Quantitative analysis of myocardial perfusion images

Piotr Slomka[a,b], Reza Arsanjani[a], Yuan Xu[a], Daniel S. Berman[a,b], Guido Germano[a,b]
a. Departments of Imaging and Medicine, and Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA
b. David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
E-mail: slomkap@cshs.org Tel: 310-423-4348

Abstract-- **Myocardial perfusion imaging is a widely used test for the detection of coronary artery disease. Automated measurements of perfusion can be obtained from three-dimensional stress and rest images. The software segments the left ventricle of the heart and compares image intensities to normal subject database. In our research, we aim at reduction and ultimately elimination of human supervision in this process to improve overall reproducibility and accuracy for disease detection. We have developed several methods to this end such as automatic detection of potentially incorrect contours and direct measurement of stress-rest changes. Current state-of-the-art analysis methods demonstrate better reproducibility and similar accuracy when compared with experienced physicians. We aim to further improve the diagnostic accuracy by data mining techniques, combining several extracted image features with clinical information about the patients. Preliminary results show further improvements in accuracy, beyond that achieved by expert observers.**

INTRODUCTION

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) imaging have been an accepted clinical gold standard for the quantification of relative heart muscle perfusion during stress and rest. In the United States alone, approximately 9 million of such myocardial perfusion scans have been performed annually [1]. These measurements are very important because they can reveal which part the heart muscle (myocardium) is in jeopardy should the heart attack occur. If there is a visible area of reduced perfusion (hypoperfusion) at stress and it improves at rest, it indicates that the patient is likely to have blockages in coronary arteries supplying this portion of the heart muscle (coronary artery disease) and is at increased risk of heart attack and death. Perfusion of the heart muscle can be restored before the heart attack by surgery or therapy; therefore, it would be more beneficial to detect abnormalities early prior to damage occurring.

Automated software for quantitative analysis of three-dimensional SPECT and PET myocardial perfusion images studies has become routinely used in clinical practice and research. This software can automatically segment the left ventricle of the heart (where perfusion needs to be estimated), establish perfusion maps on the ventricular surface, and estimate global and local measures of perfusion at stress and rest. These computer-derived quantitative measures can be used to diagnose the coronary artery disease (CAD). In this review, we discuss our latest work in quantitative analysis of perfusion. We also present some recent results comparing such fully automated systems to visual expert analysis in large patient populations.

A. Overview of processing

The standard processing sequence of PET and SPECT images is as follows. After 3D image reconstruction, 3D segmentation the heart muscle (only for the left ventricle of the heart) is performed [2] [3]. Subsequently, myocardial count density samples are extracted and mapped onto polar map coordinates (typically by computing the maximal value of perfusion for a given polar map pixel). In this way a circular 2D maps are built for the ventricular surface with different colors representing degree of perfusion at a given pixel. Finally, analysis of the polar map samples is accomplished by the comparison to the average local values in the normal population [4, 5].

B. Left ventricular segmentation

Accurate segmentation of left ventricle is a key prerequisite to obtaining accurate perfusion results. Incorrect segmentation can result in spurious defects mimicking perfusion abnormalities. However, accurate delineation of the heart muscle with nuclear imaging is challenging due to technical difficulties such as relatively low image resolution, activity present in other organs, and image noise [6]. A few techniques have been developed for nuclear imaging left ventricular (LV) segmentation. Automated software tools allow highly automatic definition of the LV contours. A widely used LV segmentation method for SPECT has been developed at our institution [7]. Other similar methods for the quantitative analysis of nuclear myocardial perfusion imaging have also been proposed [8] [9] [10] [11]. Alternatively, LV segmentation can also be performed by comparison to 3D templates (atlases) with a registration based approach [12] [13]. The software tools allow fully unsupervised LV segmentation in up to 90% of the cases [14]. Therefore, some supervision by an experienced observer is still required during the LV segmentation step; however, this can be accomplished by an experienced technologist rather than a physician.

The only time human interaction is required in the quantitative analysis of perfusion is during the adjustment of the computer-generated contours in a minority of cases. This interaction can introduce some changes to otherwise fully automatically derived results. We have attempted to objectify the user's supervision of the quality control (QC) software for automatic detection of potentially incorrect contours [14]. Such automated contour checks, have demonstrated perfect sensitivity (100%) and very high specificity (98%) for the detection of incorrect LV shapes as compared to an experienced operator (technologist). With such a tool, an experienced observer could focus its attention on only the studies, which are flagged by the computer. Further work is needed to improve automatic contour detection based on such QC tools.

