

Myocardial Perfusion in 3 Dimensions

Once in a while a study is published that could mark an important step forward but, at the same time, is long overdue. The study by Schäfers et al. (1) in this issue of *The Journal of Nuclear Medicine*, describing the measurement of myocardial blood flow (MBF) using $H_2^{15}O$ and a 3-dimensional (3D) acquisition protocol, is such a study.

After preliminary efforts, successful development of the first quantitative PET scanner (2,3) was based on several key design features. One of these features was protection of (single slice) crystals from out-of-field scatter using side shielding. In the second generation of (multislice) scanners, interplane septa were used to reduce detection of scattered events. In fact, it was believed that scatter was the main enemy of quantification. A change of thought came about in the late 1980s (4,5), when it was realized that another enemy was lack of sensitivity, especially within the context of repeated measurements on healthy subjects (brain activation studies) and increasing awareness of radiation doses. Scanners with retractable interplane septa were developed (6), and it became common practice to perform brain studies in the 3D mode (i.e., with the interplane septa retracted). This practice was based on the significant improvement in sensitivity (factor of 8 in the center of the field of view) coupled with the development of satisfactory methods to correct for scatter (7,8). However, these 3D studies were limited to the brain. Over the years, 3D studies of the thorax were reported in only a few investigations, but most of

these investigations were concerned with image quality in diagnostic (qualitative) studies. In general, it was thought that there was little or no quantitative gain of 3D compared with 2-dimensional (2D) myocardial studies.

The study by Schäfers et al. (1) is the first attempt to quantify MBF using $H_2^{15}O$ and a 3D acquisition protocol. This could mark an important step forward because the number of scanners that can acquire data only in the 3D mode (i.e., scanners without interplane septa) is increasing (9–12). Therefore, 3D data acquisition and analysis strategies need to be developed to guarantee that those scanners can also be used for quantitative myocardial studies. The study by Schäfers et al. is a nice example of that need because it was performed on a 3D-only scanner. Nevertheless, the study is long overdue. Three-dimensional PET has been commercially available since the early 1990s, but the number of 3D myocardial PET studies reported is very limited. This is true not only for the PET community at large but also for the Hammersmith group itself, because the scanner used by Schäfers et al. was installed some 6 y ago. The time gap between the introduction of 3D PET and its use in quantitative myocardial studies is probably the best illustration of how complex the issues are that need to be addressed in studies outside the brain.

There are several potential advantages of 3D PET. First, for a given dose and based on the higher efficiency, scan time could be reduced. The shorter scan time would provide higher patient throughput and, therefore, lower scanning costs (in addition, the absence of interplane septa also reduces scanner costs). This, however, applies only to qualitative (diagnostic) scans. In general, for quantification, dynamic scanning protocols are re-

quired and study duration is not determined by the number of counts but, rather, by the tracer being used and the physiologic process being studied. Because study duration is fixed, higher sensitivity would allow better statistics or a lower injected dose. For a counting technique, in which radiation dose to the patient is always important, both options are attractive.

There is no doubt that if reduction of injected dose and improved statistics were the only issues involved, 3D PET would have been the accepted standard for myocardial studies. Unfortunately, also in this case, there is no free lunch. Three-dimensional PET comes with several problems, especially for studies of the thorax. First, normalization of 3D-only scanners is not trivial and there is still scope for improvement, especially when the crystal size is reduced. Second, in contrast to 2D/3D scanners where transmission scans are obtained in the 2D mode, in 3D-only scanners the transmission scan has to be acquired in the 3D mode. At present, the accepted method is to use a single point source together with segmentation of the acquired data. Again, this is not trivial and more studies are required to validate the method. In particular, there is no experience in situations in which the range of attenuation coefficients might be larger than usual (e.g., patients with pacemakers). Third, the scatter fraction is increased significantly in 3D PET compared with 2D PET. This means that a validated method to correct for scattered events needs to be implemented. Although good methods have been developed, these methods need to be validated for each scanner design (i.e., the method used by Schäfers et al. (1) is not necessarily valid for other scanners). An important issue is the contribution of out-of-field scatter. For example, for myocardial studies this could involve

