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EDITORIAL

In Search of the Perfect PET Flow Tracer

Assessment of myocardial perfusion remains fundamental for the diagnosis of coronary artery disease and for objective evaluation of the efficacy of interventions designed to preserve myocardial blood flow. Because of its intrinsic quantitative capabilities, PET has proved to be accurate and sensitive for evaluation of myocardial perfusion. Nonetheless, there is no general consensus regarding the "best" radiotracer to use for such assessments. In this issue, Melon et al. (*1*) compare the imaging characteristics of two putative flow tracers, cyclotron-produced ^{38}K and generator-produced ^{62}Cu-pyruvaldehyde bis(N^4-methylthiosemicarbazone) (PTSM).

Production Aspects of ^{62}Cu-PTSM and ^{38}K

Blood flow tracers used in PET imaging include those prepared from cyclotron-produced radionuclides ($H_2{}^{15}O$, $^{13}NH_3$) and those prepared from generator-produced isotopes (^{82}Rb, ^{62}Cu-PTSM, future ^{68}Ga agents). In terms of convenience of radiopharmaceutical preparation, generator-produced radiopharmaceuticals for PET imaging have long been considered advantageous (*2,3*). One important advantage is the ability of a hospital to operate a PET center without having an "in-house" cyclotron. Particularly for cardiac imaging, FDG from a regional distribution center (for centers that use FDG for myocardial viability) along with a generator-produced flow agent would allow operation of a free-standing PET center.

Melon et al. (*1*) evaluated the myocardial kinetics of an alternative cyclotron-produced blood flow tracer, ^{38}K, and compared it with ^{62}Cu-PTSM, a well-studied, generator-produced radiopharmaceutical. Both radionuclides have similar half-lives and can be produced with good radiochemical purity. However, in terms of practicality, the issue of cyclotron-produced versus generator-produced radionuclides again arises.

In the study by Melon et al., ^{38}K was produced on what is referred to as a Level III cyclotron (26 MeV, 25 μA) using a sodium chloride target (^{35}Cl (α, n)). A Level III cyclotron is considered to be a "medium-energy, four particle" machine, while all medical cyclotrons currently being designed for use in PET centers are one (protons) or two (protons + deuterons) particle cyclotrons with maximum energies of 16 MeV protons and 8 MeV deuterons. Potassium-38 has been produced on a lower energy four-particle cyclotron (14.7 MeV) using a sodium chloride target (*4*), but the end of bombardment (EOB) yield at saturation (mCi/μA) was nearly a factor of four lower than at the higher energy. With a low-energy, two-particle cyclotron, ^{38}K can be produced by the ^{38}Ar(p, n) reaction (*5*), but ^{38}Ar has only 0.063% natural abundance, which makes this target cost-prohibitive. Also, recovery of ^{38}K from a gaseous target and allowing for re-use is a nontrivial task.

On first glance, the preparation of generator-produced ^{62}Cu might appear to be more convenient than that of cyclotron-produced ^{38}K, but the short half-life of the parent isotope, ^{62}Zn ($T_{1/2}$ = 9.3 hr), limits the practicality of the generator. Zinc-62 is produced on a medium-energy cyclotron (27.5 MeV) via the ^{63}Cu(p, 2n) reaction. Many medical cyclotrons are not capable of bombardment above 16 MeV; therefore ^{62}Zn is generally purchased from a centralized facility. The lifetime of the generator is 1–2 days. If there is a medium-energy cyclotron onsite, ^{62}Zn would have to be produced every 2 days for continuous supply of ^{62}Cu, otherwise ^{62}Zn would have to be purchased on a bi-weekly basis. Once the ^{62}Zn is loaded onto the generator, the ^{62}Zn/^{62}Cu generator can be eluted every 30 min.

As a radiopharmaceutical, ^{38}K is simple to prepare. There is no chemistry involved, only dissolution of the target and production of a sterile, injectable solution. In the case of many short-lived, cyclotron-produced isotopes, the system for bombardment, transfer of the target postbombardment to a hot cell and target processing has been automated for routine production of ^{38}K (*5*). The entire procedure for producing sterile, injectable solutions of ^{38}K takes 25–35 min. The preparation of ^{62}Cu-PTSM is relatively simple as well, since the ^{62}Cu-PTSM complex forms rapidly. An accepted ^{62}Cu-PTSM "kit" has not yet been developed. Many investigators use ^{62}Cu-PTSM without any purification (*6,7*), but others purify the complex away from free Cu^{2+} using C-18 Sep-Pak purification (*1,8,9*). With or without Sep-Pak purification, the time needed for preparation is under 10 min. For ^{62}Cu-PTSM, even if an acceptable kit formulation is developed, chemistry problems such as trace

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metal contamination and ligand decomposition remain potential problems.