C. *Quantification of perfusion*

After left ventricle of the heart is segmented, the surface is mapped onto polar coordinates, creating a bull's-eye map or polar maps. Perfusion (image intensity level) at a particular surface point is then displayed in such coordinates. The use of common two-dimensional polar map coordinates for all subjects allows comparison of count intensities between different patients. This is essential because analysis of perfusion is relative (image intensities in each study need to be normalized to a common level before the comparisons are made). Normal values are obtained from the analysis of normal subjects. Degree of perfusion abnormality for a given myocardial location can be defined as the statistical deviation from the lower normal thresholds. The normal limits, which are specific to a given scanner or type of imaging protocols (for example patient position during the scan), can be easily created by the user from a small group (20-40 subjects) of visually normal scans with low likelihood of disease.

Consequently, polar maps (or so called "blackout maps") can be plotted with the degree of severity mapped based on a colour scale, where all the pixels below normal limits are highlighted. An example of such quantitative polar maps and corresponding LV surfaces is shown in Figure 1. The local samples of hypoperfusion can be aggregated into regional (per vascular territory) or global (per ventricle) measures. Myocardial perfusion defect extent ("defect extent") can be expressed as a percentage of the pixels in the polar map, for which the severity is greater than a predefined statistical threshold. A parameter, which combines pixel-based defect extent and severity and estimates an overall magnitude of the abnormality, termed "total perfusion deficit" (TPD) has been developed [4]. TPD can be computed for the entire myocardium, or separately for each vascular territory. In addition, segmental perfusion scores for the American Heart Association 17-segment model of the ventricle can also be derived based on the average defect severity for a given segment. Segmental scores can be summed per whole myocardium, and the summed stress score (SSS), the summed rest score (SRS), and the summed difference score (SDS) can be derived. Such 17-segment scores are routinely used by the visual observers to estimate and report local abnormalities [15]. Several validation studies for these techniques have been reported, with invasive depiction of the artery blockages as the gold standard [16, 17] [18].

