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Operator dependent variability in quantitative analysis of myocardial perfusion images

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Summary

The purpose of this study was to evaluate variability in the quantification of myocardial perfusion images obtained by a group of experienced operators using two widely used programs. The Cedars Emory quantitative analysis program (CEqual) was used to quantify the size of perfusion defects and the Cedars-Sinai quantitative gated single-photon emission tomography program was used to quantify left ventricular function. Five patients with reversible apical defects, five with fixed apical defects and three patients with normal perfusion were selected. Eight experienced medical laboratory technologists processed the studies from raw projection data. The manual steps consisted of defining two alignment axes parallel to the long axis of the left ventricle, and for the CEqual program selecting apex and base in the short axis slices in the rest and stress studies. Wide variability between the operators in the quantification of reversibility could be seen in all three vascular territories. A range >10% was found in at least one vascular territory for nine of the 13 patients. The differences in left ventricular ejection fraction (LVEF) between operators were <5% for all 13 patients. The large variability in the quantification of reversible apical perfusion defects may influence the clinical interpretation and cause false conclusions. In contrast, inter-operator variability for the quantification of the LVEF was low.

Introduction

Myocardial perfusion single-photon emission tomography (SPECT) is a well-established clinical procedure for the diagnosis and evaluation of patients with suspected or known coronary artery disease. The visual interpretation of myocardial perfusion SPECT images can be very difficult, and tools for quantification of the images have therefore been developed to assist physicians. The use of quantitative analysis can improve both the reliability and reproducibility of interpretations (Garcia *et al.*, 1990a; Van Train *et al.*, 1993; Germano *et al.*, 1995; Kang *et al.*, 1997; Choi *et al.*, 1998; Sharir *et al.*, 1999; Soman *et al.*, 1999). It is, however, important that the quantitative analysis should have a high degree of accuracy and reproducibility.

Quantitative analysis of the myocardial perfusion SPECT images is usually performed by a medical technologist (MLT). The processing from raw images to the final result is to a great extent an automated process, but some manual steps remain which can cause variability between operators (Garcia *et al.*, 1990b; DePuey, 1994; Cullom *et al.*, 1998; Germano, 2001). The critical steps in this procedure are the determination of the two alignment axes parallel to the long axis of the left ventricle for creation of short axis slices, and the selection of apical and basal slices in the rest and stress study to make an alignment of the two studies. These steps are usually relatively easy for the operator to perform in a normal-sized heart without perfusion defects, but much more demanding in patients with perfusion defects, for example in the apical region. It is, however, important that the quantification analysis should be equally reliable in patients with perfusion defects because their myocardial perfusion images are often difficult to interpret, and consequently the need for quantitative data on the part of physicians is high.

The purpose of this study was to evaluate the variability in quantifications obtained by a group of experienced MLTs using two widely used programs for analysis of myocardial perfusion images. The Cedars Emory quantitative analysis program smv(CEqual) was used to quantify the size of fixed and reversible perfusion defects, and the Cedars-Sinai quantitative gated SPECT (QGS) program was used to quantify the left ventricular function.

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Methods

Patient selection

Myocardial perfusion SPECT images from 13 patients were selected for the study. Three patients with normal perfusion were selected to represent uncomplicated cases to be processed. Apical perfusion defects can cause problems in data processing, especially for determination of the alignment axes of the heart and the identification of the apex for the quantitative analysis. For this reason, 10 patients with abnormal myocardial perfusion in the apical area of the myocardium were selected, five patients with large fixed defects and five patients with reversible defects. Classification of the images as normal, fixed apical defect or reversible apical defect were based on the clinical interpretation of a physician.

Image acquisition

The rest and stress studies were performed in a 2-day 99 m Tc-tetrofosmin protocol. The dose was based on the body weight of the patients (633 MBq for patients <70 kg; 700 MBq for patients weighing 70–80 kg and 933 MBq for patients >80 kg). Eleven of the patients underwent symptom-limited exercise on a bicycle ergometer and the remaining two patients underwent pharmacological stress-provocation with dipyridamole. Acquisition began at least 60 min after the rest injection and 45–90 min after the injection at stress. Images were acquired with an ADAC/Vertex rotating dual-head SPECT camera (ADAC Laboratories, Milpitas, CA, USA) equipped with low energy, high resolution collimators. The projection data were acquired in 32 steps (80 s/step) in a 64 × 64 matrix. The patients were positioned supine on the SPECT table and monitored with a three-lead ECG. The acceptance window was opened to 40% of the predefined R-R interval. Other beats were rejected. Each R-R interval was divided into eight equal time intervals. The perfusion SPECT images were calculated from the summed gated SPECT. The data acquired were transferred from the ADAC system to be processed on an SMV (Sopha Medical Vision, BUC Cedex, France) station.

