New Vistas in Cardiovascular Nuclear Medicine

An elusive goal in cardiovascular nuclear medicine has been the quantification of myocardial perfusion and regional myocardial blood flow. Since the early 1970s when myocardial perfusion imaging was performed using cesium-129 and potassium-43, there has been substantial interest in tracer techniques for this purpose. The major goal of these early studies was to develop radionuclide imaging procedures for clinical use to characterize perfusion abnormalities due to myocardial infarction or transient myocardial ischemia. Subsequently, thallium-201 replaced potassium-43 and became the myocardial perfusion tracer of choice. This radiotracer has far better characteristics for myocardial imaging than potassium-43 and permits high resolution imaging with modern gamma scintillation cameras. Major emphasis has been placed on the visual interpretation of multiview planar thallium-201 images (*1*,*2*).

Exercise planar thallium-201 imaging is used widely for the diagnosis of coronary artery disease; but, this technique is far from perfect. For the determination of the presence or absence of coronary artery disease, this method does provide important diagnostic information; however, for assessment of the severity of disease, for detection of the physiologic effects of subcritical coronary lesions, and for evaluation of the overall extent of jeopardized myocardium, qualitative analysis of planar images is not sufficient. Furthermore, unprocessed studies are often difficult to interpret, and reproducibility is not optimal, especially in patients with subtle abnormalities.

During the past five years, there have been two major advances in myocardial perfusion imaging—quantification of thallium-201 and the use of emission tomography. Quantitative analysis of thallium-201 uptake and washout has been applied to multiview planar studies. After background correction, either circumferential or linear profiles are obtained to quantify the relative uptake of thallium-201 in the myocardium (*3*,*4*). By comparing stress and delayed images, the extent of thallium-201 washout, a marker of myocardial thallium-201 kinetics, can be quantified in the clinical setting. Application of these new image-processing techniques has improved the value of planar thallium-201 imaging, specifically in the detection of individual coronary stenoses (*5*). Importantly, using the circumferential profile analysis technique, data in an individual patient can be compared with standardized normal files for stress and delayed tracer uptake, as well as for washout. Although quantitative methods have improved the analysis of thallium-201 imaging, they have not eliminated the need for visual interpretation of the same images by experienced observers. Optimal results are obtained by combining the interpretation of the images and the quantitative profiles. There are limitations to quantitative methods, however, especially with respect to the difficulties associated with accurate background correction, the variable effects of attenuation on myocardial regions, the critical need for accurate realignment of stress and delayed images, and the difficulties in defining normal standards. Furthermore, as with all planar techniques, there is overlap of normal and abnormal myocardial segments, potentially obscuring more subtle abnormalities.

These problems led to the second major advance in myocardial perfusion imaging, namely, single photon emission computerized tomography (*6*,*7*). Early results with quantitative seven pinhole and rotating slant-hole tomography were encouraging, but it appears that these methods were no better than planar imaging because of limited-angle sampling and blur artifacts. Probably the major benefit of tomography is the increased contrast obtained. The predominant tomographic approach currently used is rotational tomography. At this time, studies generally are performed over 180°, from the right anterior oblique to the left posterior oblique position. Inclusion of the more posterior data, and thus imaging over 360°, appears to degrade the image quality. A tomographic study, which is obtained in approximately 20 min, provides a series of transaxial images using filtered back projection. With oblique angle reconstruction methods, tomographic slices then can be obtained relative to the axis of the heart, specifically the vertical and horizontal long axis as well

as the short axis. This technique provides high-quality thallium-201 tomograms in orientations that are easier to analyze and offers excellent topographic localization of myocardial perfusion abnormalities. Recently, quantitative circumferential profile analysis has been applied to the tomographic data, further enhancing the clinical value of this technique (*8*, Eisner RL, et al., unpublished data). Compared with planar imaging, preliminary studies have demonstrated an improvement in the predictive accuracy of thallium-201 rotational tomography, especially with quantification, for the identification of individual coronary lesions. Currently, tomography appears to be the method of choice for thallium-201 myocardial perfusion imaging. Elliptical orbit tomography, in which the detector is maintained at a constant distance from the chest wall may further improve the accuracy of this method by providing better tomographic resolution (*9*). A major limitation of rotational thallium-201 tomography, however, especially when quantitative analysis is applied, is the lack of adequate attenuation correction, which remains an elusive goal.