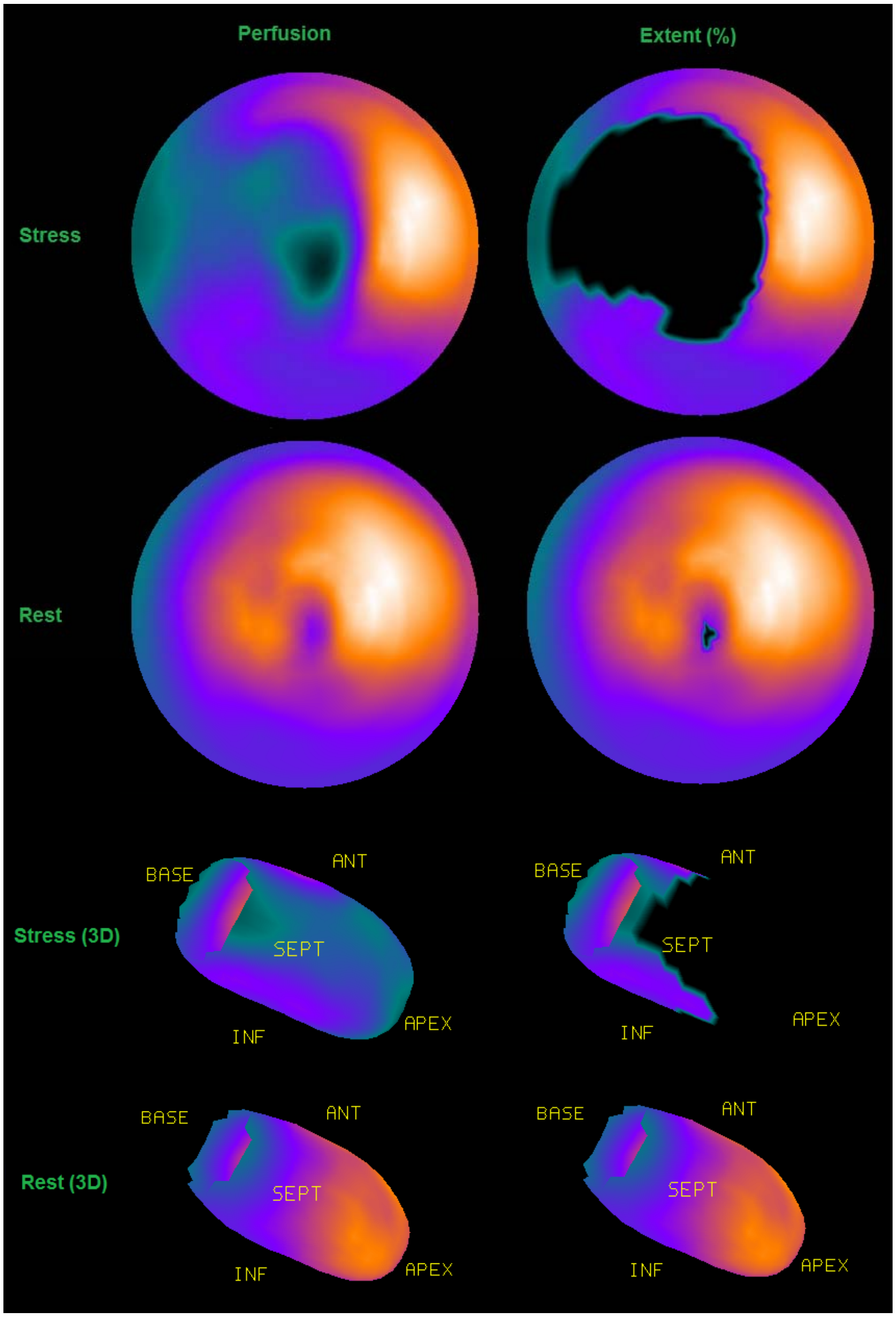

Fig. 1 An example of stress and rest quantitative polar map displays (top) with abnormal areas shown as blackout maps (left) and corresponding 3D surfaces of the left ventricle (bottom). In this case, there is severe abnormality during stress, which becomes normalized during rest.

D. *Perfusion change analysis*

A key aspect in the detection of the perfusion abnormalities is the detection of significant differences between stress and rest images. The visual assessment of the amount of change between stress and rest studies can be challenging for the visual observer, because these changes can be subtle. In addition, there can be differences in stress and rest 3D image orientation. Furthermore, the image intensities may be normalized differently for the stress and rest images. In efforts to improve the quantitative analysis of these changes, new software methods based on image registration have been proposed to analyze the stress/rest studies in pairs. One advantage of this approach is that there is no need for normal subject reference data (stress images are compared directly to rest images). A method for automatic quantification of local myocardial perfusion stress–rest changes by 3D registration and stress-rest normalization has been proposed, guaranteeing the same orientation for the stress and rest studies [19]. Further enhancements of such change analysis methods, where normal limits of allowable stress-rest change are established, have also been proposed and have shown promising results [20].

COMPARISON TO HUMAN OBSERVERS

A. *Reproducibility of automated and visual analysis*

The automated perfusion software has been shown to be more reproducible than most experienced experts (cardiologists). Lower variability directly translates into improved detection of true differences in hypoperfusion. The reproducibility of quantitative perfusion analysis has been compared to visual analysis for a stress/and rest SPECT scan, which was repeated on the same day with the same injection [21]. Quantitative analysis was significantly more reproducible than the visual analysis. Quantitative and visual analysis for stress perfusion is shown in Figure 2. These comparisons clearly demonstrate the advantages of the quantitative perfusion analysis over the visual expert analysis.

B. *Computer detection of disease and prediction of death or heart attacks*

The diagnostic accuracy of the latest quantitative myocardial perfusion methods is similar to that achieved by expert physicians. In a recent preliminary study quantitative analysis of perfusion images with and without attenuation correction was compared to an expert clinical read [22]. An expert clinician was equivalent in the accuracy, even when additional information such as patient age and symptom history (not used by the computer software) was revealed to the reader (Figure 3). This highlights one of the difficulties in comparing the diagnostic accuracy of the visual observer versus quantitative analysis. The physician can mentally combine all the available information, such as patient history and image data. Despite this, equivalence to visual diagnostic performance was demonstrated for the experienced reader, even if all clinical information was also available.