Data processing

Eight experienced MLTs working at the same department processed the 13 patient studies separately. All MLTs had worked with myocardial perfusion imaging for several years. They had all been trained to process myocardial perfusion images at the same department using the same structured manual. The studies were presented to the MLTs in random order. The processing was done in a blind fashion, i.e. the studies were presented to the MLTs without any clinical data, exercise data, or the results of processing by other MLTs. The MLTs started from raw projection data and created short axis slices by defining the components of the left ventricular long axis in a transaxial and a sagittal image plane. The alignment axes were termed azimuth and elevation, respectively.

Quantification of perfusion defects

Quantitative analysis of the myocardial perfusion SPECT images was performed using the CEqual program (Cedars Sinai Medical Center, La, CA, USA). Summed ECG-gated short axis slices were used as input. The MLTs identified apex and base in the short axis slices in the rest and stress studies, thereby aligning the slices in the two studies. Polar plot images were created from the short axis slices and perfusion abnormalities were quantified in relation to a normal database. Normal limits for a 2-day Tc 99 m Sestamibi protocoll were used, because a normal database for a 2-day Tc 99 m Tetrofosmin protocol was not available. Total reversibility expressed as percentage of the left ventricle as well as reversible perfusion defects in the three vascular territories, left anterior descendent (LAD) artery, left circumflex (LCX) artery and the right coronary artery (RCA) were studied. The definition of the territories according to the quantification program was used. The extent of each perfusion defect was calculated as percentage of the total vascular territory. For each patient and each vascular territory, eight independent measurements of reversible defects were available, i.e. one for each operator.

Quantification of left ventricular volumes

Gated short axis slices from the poststress study were used as input to the QGS program (Emory University, GA, USA). This program was used to calculate left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV). The automatic algorithm identifies the endocardial and epicardial contours for each of the eight sets of short axis slices in the cardiac cycle to calculate volume changes. The largest and the smallest left ventricular volumes correspond to the LVEDV and LVESV. The LVEF, LVEDV and LVESV for each patient were calculated as the mean of the eight measurements by the MLTs. The differences between the mean value and the eight different measurements by the MLTs were calculated.

Results

Quantification of perfusion defects

Wide variability between the operators in their quantification of reversible perfusion defects was found. The total reversibility of the left ventricle showed a range >10% in five of the patients and similar results were found in all three vascular territories (Fig. 1). The greatest variability was found in the patient group with reversible apical defects. For one patient in this group the reversibility in the LCX territory was 0, 1, 6, 16, 18, 31, 39, and 42% for the eight operators, respectively (Fig. 2). For another patient in this group the range was 0–36% in the RCA territory and 2–19% in the LAD territory. A range >10% was found in at least one territory for all five patients with reversible apical defects.

The patients with fixed apical defects according to the clinical interpretation of the myocardial perfusion study showed less variability in the quantification of reversible defects. A range