The future of myocardial perfusion imaging undoubtedly will include radiotracers other than thallium-201. In fact, a major direction of the radiochemistry research community is the development of a technetium-99m labeled myocardial perfusion tracer (*10*). Substantial enthusiasm was generated in recent years for technetium-99m dichlorobis(1,2-dimethylphosphino)ethanol [DMPE] (*11*). Unfortunately, this radiopharmaceutical has a different biodistribution in humans than in other species, including primates, and therefore, the quest for a technetium-99m labeled perfusion tracer continues. Numerous cationic tracers are currently under investigation. Many of the limitations of thallium-201 rotational tomography could be overcome with the availability of a better technetium-99m tracer. Additionally, clinical results could be further improved by using an increased dose with consequent increased uptake in the heart and minimizing the effects of soft-tissue attenuation.

One asks, therefore, what are the needs for the future? Is there a role for positron emission tomography in myocardial perfusion imaging? This technique overcomes many of the limitations of single photon studies. Positron emission tomography clearly provides reconstructed images that characterize biochemical events in vivo. The resolution of state-of-the-art positron tomographic cameras is approximately 8 mm, considerably better than that in single photon emission computed tomography. However, the major advantage of positron emission tomography over single photon techniques is not resolution alone. If better delineation of anatomy were the primary goal, then magnetic resonance imaging would appear to be the preferable approach. Of greater importance is the absolute quantification of myocardial perfusion that may be achieved with positron emission tomographic techniques.

Considering the great promise of positron emission tomography, why has it not undergone wider utilization, such as is projected for magnetic resonance imaging? The costs of establishing a laboratory dedicated to positron tomography and one dedicated to magnetic resonance imaging are relatively comparable. Aside from costs, however, successful utilization of positron emission tomography requires the availability of unique radiopharmaceuticals, which generally have required on-site cyclotrons and extensive radiochemistry programs for their production. It is these factors that have limited the growth of positron tomography as a clinical tool. Of note, a recently published cost analysis of positron emission tomography has demonstrated that this technique can be cost effective, although the charges for clinical procedures may be among the highest of all charges for diagnostic imaging procedures (*12*). The most promising approach to cost reduction is the potential availability of positron-emitting radioisotopes from commercial sources, rather than from an on-site medical cyclotron. This has led to interest by the radiopharmaceutical industry in development of generator systems for positron-emitting radionuclides (Table 1) (*13*). The first generator of this type was the rubidium-82 generator. This radionuclide has been utilized for a number of years for measurement of myocardial blood flow based upon fractional distribution, as originally proposed by Saperstein (*14*). The methodology assumes that the uptake and release of intravenously injected radionuclides by myocardial cells are independent of regional blood flow and the metabolic state of the myocardium. Unfortunately, the first-pass extraction of tracers, such as rubidium, is inversely related to myocardial blood flow, posing a major problem for their use in myocardial perfusion imaging (*15*,*16*). Recent studies have suggested, however, that rubidium-82 can be used for this purpose if corrections are made for the variable extraction fraction with flow (*17*,*18*). For clinical studies, time-of-flight positron emission tomographic cameras that permit short sampling intervals may be required for determination of first-transit time-activity curves

TABLE 1. POTENTIAL GENERATOR SYSTEMS FOR SHORT-LIVED ISOTOPES

Isotope	Physical half-life	Generator system	Parent half-life
Positron emitters			
Rubidium-82	75 sec	Sr-82 → Rb-82	25.0 days
Cesium-128	3.8 min	Ba-128 → Cs-128	2.4 days
Manganese-52m	21.1 min	Fe-52 → Mn-52	8.3 hr
Gallium-68	68.3 min	Ge-68 → Ga-68	275 days
Copper-62	9.8 min	Zn-62 → Cu-62	9.2 hr
Iodine-122	3.6 min	Xe-122 → I-122	20.1 hr
Single photon gamma emitters			
Gold-195m	30.5 sec	Hg-195m → Au-195m	40.0 hr
Iridium-191m	4.9 sec	Os-191 → Ir-191m	15.4 days
Tantalum-178	9.4 min	W-178 → Ta-178	21.5 days
Krypton-81m	13 sec	Rb-81 → Kr-81m	4.7 hr

(*19*). Whether or not this technique can be translated from animal research to patient studies remains to be determined.

The article by Mullani in this issue is the third in a series that investigate myocardial perfusion with rubidium-82 (*17*,*18*,*20*). This article presents the theoretical bases for relating a quantitative perfusion defect to the severity of coronary stenosis using a simple model. This study is of interest because it suggests that by measurement of regional myocardial perfusion under basal conditions and during maximal coronary vasodilatation the severity of a coronary stenosis can be quantified. Of concern are some of the assumptions upon which this analysis is based, specifically, the presence of a single uniform stenosis in a single vessel without collaterals or superimposed necrosis. The theoretical analysis provided by the author will need to be confirmed in patients with coronary artery disease using positron emission tomography. Before this approach can be advocated, however, it is essential that rubidium-82 myocardial perfusion imaging be compared rigorously with state-of-the-art single photon emission computed tomography, with either thallium-201 or with a newer technetium-99m tracer.