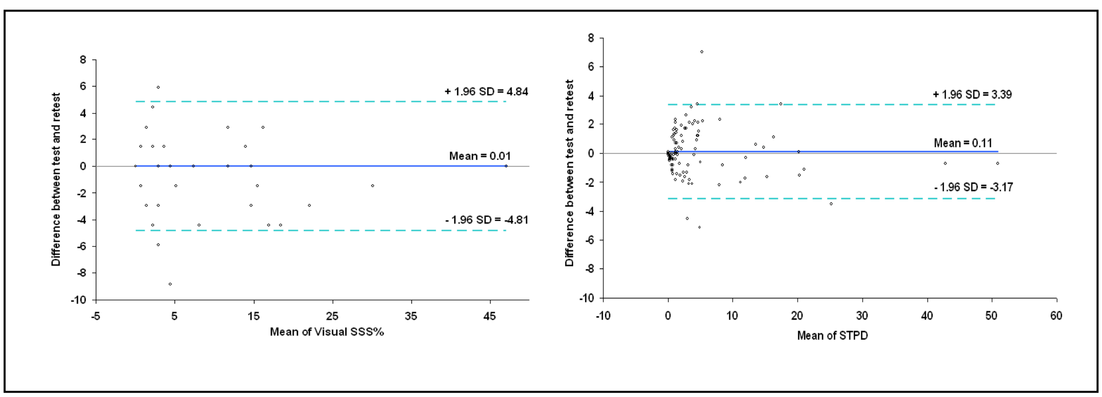

Fig. 2 Bland-Altman plots for visual (left) and automatic (right) repeated measurements of myocardial perfusion at stress.