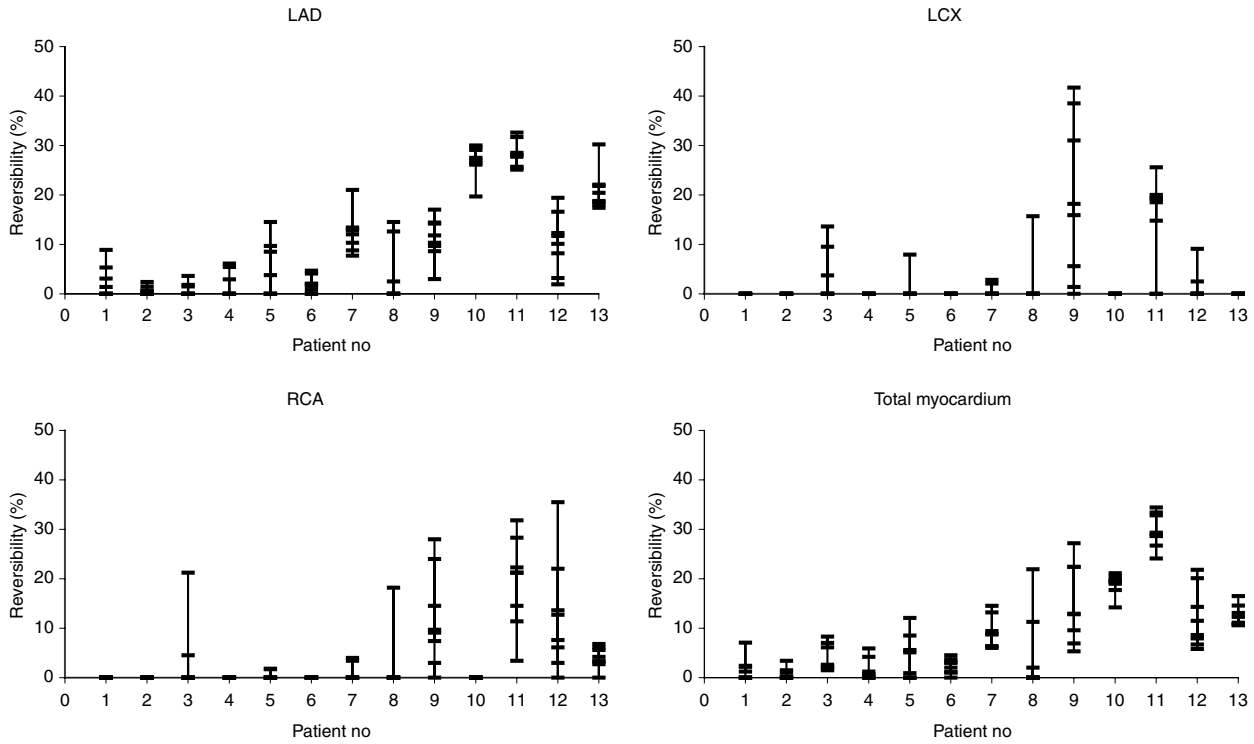

Figure 1 Quantification of % reversible defects in the three vascular territories and in the total left ventricular myocardium. Patient 1–3 with normal perfusion, patient 4–8 with fixed apical defects and patient 9–13 with reversible apical defects. Each patient has eight different measurements, one for each MLT. A single point can represent more than one measurement.

>10% was found in at least one territory for three of the five patients in this group. An example from this patient group is shown in Fig. 3. In the LAD territory, no reversible defect was found by four of the eight MLTs. The other four MLTs found reversible defects of 4, 9, 10 and 15%, respectively.

In the patients with normal perfusion, four of the nine territories (three patients and three territories each) showed no reversible defects for all eight MLTs. In two territories of one patient, a range >10% was found.

Quantification of left ventricular volumes

The mean LVEF for the 13 patients ranged from 9 to 66%. The differences in LVEF between operators were <5% for all 13 patients (Fig. 4). The mean LVEDV ranged from 66 to 380 ml. In seven patients, the difference in LVEDV between the operators was >10 ml. The largest observed difference was 16 ml. The mean LVESV ranged from 24 to 346 ml. In two patients, the difference in LVESV between the operators was >10 ml. These two patients had a mean LVESV of more than 100 ml.

Manual steps

The variability between operators in definition of alignment axis was studied in the poststress images. In six of thirteen patients the variability for one of the two axes was at least 10°. The variability in definition of the alignment axes azimuth and

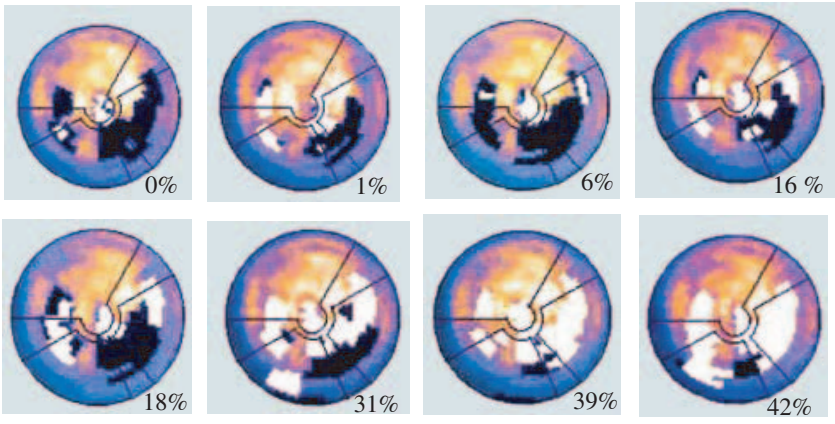

Figure 2 Eight polar plots from patient no. 9, one for each MLT. The extent of the reversible defect in the LCX territory is indicated beside each plot. Blackout areas indicate fixed defects and white areas indicate reversible defects.

