
Quantification of Serial Changes in Myocardial Perfusion

Myocardial perfusion SPECT (MPS) studies are frequently performed serially to monitor progression of coronary artery disease. MPS also plays an important role in evaluating therapies for coronary artery disease (1). Sensitive methods for detection and estimation of changes in myocardial perfusion over time could improve confidence in using MPS for these applications (2–5). The use of the most reproducible and accurate analysis would be especially important in clinical trials of new therapies, since it could enhance the reliability of the results and reduce the sample size required to prove the effectiveness of therapy (6). Although the inherent variability of serial MPS imaging cannot be eliminated, finding the optimal quantification method will help in reducing the overall test variability.

Current MPS quantification methods typically characterize hypoperfusion in terms of stress and rest defect extent and severity or automatically derived segmental scores (7–9). The perfusion parameters are obtained by statistical comparisons of polar-map pixels derived from a scan of a given patient to the normal limits derived from scans of many subjects. These quantitative MPS tools have been developed and evaluated for the assessment of perfusion defects in a single

nuclear study, which may include stress and rest scans (10), but have not been explicitly validated for comparisons of serial studies. For example, a true improvement of a perfusion deficit in a given region coupled with deterioration in another area will not be detected accurately by these standard techniques.

When such techniques are applied to estimate changes in perfusion over time, 2 independent statistical comparisons are made to the normal limits. However, the intrasubject variability of scans obtained from the same patient is likely smaller than the intersubject variability in the normal database, which includes data of patients of various shapes and sizes. Therefore, the perfusion changes obtained in this manner may be underestimated. Furthermore, existing tools require independent detection of myocardial contours and transformation to standard reference coordinates for each study. Inconsistencies in the contour definition or in the alignment with polar-map coordinates may result in apparent false-positive changes in myocardial perfusion (11). Substantial variability has been observed in quantification of serial MPS when standard methods have been used (12).

The limitations of traditional methods applied to analysis of changes in MPS have previously been recognized. Various attempts have been reported to improve the quantification of sequential (stress/rest) (13) or serial (14,15) changes, using direct image comparisons. A computer simulation study has demonstrated that current techniques are inadequate for detection of perfusion severity changes as large as 10% (15). In clinical studies, one major lim-

itation in the development of quantification for serial changes is the absence of an accurate gold standard. In animal studies, reference standards are available. deKemp et al., for example, used microspheres to validate their direct paired-comparison method for serial quantification of perfusion by PET (14), but such validation methods are not suitable for patient studies.

On pages 1981–1988 of this issue of *The Journal of Nuclear Medicine*, Itti et al. report a unique study that addressed the important question of how to accurately quantify changes in myocardial perfusion due to therapy. The authors analyzed changes in stress and rest myocardial perfusion in 49 patients who underwent delayed revascularization 3–4 wk after myocardial infarction (16). The study was prospective, with 3 angiographic and 2 MPS datasets obtained within 3–5 mo before and after revascularization. Serial perfusion changes were evaluated both visually and quantitatively by an automated method. A remarkable aspect of this study was the use of serial coronary angiography as a reference standard for the perfusion changes observed by MPS. This use allowed the investigators to definitively distinguish revascularized arteries that had reoccluded from those that had remained open. Prior clinical studies of serial MPS have simply compared revascularized and nonrevascularized patients, assuming that the intervention would improve perfusion (2).

In addition, the authors applied a voxel-based method for quantification of reperfusion after the revascularization procedure. Patient images were automatically registered to 3-dimensional (3D) reference templates, which

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were used instead of the more traditional 2-dimensional polar maps. Subsequently, the perfusion changes were considered only within the volume of the significant hypoperfusion detected in the first study. Using such an approach, the authors established that the voxel-based technique, unlike visual segmental scoring, could distinguish between patients with patent arteries and patients with reoccluded arteries, when assessing reperfusion at rest. The voxel-based quantification was also the only technique able to distinguish patients with patent arteries when analysis was restricted to the volume of the initial ischemic defect. The sensitivity and specificity of the voxel-based 3D technique for the detection of reocclusion by SPECT were reported to be 67% and 73%, respectively. The authors attributed the superior performance of their quantitative measure (deficit load) to confinement of the deficit load to the defect location in the first study, linear capture of defect severity, and the continuous character of the measure, unlike coarse visual scoring (17). These results are significant because many of the previously published clinical trials that evaluated improvement in myocardial perfusion due to various therapies used global measures such as visual summed stress scores (18) or quantitative defect extent (1) without the enhancements proposed by Itti et al. (16).

A few limitations should be highlighted with respect to the study of Itti et al. (16). After myocardial infarction, marked disparity between angiography and MPS findings would be expected in the transmural infarct regions, and the study was performed on patients with recent myocardial infarction. Undoubtedly, the observed relationship between angiographic and MPS findings would have correlated more closely in patients without myocardial infarction. Additionally, the voxel-based technique still requires 2 separate comparisons to the intersubject normal limits and 2 registrations to 3D

reference templates. A possible improvement would be to register and compare serial scans directly with each other (13,14). However, the errors due to the above factors may have been reduced in the approach proposed by Itti et al., since their deficit load measure was restricted only to the defect location on the first scan.

Furthermore, nonlinear adjustments of myocardial shape may be needed to accurately match a patient scan to the 3D reference templates (19). In the study of Itti et al. (16), however, only one global scaling parameter was considered to compensate for the individual variation in myocardial size. The nonlinear adjustments would be of lesser importance if direct registration of serial images were used. Significant errors in the quantification could potentially also be introduced by the process of count normalization (20). In the study of Itti et al., the count normalization factor was calculated independently for the reference study and the follow-up study—an approach that may compound quantification errors.

The authors applied a voxel-based quantification scheme and compared it with the visual and quantitative segmental analysis. Similar voxel-based techniques were previously proposed by other investigators (19,21) but have not been applied to analyze serial MPS studies. Voxel-based techniques allow identification of defects on tomographic slices and do not require conversion from 3D image coordinates to polar-map representation. To date, no published study has directly compared the performance of the voxel-based and polar-map approaches. From the study presented by Itti et al. (16), we can, however, conclude that the voxel-based method performs better than visual scoring for detection of serial changes.

In summary, the results presented by Itti et al. (16) show that traditional visual scoring methods, commonly used for the evaluation of perfusion changes in trials of therapies and in clinical practice, are not optimal. Au-

tomated MPS quantification methods, which use continuous voxel-based measures and consider changes only in the original defect location, may be more appropriate. The study by Itti et al. suggests potential improvements and presents a unique validation approach for quantification of serial changes in myocardial perfusion.

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