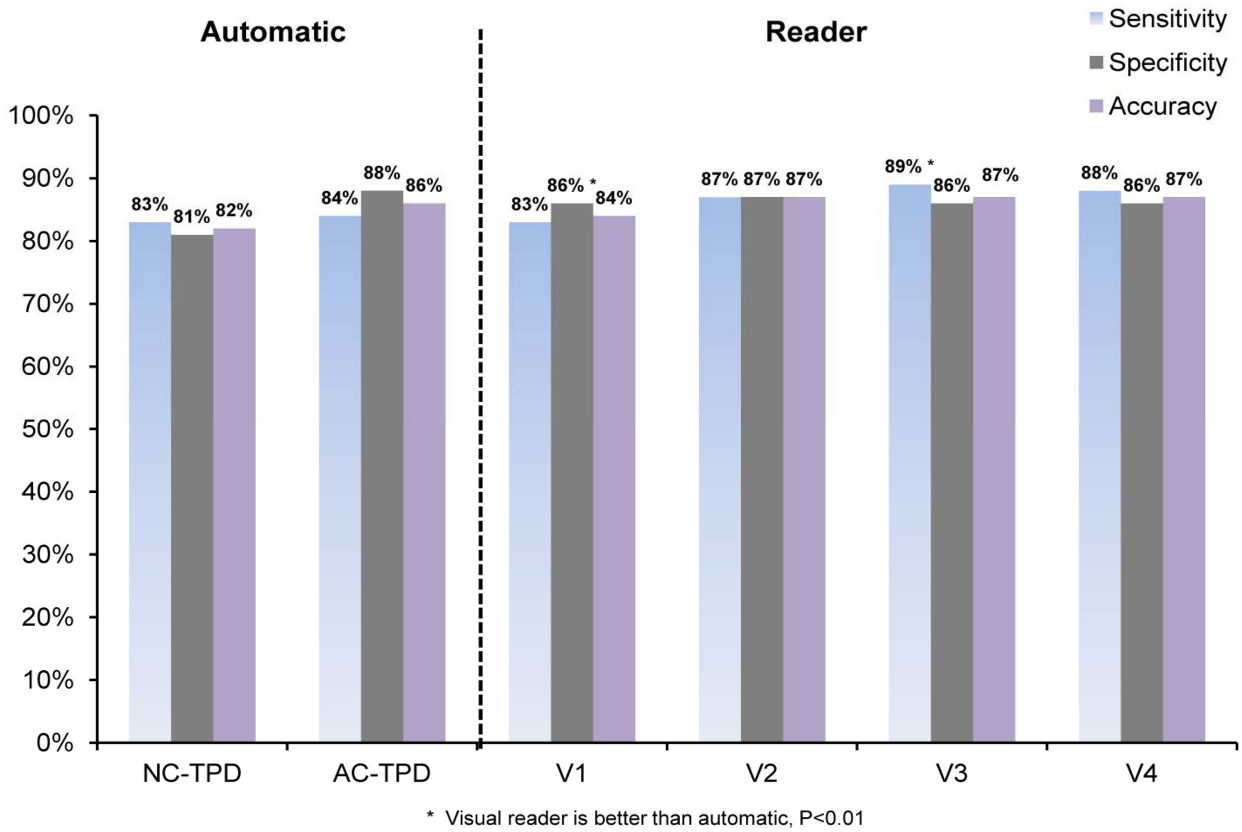

Fig. 3 Automatic analysis without (NC) and with attenuation correction (AC) versus 4 steps of visual analysis in 995 patients by an experienced reader (V1: no attenuation correction, V2: attenuation correction, V3: visual AC analysis with the computer results available, V4: visual AC with computer results and clinical information available). *Visual better than automatic ($P < 0.05$).

In addition to disease detection, automatic analysis also has the potential to provide probability of death or heart attacks within a given period of time. Previously, a number of studies have demonstrated this concept based on the clinical visual scoring rather than on quantitative measures [23-29]. However, quantitative image features and clinical variables can be easily incorporated by computer algorithms into comprehensive risk scores [23]. Prediction of cardiac death from automatically derived image features has also been directly compared with visual analysis in our recent study [30]. The automatically derived stress TPD and expert visual analysis had similar prognostic performance, based on the Receiver Operator Characteristics (ROC) analysis.

C. Towards fully unsupervised left ventricular segmentation

Can fully automated analysis of these images be performed with no physicians or technologists involved? We aimed to assess the possibility of image perfusion quantification with limited visual verification used only in cases, where the automated QC flags as described above indicated contour failure. We have analyzed 651 consecutive Tc-99m sestamibi rest/stress perfusion studies consisting of rest/stress scans in four stages: without any visual inspection (pass 1), with visual inspection of contours only when LV shape errors were indicated (pass 2), with visual inspection of contours only when LV shape and valve plane errors were indicated (pass 3), and with inspection of all contours (pass 4). Perfusion parameters (total perfusion deficit – TPD and quantitative summed scores) and ejection fraction (EF) for all passes were automatically derived. We noted that there were small but still significant differences in quantitative perfusion between pass 1 (no visual inspection) and pass 4 (visual inspection for all LV contours) ($P < 0.006$) by the ROC analysis (Figure 4). We had similar findings for EF, where significant differences were noted between pass 1 and pass 4. However, in pass 3, when only 26% static stress, 31% in static rest, and < 16% of the gated stress and rest images were visually inspected, the accuracies of the perfusion parameters were similar to pass 4 (all contours examined) and the changes in the EFs were not significant ($P > 0.05$). This work illustrates that it is possible to dramatically reduce the percentage of cases where visual inspection is required, without detrimental effect on diagnostic accuracy. Consequently, quantitative analysis can be performed in a more objective and cost-effective manner. However, further work is still needed to be able to generate reliable quantitative results with fully unsupervised processing.

D. Machine learning techniques for integration of multiple parameters

When visual observers derive their final diagnosis, they usually integrate several imaging features, as well as associated clinical information such as patient response to exercise as well as symptoms. Additionally, visual observers typically integrate information from multiple image datasets, which include functional and perfusion information. For example it has been shown that the combination of functional assessment obtained from post-stress data and relative perfusion analysis may improve disease detection [31]. Multiple (and sometimes conflicting) imaging features obtained by image processing and additional clinical information such as patient age and history of disease could also potentially be combined in a fully automated fashion to gain an overall improvement in diagnostic accuracy in detecting disease– just as it is now mentally integrated by the physicians.

Recently we have investigated the possibility of combining multiple imaging features to improve the overall accuracy of myocardial perfusion SPECT using machine learning techniques. In one study, we have shown that integration of several quantitative perfusion and functional variables (describing pumping function of the heart) by a support vector machines (SVM) algorithm, a computer method for machine learning, significantly improved the diagnostic accuracy [32]. SVM is a classifier, where a set of input data with several features are used to assign objects to multiple categories [33]. It uses the concept of margin maximization (distances between hyper-surfaces defined in multi-dimensional variable space) to discriminate between two categories. The SVM using second order polynomial fitting was trained using a group of 125 pts (50 normal and 75 abnormal cases). Patients in the validation dataset (N = 832) were categorized based on probability estimates, with disease defined as (probability estimate > 0.50). In addition, the diagnostic accuracy of SVM was compared to visual segmental scoring by two experienced physicians. SVM was provided with several input variables including total perfusion deficit, stress rest perfusion changes, and ejection fraction changes, all of which were computed automatically by image processing software. The diagnostic accuracy (85%) and ROC area-under-the-curve (ROC-AUC) (0.92) of the SVM method was significantly better than the accuracy (81%) and ROC-AUC (0.90) for the best individual computer variables. These results show that machine learning approach such as SVM allows improvement of diagnostic accuracy by computational integration of several myocardial perfusion imaging variables.