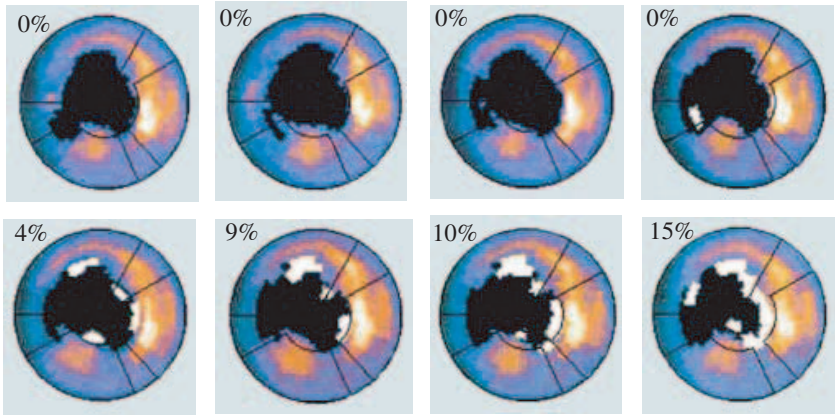

Figure 3 Polar plots from patient no. 5. The extent of the reversible defect in the LAD territory is indicated beside each plot.

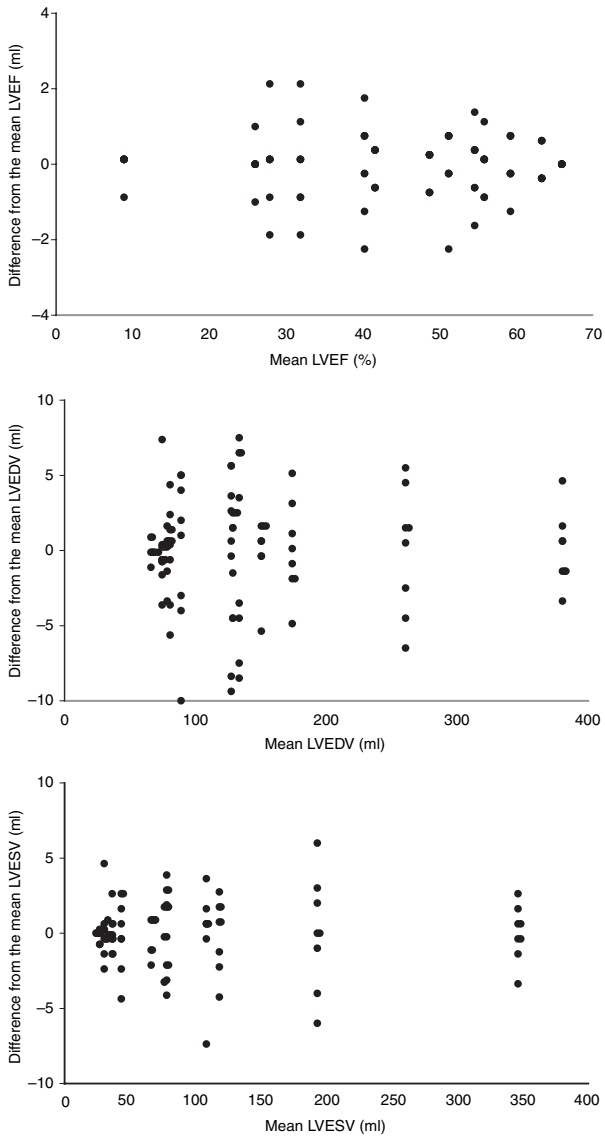

Figure 4 Difference from the mean LVEF, LVEDV and LVESV for each operator in relation to the corresponding mean value. Each point can represent more than one observation.

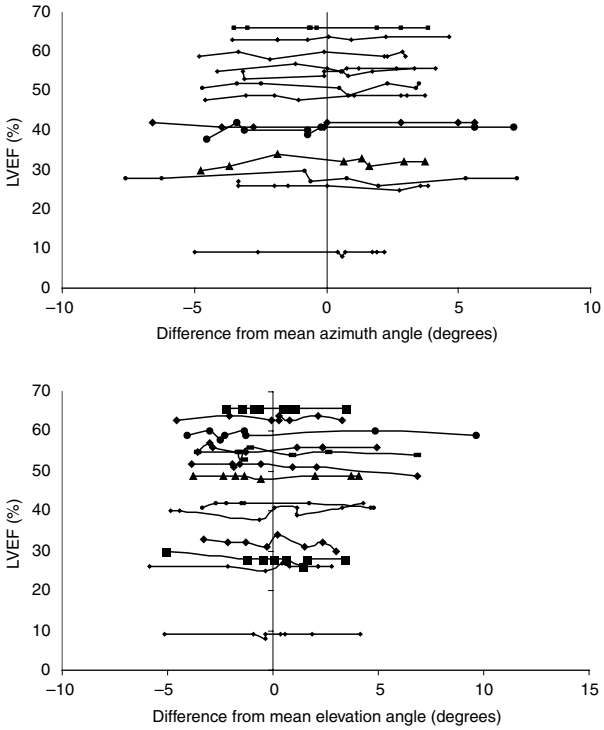

Figure 5 LEVF values obtained from each of the eight operators, related to the difference from mean azimuth and elevation angle (degree). Each line represents LVEF measurements for one patient.

elevation between the operators had no notable effect on the LVEF results (Fig. 5).