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counts originating from the liver if the liver is outside the axial field of view. Finally, randoms and singles (dead time) need to be accounted for. Although validated methods exist to correct for randoms, these corrections have impact on the statistical quality of the data (basically, if the randoms fraction is very high, the correction involves subtracting 2 large numbers from each other). Randoms and dead-time corrections dictate that the scanner should not be operated above a certain critical counting rate (maximum noise equivalent count rate). Consequently, the potential choice between a lower injected dose and better statistics often is not a real one. The only option is to reduce the dose. Although this might not be a fundamental problem (i.e., if the dose does not become too low), limitation of the dose because of scanner characteristics does impose a practical problem. To achieve optimal statistical quality, and taking into account that the counting rate might be dependent on patient characteristics (e.g., weight, diameter), requires that the dose be calculated individually for each patient.

Of course, the study by Schäfers et al. (1) does not stand on its own. It is based on a detailed assessment of the characteristics of the 3D scanner used (12). Despite the problems mentioned above and addressed by Spinks et al. (12), the results of the study by Schäfers et al. are very promising. They show a very good correlation between MBF values as measured by $H_2^{15}O$ and PET and those measured by the invasive microsphere procedure. In fact, their results are no worse than those reported earlier for 2D scanners. Unfortunately, Schäfers et al. were unable to perform a direct comparison between 2D and 3D modes because they used a 3D-only scanner. Clearly, such a study would be of great interest, especially for future multicenter studies in which, ideally, 2D and 3D data could be combined.

A point of some concern in the study of Schäfers et al. (1) is the rather low recovery coefficient for the left ventricular region of interest (ROI), ob-

tained from a separate $C^{15}O$ scan, potentially resulting in a small overestimation of MBF. Ideally, reconstructions should have been performed with a ramp filter to have optimal spatial resolution and, consequently, the best possible recovery. Apparently, this was not possible because of noise considerations. Unfortunately, the injected dose was limiting and this should be a challenge to scanner manufacturers, providing the user with a real choice between statistics (i.e., spatial resolution feasible) and dose. The low recovery coefficient could result in some bias and should be considered when comparing results with data from other scanners. A more serious concern related to the limited dose that can be injected is the potential impact on human studies, in which tissue attenuation and, thus, noise levels could be higher. It will be interesting to see how the method (i.e., scanner) will perform in human studies. This is particularly important in studying patients with reduced MBF because low-uptake regions are more vulnerable to scatter contributions.

Because the study of Schäfers et al. (1) deals primarily with validating the measurement of MBF using a 3D-only scanner, another important novelty might be overlooked. To define ROI without having to perform a separate measurement of blood volume ($C^{15}O$ scan, used only as quality control in the study), the factor analysis method of Hermansen et al. (13) was implemented. This method produces factor images of the right ventricle, the left ventricle, and myocardial tissue from the time course of $H_2^{15}O$ itself. These images can be used subsequently to define blood and tissue ROIs for further quantitative analysis. This method has been criticized recently (14), because it requires definition of lung ROI and some assumptions about the delay between the lung and left and right ventricles. Schäfers et al. have circumvented this problem (and, thereby, the criticism) by preceding factor analysis by cluster analysis (15). The cluster analysis step automatically generates time-activity curves for the 3 struc-

tures mentioned, and these time-activity curves are then used as input into the factor analysis step. This is a very elegant approach and an important addition to the method. In theory, the method can be fully automated, which will be important for the use of $H_2^{15}O$ in future clinical studies (e.g., determining flow reserve). Two challenges remain. The first is to assess whether the blood curves generated by the cluster analysis procedure could not be used directly as input to the quantitative calculation of MBF. The second is the ultimate goal—that is, the generation of accurate functional MBF (and tissue fraction) images. For the latter challenge, good statistics are required. This, in turn, requires scanners that can cope with higher levels of activity within the field of view. The introduction of scanners with faster lutetium oxyorthosilicate crystals, thereby reducing the randoms rate and dead-time losses, might be an important step in this quest for automatic generation of functional myocardial perfusion images in 3D. It should then be possible to routinely generate fully quantitative functional images of MBF, tissue fraction, and flow reserve within a scan time of <30 min, thus challenging the final enemy of PET: patient movement.

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