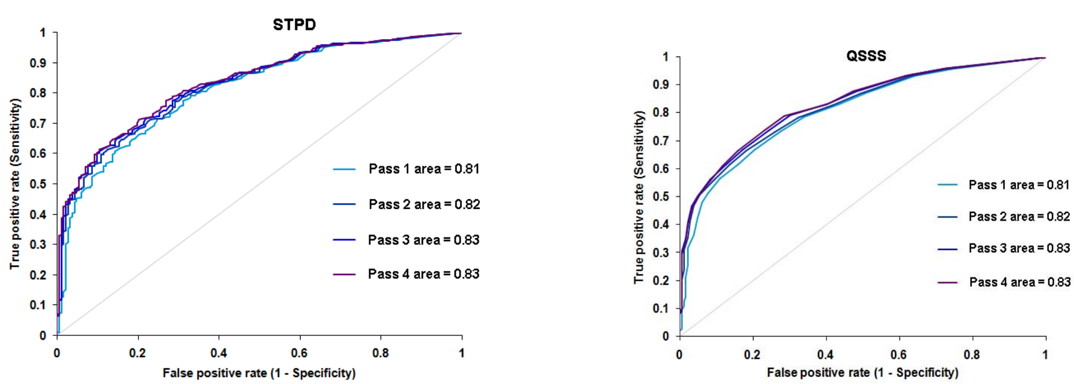

Fig. 4 ROC curves for detection of CAD by quantitative perfusion measures: Stress TPD STPD (left) Quantitative Summed Segmental Score (QSSS) (right), generated in each pass (Pass1-fully unsupervised analysis, Pass2 –supervised only if shape flag abnormal, Pass 3-supervised when shape or valve plane flag abnormal, Pass4 –fully supervised.

In a preliminary study, we have also used Waikato Environment for Knowledge Analysis (WEKA)[34] machine learning environment to see if integration of larger number of imaging features as well as clinical information about the patient could further enhance the accuracy of the final diagnosis [35]. We have analyzed 997 rest/stress 99m-technetium gated perfusion studies. In total 20 clinical, visual, and image parameters were considered. WEKA models were built with multiple different classifiers: including multivariate linear regression, artificial neural network (ANN), radial basis function networks (RBF net), J48 tree, Random Forest, classification and regression trees (CART), and Bagging. The sensitivities, specificities, accuracies, and ROC-AUC are shown in Table 1. Linear regression and backdrop ANN provided the best results based on 10-fold cross validation with an overall higher performance (accuracy, specificity, ROC-AUC) when compared to the standard analysis by Total Perfusion Deficit. This study illustrates that machine learning methods are promising tools for computational integration of several clinical and imaging features from myocardial perfusion studies.

Table 1

Comparison of various machine learning methods applied to detection of disease from myocardial perfusion images

Classifier	Sensitivity %	Specificity %	Accuracy %	ROC – AUC
Regression	81	92	87	0.939
ANN	87	88	88	0.935
RBF net	76	91	84	0.896
J48 (tree)	83	86	85	0.851
Random Forest	81	87	84	0.910
CART	83	87	85	0.880
Bagging	85	88	86	0.924
TPD	84	85	85	0.918

In addition to the application of machine learning techniques to integrate global imaging and clinical features, we have also investigated a combination of functional and perfusion values on a pixel level for each point in the myocardium in a fully automated quantitative study utilizing standard measures of perfusion and novel measures of heart motion changes between stress and rest [36]. Combined motion/thickening/perfusion imaging features were subsequently derived. We demonstrated that a pixel-by-pixel combination of motion/thickening along with perfusion results in almost 2-fold sensitivity increase for the detection of triple vessel disease pattern (abnormalities in all three main vascular territories).

The recent efforts in software developments both by machine learning methods and image processing methods show that it should be possible to emulate such integrative characteristics of visual reading with automated software.

