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iVIEW

EDITOR'S PAGE

Seeking Remedy for Molly's Woe

Time for a Thallium Pill?

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The strength of radionuclide-based procedures is in its ability to measure physiologic and biochemical processes in various organs. In cardiology, stress testing originated and continues to evolve from the need to identify clinically significant coronary artery disease (CAD). Nearly 9 million radionuclide myocardial perfusion imaging studies are performed annually in the U.S. The majority of the studies are performed to determine the physiological consequence of luminal narrowing of coronary arteries (and downstream adaptation by the resistance vessels and collaterals) in various myocardial regions of the left ventricle. The advent of localized therapies to specific vessels with bypass surgery or specific lesions with percutaneous coronary intervention has extended this indication of radionuclide-based myocardial perfusion imaging from diagnosing CAD to pinpointing areas of myocardial ischemia and guiding interventional therapies to culprit vascular lesions. Additionally, the physiologic significance of CAD burden provides prognostic information in settings such as post-myocardial infarction and pre-operative states.

The introduction of thallium-201 (^{201}Tl) myocardial perfusion imaging in the mid-1970s as an adjunct to electrocardiography treadmill studies has evolved into the discipline of nuclear cardiology today (1). Advances in both technology and radiopharmaceuticals over the past 30 years have contributed significantly to the maturation of the field. Technological advances include the transition from planar to single-photon emission computed tomography (SPECT), and recently to high speed SPECT systems, as well as positron emission tomography (PET). Radiopharmaceutical advances include a transition from a single ^{201}Tl-dominated myocardial perfusion tracer, to several technetium-99m (^{99m}Tc)-labeled perfusion tracers, and various PET radiotracers. Currently, nuclear cardiology studies represent nearly one-half of the approximately 20 million nuclear medicine procedures performed in the U.S. each year. Since the introduction of ^{99m}Tc-labeled perfusion tracer in the 1990s, a majority of the laboratories in the U.S. have switched from ^{201}Tl- to ^{99m}Tc-based myocardial perfusion stress protocols.

Following the discovery of the element Tc and ^{99m}Tc in 1938, and the molybdenum-99 (^{99}Mo)/^{99m}Tc generator in the early 1950s, the field of nuclear medicine has gained tremendous growth. The subsequent development of the stannous reduction "instant kit" technique in the 1970s, contributed significantly to the widespread clinical use of ^{99m}Tc-labeled radiotracers (2). The instant kit technique allowed the preparation of a variety of radiopharmaceuticals using a standard format of adding pertechnetate to a vial containing a small amount of stannous ion as a reducing agent and targeting molecule. Advances in ^{99m}Tc-labeled radiopharmaceuticals in concert with its synergy for producing good quality external imaging of the radiotracer in vivo, were the main factors contributing to the wide-scale introduction of ^{99m}Tc into routine clinical use. Unlike other radionuclides, ^{99m}Tc had the best nuclear properties for imaging with the Anger camera because the 140-keV gamma emission had satisfactory tissue penetration (less soft tissue attenuation and scatter), yet the energy was low enough to be collimated easily. In addition, because of its relatively shorter physical half-life (6 h) compared to Tl (72 h), higher doses of ^{99m}Tc-labeled perfusion trac-

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ers could be injected in patients at a comparable radiation burden to that of Tl.

