusions, the study by Sawada et al. (4), by using the basic principles of study design and appropriate statistics, present more convincing results. They present a comparison of technetium activity and 18F-FDG uptake in the same segments and go on to give positive and negative predictive values that validate their conclusion that 99mTc-MIBI scanning underestimates the viability of infarcted myocardium (PPV=53%, NPV=79%).

A general criticism of all three study designs is that it is difficult to analyze the data from different segments within the same heart and treat them as separate points of data (8). It is conceivable that two sections of myocardium supplied by the same artery would be affected in a similar way if the perfusion was suddenly altered. Thus, when making comparisons of viability within an individual heart one must account for the fact that there is a degree of dependence between the adjacent segments. Therefore, each segment evaluated independently of the others may allow for the introduction of error into the results, giving inaccurate and false conclusions. Because the segments can be plotted on a map that could be related to a blood flow map, interrelations between segments could be attained and more accurate results obtained.

In conclusion, the results from all three studies show that 99mTc-MIBI on SPECT scanning does not predict the extent of myocardial viability as well as 18F-FDG PET scanning does. In practical terms, however, the cost of PET scanning makes its widespread application unlikely.

REFERENCES

1. *Personal communication* with Dr. Lalonde.
2. Uren, N and Camici P. Hibernation and Myocardial Ischemia: Clinical Detection by Positron Emission Tomography. *Cardiovasc Drugs Ther* 1992; 6: 273-79.
3. Altehoefer C, Kaiser H, Dorr R, Feinendegen C, Beilin I, Uebis R, Buell U. 18F-FDG PET for assessment of viable myocardium in perfusion defects in 99mTc-MIBI SPECT. *Eur J Nucl Med* 1992; 19: 334-42.
4. Sawada S, Allman K, Muzik O, Beanlands R, Rolfe W, Gross M, Fig L, Schwaiger M. PET Detects Evidence of Viability in Rest 99mTc-MIBI Defects. *J Am Coll Cardio* 1994; 23: 92-8.
5. Altehoefer C, vom Dahl J, Biedermann M, Uebis R, Beilin I, Sheehan S, Hanrath P, Buell U. Significance of defect severity in 99mTc-MIBI SPECT at rest to assess myocardial viability: Comparison with 18F-FDG. *J Nucl Med* 1994; 35: 569-74.
6. Marzullo P, and Sambuceti G. 99mTc-MIBI: Its role as a Viability Agent. *J Nucl Biol Med* 1992; 36: 259-66.
7. Glantz, S. "Primer of Biostatistics" 3rd Ed. Toronto: McGraw-Hill Inc, 1992, p. 374.
8. *Personal communication* with Dr. David Barnes.
9. *Personal communication* with Dr. George Mawko.
10. *Personal communication* with Dr. Chris Thompson.
11. *Persomal communication* with Mr. Rick Nickerson.

The Ethics of Medical Education

The ethical issues addressed in undergraduate curricula these days focus quite properly on physician duties and responsibilities to patients and colleagues. These important considerations should be dealt with well and the teaching experience should be constantly improved. However, there are some significant ethical issues inherent in medical education itself and in the fact of being a medical student. These rarely receive the attention they require. They may be more significant in physician formation than anything that is explicitly taught. Some of these issues are being reflected upon in the ethics and medical education literature as the "hidden curriculum".

Some of the ethical issues in being a student which have been identified here at Dalhousie include performing first time procedures, giving bad news, experiencing violations of patient privacy and confidentiality, participating in inadequately obtained informed consent, inappropriate professional behaviors including sexual innuendo and racial and ethnic slurs, inappropriate patient behaviors, uncertainty with how to respond to incompetent colleagues and discomfort with being introduced as "doctor". Bound up with these particular issues are two unique experiences of students in their clerkship encounters, namely, coming to know patients as persons and wanting and needing to be known as a "good team player". As ethics education at Dalhousie develops to address more basic questions and answer more needs, these particular concerns in being a medical student need to be addressed. The first step in solving an ethical issue or dilemma is to recognize that it is ethical and to feel both comfortable and competent enough to identify the issue appropriately. What are the issues that urgently need to be addressed so that we can make the experience of being a medical student at Dalhousie a "good" one?

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