SUMMARY

Tools for automated quantification of myocardial perfusion are available to cardiologists and researchers. These methods have demonstrated superior reproducibility with comparable diagnostic and prognostic performance, when compared with visual analysis by expert observers. Some challenges remain in the routine application of automated perfusion quantification. Left ventricular segmentation needs to be verified by a skilled operator, but new software has been developed to minimize such supervision. Multiple quantitative parameters may need to be reconciled by the expert reader for the final diagnosis; however machine learning techniques could also potentially emulate this process.

REFERENCES

[1] P. J. Slomka, *et al.*, "New Imaging Protocols for New Single Photon Emission CT Technologies," *Curr Cardiovasc Imaging Rep,* vol. 3, pp. 162-170, Jun 2010.

[2] G. Germano, *et al.*, "Automatic reorientation of three-dimensional, transaxial myocardial perfusion SPECT images," *J Nucl Med,* vol. 36, pp. 1107-14., 1995.

[3] T. L. Faber, *et al.*, "Left ventricular function and perfusion from gated SPECT perfusion images: an integrated method," *J Nucl Med,* vol. 40, pp. 650-9., 1999.

[4] P. J. Slomka, *et al.*, "Automated Quantification Of Myocardial Perfusion SPECT Using Simplified Normal Limits," *J Nucl Cardiol,* vol. 12, pp. 66-77, 2005.

[5] K. F. Van Train, *et al.*, "Quantitative same-day rest-stress technetium-99m-sestamibi SPECT: definition and validation of stress normal limits and criteria for abnormality," *J Nucl Med,* vol. 34, pp. 1494-502., 1993.

[6] C. Tobon-Gomez, *et al.*, "Automatic construction of 3D-ASM intensity models by simulating image acquisition: application to myocardial gated SPECT studies," *IEEE Transactions on Medical Imaging,* vol. 27, pp. 1655-67, Nov 2008.

[7] G. Germano, *et al.*, "Automatic quantification of ejection fraction from gated myocardial perfusion SPECT," *Journal of Nuclear Medicine,* vol. 36, pp. 2138-47, 1995.

[8] E. P. Ficaro, *et al.*, "Corridor4DM: the Michigan method for quantitative nuclear cardiology," *Journal of Nuclear Cardiology,* vol. 14, pp. 455-65, Jul 2007.

[9] E. V. Garcia, *et al.*, "The increasing role of quantification in clinical nuclear cardiology: the Emory approach," *Journal of Nuclear Cardiology,* vol. 14, pp. 420-32, Jul 2007.

[10] D. D. Watson and W. H. Smith, 2nd, "The role of quantitation in clinical nuclear cardiology: the University of Virginia approach," *J Nucl Cardiol,* vol. 14, pp. 466-82, Jul 2007.

[11] Y. H. Liu, "Quantification of nuclear cardiac images: the Yale approach," *Journal of Nuclear Cardiology,* vol. 14, pp. 483-91, Jul 2007.

[12] P. J. Slomka, *et al.*, "Automated alignment and sizing of myocardial stress and rest scans to three-dimensional normal templates using an image registration algorithm," *Journal of Nuclear Medicine,* vol. 36, pp. 1115-22, 1995.

[13] J. Declerck, *et al.*, "Automatic registration and alignment on a template of cardiac stress and rest reoriented SPECT images," *IEEE Transactions on Medical Imaging,* vol. 16, pp. 727-37, Dec 1997.

[14] Y. Xu, *et al.*, "Automated quality control for segmentation of myocardial perfusion SPECT," *J Nucl Med,* vol. 50, pp. 1418-26, Sep 2009.

[15] D. S. Berman, *et al.*, "Normal myocardial perfusion SPECT does not imply the absence of significant atherosclerosis," *Circulation,* vol. 108, pp. 562-562, Oct 28 2003.

[16] E. P. Ficaro, *et al.*, "Simultaneous Transmission/Emission Myocardial Perfusion Tomography : Diagnostic Accuracy of Attenuation-Corrected 99mTc-SestamibiSingle-Photon Emission Computed Tomography," *Circulation,* vol. 93, pp. 463-473, February 1, 1996 1996.

[17] P. J. Slomka, *et al.*, "Simplified normal limits and automated quantitative assessment for attenuation-corrected myocardial perfusion SPECT," *J Nucl Cardiol,* vol. 13, pp. 642-51, Sep 2006.