Because of its long half life, the rubidium-82 generator has great potential appeal, since only one generator per month would be needed. The generator has been incorporated into a microprocessor-controlled infusion system, in which a minaturized multichannel analyzer is utilized to monitor the rate of infusion and the total administered dose (Fig. 1). Administration of this positron-emitting radionuclide appears to be almost as easy as elution of the technetium-99m generator, which has become the foundation for many nuclear medicine procedures.

We hope that the availability of this generator will be the impetus for detailed clinical studies on rubidium-82 and for the commercial development of other specialized generators that produce positron emitters or for minicyclotrons that produce short-lived tracers, such as oxygen-15. With the availability of oxygen-15, it would be relatively straightforward to obtain oxygen-15 labeled water to measure myocardial blood flow, oxygen-15 labeled carbon monoxide to measure blood volume, and oxygen-15 oxygen to measure oxygen utilization and overall metabolism (*21*). Additional insights into myocardial metabolism could be obtained from (F-18) fluorodeoxyglucose synthesized with fluorine-18 produced by a nuclear reactor and distributed regionally by radiopharmacies. This series of developments could lead to the design and manufacture of less expensive positron emission tomographic systems, which would allow broader utilization of positron techniques and a markedly expanded role for nuclear medicine in diagnostic imaging (*22*). If clinical trials with rubidium-82 and dipyridamole infusion are successful, this may become the foundation for the broader application of positron techniques to clinical practice. Furthermore, if six to ten patients can be studied daily, this would ensure that a positron tomographic camera would be used and that the cost/benefit ratio would be advantageous (*13*). Adequate time for additional clinical and research studies using other tracers also would be available. With the development of each

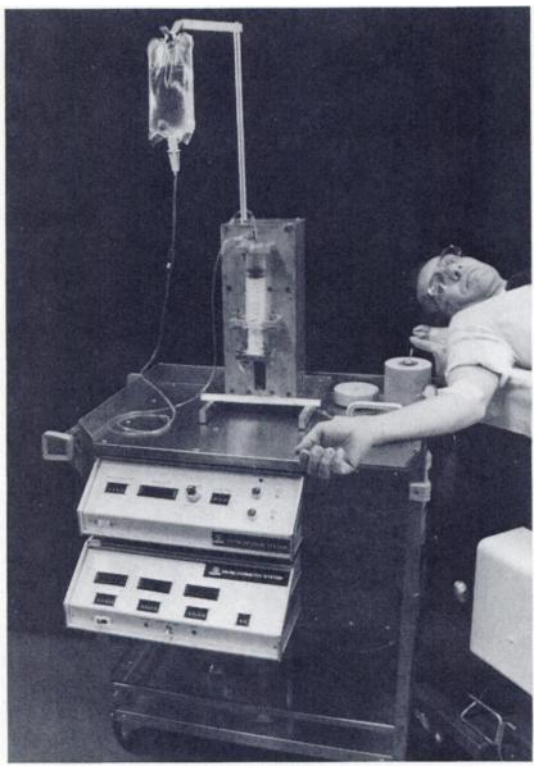

FIG. 1. Prototype infusion systems for Rb-82 generator. Microprocessor controls rate of infusion and total administered dose. (Courtesy of Gerd Muehllehner, Ph.D).

new radiopharmaceutical, nuclear medicine should continue to grow, even in the face of competition from higher resolution imaging modalities. The future of nuclear medicine does not appear to be limited by the spatial resolution of instruments, but rather by the creativity and innovation of investigators.

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Announcement of the Paul C. Aebersold Award for Outstanding Achievement in Basic Science Applied to Nuclear Medicine—1985

Nominations are invited for this award, which commemorates the contributions of Dr. Paul Clarence Aebersold to the applications of nuclear physics to nuclear medicine and radiation biology, and his contributions to the Society of Nuclear Medicine. Dr. Aebersold contributed greatly to the emergence of nuclear medicine as a discipline by his energetic leadership in the provision of cyclotron-generated and reactor-produced radionuclides, and by his numerous publications and lectures.

In giving this award, the Society thus symbolocially signifies its appreciation of the warm and vital person who became our first Honorary Member and whose enthusiastic encouragement and support contributed importantly to the formation and success of the Society of Nuclear Medicine.

Nominations should be supported by the curriculum vitae of the nominee and at least two letters supporting the nomination. These letters should describe briefly the contributions in basic science for which the nominee is proposed. The nominee need not be a member of the Society of Nuclear Medicine.

Please submit nominations and supporting documents to:

Leonard M. Freeman, M.D.
c/o Society of Nuclear Medicine
475 Park Avenue South
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Deadline for nominations: December 31, 1984