Cardiological Aspects of Flow Tracers

In comparing the convenience of preparing ^{38}K with ^{62}Cu-PTSM, there are clearly advantages and disadvantages for both tracers. As Melon et al. point out (*1*), all currently used positron-emitting flow tracers have limitations that have been recently reviewed (*10*). Cyclotron-produced $H_2{}^{15}O$, the only tracer in use that is nearly freely diffusible in the heart permits absolute quantification of regional myocardial perfusion with PET (*11*); however, image quality is not as good as that obtained by other flow tracers, because $H_2{}^{15}O$ circulating in the vascular pool must be corrected for in order to visualize the myocardium. Cyclotron-produced $^{13}NH_3$ provides the best quality images of the myocardium. The half-life of ^{13}N (10 min), however, limits rapid rest and stress flow imaging protocols. In addition, recent studies suggest that there may be regional heterogeneity in the myocardial uptake of $^{13}NH_3$ (*12*) possibly related to regional differences in the metabolism of extracted $^{13}NH_3$, and although absolute quantification is possible, the tracer is metabolized in blood rapidly after administration (*13*). On the other hand, ^{82}Rb, a generator-produced tracer that permits quantification of flow (*14*), has a 76-sec half-life which permits rapid rest and stress imaging protocols but limits counting statistics and accordingly does not produce images of as high quality as $^{13}NH_3$. The extraction and retention of both $^{13}NH_3$ and ^{82}Rb are affected by the metabolic state of the myocardium and thus mathematical models used to quantify regional flow with these must account for decoupling between flow and extraction.

As demonstrated by Melon et al., both ^{38}K and ^{62}Cu-PTSM provide high-quality images of the myocardium similar to that obtained with $^{13}NH_3$. Thus, they may be useful diagnostically although that was not addressed in this initial characterization. As has been pointed out previously (*9*), liver uptake of ^{62}Cu-PTSM is high and represents a relatively undesirable feature since it limits delineation of flow in the inferior wall of the myocardium. The physical half-life of ^{62}Cu (9.7 min) is less than ideal for performing rest and stress images in a single setting since one needs to wait at least 45–60 min after the first administration for radioactivity in the myocardium to decline sufficiently to allow a subsequent injection. In addition, after administration in humans, ^{62}Cu-PTSM binds to human albumin (*15*), precluding accurate recording of the arterial input function, which is critical for quantification (*16*).

Radiolabeled potassium has several characteristics that would, at first blush, make it an attractive candidate for evaluation as a flow tracer, including high extractability by the myocardium and rapid clearance from the blood. These attributes have been previously recognized (*17–19*). Its 7.6-min half-life would allow rest and stress images to be obtained at one setting.

As is the case for all extractable flow tracers, myocardial uptake of ^{62}Cu-PTSM and ^{38}K are inversely and nonlinearly proportional to flow. Thus, at higher flow rates, proportionally less tracer is extracted by the myocardium. This is graphically demonstrated by Melon et al. in that net tracer content after intravenous injection of dipyridamole increased 1.6 times at rest with ^{38}K and 1.4 times with ^{62}Cu-PTSM. At the standard dose of dipyridamole used, myocardial perfusion would be anticipated to increase at least three- to fourfold over rest in the myocardium of young, healthy volunteers (*10,11*). However, the mathematical approach used by Melon et al. only looked at net uptake, and more sophisticated mathematical approaches (similar to those used for quantification of flow with $^{13}NH_3$ and ^{82}Rb) would be necessary for accurate quantification (*8,20*). A recent initial report in experimental animals demonstrated the ability to quantify myocardial perfusion with ^{38}K in absolute terms over a wide range of flows using mathematical modeling, although the accuracy of flow quantification was less for ^{38}K than for $H_2{}^{15}O$ (*20*). In contrast, a study performed in five patients with chest pain but angiographically normal coronary arteries using arterial-coronary sinus sampling indicated that myocardial ^{42}K uptake was not related to myocardial perfusion (*21*). Clearly, additional investigation will be needed to resolve these issues.

Of importance, since the trapping of potassium by the myocardium is primarily regulated by the Na/K pump, and because this pump is exquisitely sensitive to metabolism (*22*), use of radioisotopes of potassium may be less sensitive to flow and more sensitive to metabolism than other tracers. The efflux of potassium from ischemic myocardium is dependent on both the magnitude and the duration of ischemia (*19*). Myocardial cells can concentrate potassium when flow is decreased by 50%, but more severe impairment is likely to result in diminished myocyte trapping capability. Flow estimates using radiolabeled potassium which do not account for this could result in erroneous underestimation of myocardial perfusion. On the other hand, it is possible that this sensitivity to metabolism could be exploited as a marker of myocardial ischemia. Obviously additional studies will be needed to delineate the utility of this concept and the ability to accurately quantify these rapid kinetic events.

Although the study by Melon et al. is a valuable addition to the PET literature on myocardial flow tracers, it appears likely that the search for the perfect flow tracer continues.

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