The tremendous growth for ^{99m}Tc-labeled radiopharmaceuticals translates to higher demand for ^{99}Mo, which is derived from the irradiation of uranium targets in nuclear reactors. Of the approximately 245 operating research reactors in the world, 173 are more than 30 years old. Many of the reactors available in the U.S. are at universities and some of these aging reactors have been closed (3). Most importantly, isotope production in the U.S. is limited to material testing and small quantities of research isotopes rather than for clinical or commercial use. Only 5 of the world's reactors support commercial radioisotope supply of ^{99}Mo derived from the irradiation of uranium targets; none are located in the U.S. Thus, there are no facilities in the U.S. that are dedicated to manufacturing ^{99}Mo for ^{99}Mo/^{99m}Tc generators for clinical or commercial use at the present time. Realizing the importance of the ^{99}Mo shortage, the International Atomic Energy Agency met in Rockville, Maryland, in August 2008 to address the nation's needs for isotopes by enhancing isotope availability and reliability at a reduced cost. While the goals of the meeting were laudable, unfortunately, they did not provide solutions for the ongoing shortage. On the other hand, a recent press release from the European Association of Nuclear Medicine has characterized the ^{99}Mo shortage situation as a "chronic disease" rather than a "short term shortage" (4).

The supply of ^{99}Mo is rather complex with vulnerability at several points in the chain. Some of the short term solutions include authorization to substitute other radiopharmaceuticals for ^{99m}Tc, and new transport routes for purifying ^{99}Mo. While an alternative method for Tc chemistry can be applied using ^{94m}Tc, which is a positron emitter and is produced using an enriched ^{94}Mo target and a low-energy cyclotron. However, its short half-life of 52.5 min, the large number of gamma rays emitted with the positron, and the expensive cyclotron production method limit its clinical use. Other clinically available Food and Drug Administration-approved myocardial perfusion radiotracers in the U.S. include ^{201}Tl, ^{82}Rubidium, and ^{13}N-ammonia. Both ^{82}Rubidium and ^{13}N-ammonia require PET technology for imaging, which is not as readily available as SPECT systems. There are approximately 12,000 SPECT cameras compared to only 1,600 PET cameras in the U.S. Thus, PET-based radiotracers cannot, for now, realistically fulfill the current clinical demand for myocardial perfusion studies as an alternative to ^{99m}Tc-based SPECT studies.

What about ^{201}Tl? ^{201}Tl is a potassium analog and is injected as thallous chloride. The radionuclide element ^{201}Tl itself serves both as the mercury X-rays emitter (for external imaging with SPECT) and the myocellular probe (for detecting CAD). In the case of ^{99m}Tc-labeled perfusion tracers, it is the physicochemical properties of the ^{99m}Tc-ligand complex that controls the biodistribution, retention, and clearance in various organs. The lipophilicity of the ligand is good for crossing membranes and the positive charge is good for directing the movement across lipid membranes. ^{201}Tl requires no complicated chemistry for labeling a ligand. ^{201}Tl has a higher first-pass myocardial extraction fraction than ^{99m}Tc-labeled sestamibi or tetrofosmin, providing a stronger relationship to myocardial blood flow for identifying CAD. On the other hand, the key advantage of ^{99m}Tc over ^{201}Tl has been primarily based on its nuclear properties for imaging with the Anger camera and the sodium iodide crystals used in most conventional SPECT cameras. However, with the advent of high speed SPECT cameras that use different crystals, it may be wise to revisit the application of ^{201}Tl for myocardial perfusion imaging. ^{201}Tl is cyclotron-produced, readily available, and is not expensive. Although the radiation burden to patients (in terms of mSv) may have been somewhat higher than ^{99m}Tc when using conventional SPECT systems, recent studies have suggested that lower doses of ^{201}Tl, in the range of 2.0 to 2.5 mCi, could provide excellent image quality (even in patients with large body habitus) when applied with high speed SPECT cameras and at a similar radiation dosimetry to that of ^{99m}Tc-based cardiac protocols (5). In addition, although ^{99m}Tc has also been used for radiolabeling of the targeting tracers for molecular imaging, the chemistry of attaching ^{99m}Tc to small molecules, such as hormones, enzymes, and various drugs, can be quite challenging. Transition

to other radiotracers, such as iodine-123, may allow more convenient coupling, because the small radius of iodine compared to Tc chelate makes radioiodine better suited for radiolabeling small molecules and peptides. We believe that in addition to addressing the problem of shortage, we should reconsider our options and strive to continuously evolve.

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