[18] C. A. Santana, *et al.*, "Quantitative 82Rb PET/CT: Development and Validation of Myocardial Perfusion Database," *J Nucl Med,* vol. 15, p. 15, Jun 15 2007.

[19] P. J. Slomka, *et al.*, "Automatic quantification of myocardial perfusion stress-rest change: a new measure of ischemia," *J Nucl Med,* vol. 45, pp. 183-91, Feb 2004.

[20] M. Prasad, *et al.*, "Improved quantification and normal limits for myocardial perfusion stress-rest change," *J Nucl Med,* vol. 51, pp. 204-9, Feb 2010.

[21] Y. Xu, *et al.*, "Automatic and visual reproducibility of perfusion and function measures for myocardial perfusion SPECT," *Journal of Nuclear Cardiology,* vol. 17, pp. 1050-7, Dec 2010.

[22] Y. X. PJ Slomka, M Fish, J Gerlach, S Dorbala, DS Berman, G Germano. , "Comparison of fully automated computer analysis and visual scoring for detection of coronary artery disease (CAD) from myocardial perfusion SPECT (MPS) in a Large Population," *J Nucl Med. ,* vol. 50(Supp 2), 2009.

[23] R. Hachamovitch, *et al.*, "A prognostic score for prediction of cardiac mortality risk after adenosine stress myocardial perfusion scintigraphy," *J Am Coll Cardiol,* vol. 45, pp. 722-9, Mar 1 2005.

[24] L. J. Shaw, *et al.*, "Prognosis by coronary computed tomographic angiography: matched comparison with myocardial perfusion single-photon emission computed tomography," *J Cardiovasc Comput Tomogr.,* vol. 2, pp. 93-101. Epub 2008 Jan 12., 2008.

[25] R. Hachamovitch, *et al.*, "Prognostic implications of myocardial perfusion single-photon emission computed tomography in the elderly," *Circulation,* vol. 120, pp. 2197-206, Dec 1 2009.

[26] R. Hachamovitch*, et al.*, "Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction," *Circulation,* vol. 97, pp. 535-43., Feb 17 1998.

[27] R. Hachamovitch*, et al.*, "Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia," *Am J Cardiol,* vol. 80, pp. 426-33, Aug 15 1997.

[28] A. M. Amanullah*, et al.*, "Incremental prognostic value of adenosine myocardial perfusion single-photon emission computed tomography in women with suspected coronary artery disease," *Am J Cardiol,* vol. 82, pp. 725-30, Sep 15 1998.

[29] A. P. Pazhenkottil*, et al.*, "Improved outcome prediction by SPECT myocardial perfusion imaging after CT attenuation correction," *J Nucl Med,* vol. 52, pp. 196-200, Feb 2011.

[30] Y. Xu*, et al.*, "Prognostic value of automated vs visual analysis for adenosine stress myocardial perfusion SPECT in patients without prior coronary artery disease: A case-control study," *J Nucl Cardiol.,* vol. 18, pp. 1003-9. Epub 2011 Sep 20., 2011.

[31] L. Emmett*, et al.*, "Reversible regional wall motion abnormalities on exercise technetium-99m-gated cardiac single photon emission computed tomography predict high-grade angiographic stenoses," *J Am Coll Cardiol,* vol. 39, pp. 991-8, Mar 20 2002.

[32] R. Arsanjani*, et al.*, " Improved accuracy of myocardial perfusion SPECT (MPS) for detection of coronary artery disease (CAD) by utilizing a support vector machine (SVM) algorithm," *Journal of Nuclear Medicine,* vol. 53, p. 143, 2012.

[33] C. Cortes and V. Vapnik, "Support-Vector networks," *Machine Learning,* vol. 20, pp. 273-297, 1995.

[34] I. Witten*, et al.*, *Data Mining: Practical machine learning tools and techniques*: Elsevier, 2011.

[35] R. Arsanjani*, et al.*, "Improved Accuracy of Myocardial Perfusion SPECT (MPS) for Detection of Coronary Artery Disease (CAD) by Utilizing Machine Learning Methods," *Journal of Nuclear Cardiology (in press abstract),* vol. 19, p. 827, 2012.

[36] S. Karimi-Ashtiani*, et al.*, "Development of new rest-stress motion change measure for myocardial perfusion SPECT," *J Nucl Cardiol. ,* vol. 18, pp. 748-800, 2011.