The number of selected short axis slices that the operators included for the quantitative analysis of perfusion defects varied. The largest variation was found in the group of patients with fixed apical defects. The number of selected slices (thickness 6·4 mm) varied by five or six slices in nine of ten studies (five rest studies and five stress studies). In the patients with normal perfusion or with reversible apical defects, this difference was three to four slices in most images.

Discussion

Main findings

This study shows a considerable variability between experienced operators in the quantification of reversible perfusion defects. The processing included manual steps such as the definition of two alignment axes parallel to the long axis of the left ventricle and the identification of apex and base in the short axis slices of the rest and stress studies. The variation between the operators in these manual steps caused differences in the extent of reversible defects from 0 to over 40%. The largest variability was seen in the group of patients with apical defects, but there was also variability in the patients with normal myocardial perfusion. It is known that operator interference in the processing of myocardial perfusion SPECT could be a source of this variability, but it is important to evaluate the extent to which the variability affects the final result. Previous studies have demonstrated that quantitative analysis of perfusion defects has a high degree of accuracy for detection and localization of coronary artery disease and correlates well with expert visual analysis (Garcia *et al.*, 1990a; Van Train *et al.*, 1993; Kang *et al.*, 1997). To our knowledge, this is the first study in which variability between operators in the quantitative analysis of reversible defects by CEqual software has been evaluated.

The reproducibility of ventricular volumes and LVEF between different operators was very high, even in patients with large apical defects and low LVEF. The processing included manually defined alignment axes by the operators, and although variability in the axis definitions was observed, this did not have a major influence on the ventricular volumes and LVEF. We found a very low variability between operators in LVEF measurements. This corresponds well with the results of Bavelaar-Croon *et al.* (2001) who showed that the LVEF variability was within ±2%, whereas Johnson *et al.* (1997) found a serial reproducibility of ±5·2 %. Fredericks *et al.* (1999) investigated how changes in the short axis orientation of 5° and 10° from the optimal angle could affect the LVEF result. They found that in three of 20 patients, the variation in LVEF was >5%, but these patients also had a normal LVEF.

Clinical implications

Physicians interpreting myocardial perfusion images should take the appreciable inter-operator variability in quantification of reversible perfusion defects into consideration. This variability is more pronounced for cases with apical defects and these are also important to interpret correctly and the need for supporting data from quantification software is high. The large operator variability could limit the value of this type of quantification. In contrast, the small differences in ventricular volumes and LVEF even in a group of difficult cases indicate that the inter-operator variability for this type of quantification is not a clinical problem.

Study limitation

This study was designed to illustrate the possible problem of inter-observer variability in the quantification of myocardial perfusion images. We therefore selected a number of cases known to be difficult to process, namely patients with apical perfusion defects. The number of cases is limited but the results clearly show that there is a problem of wide variability in the quantification of apical perfusion defects. This variability could be less in patients with perfusion defects at other locations, but we also found a variability of more than 10% in one of the patients without perfusion defects.

The MLTs in this study were all experienced and they worked at the same department which always applied the same manual for data processing. The variability between less experienced operators and operators from different clinical sites could be expected to be even larger.

The quantification of perfusion defects was based on normal limits for a 2-day Tc 99 m Sestamibi protocol because normal limits for a 2-day Tc 99 m Tetrofosmin protocol were not available. We acknowledge that the absolute value of the quantification could be influenced by differences in the normal limits, but the inter-operator variability analysed in this study would probably not have been significantly affected.

Future perspectives

The results of this study show much less inter-operator variability for the most automated software of the two. Both software packages used the short axis slices as input and the manual steps in the creation of these images can cause variability in quantification. The quantification of perfusion defects also included manual selection of apex and base, and this important step affects the reproducibility of the quantification. Therefore, development of new automatic algorithms for quantification of myocardial perfusion images would be of value. High reproducibility is of course only one important feature of completely automated software. It should also have high accuracy.

Conclusion

Wide variability between experienced operators quantifying reversible apical defects using the CEqual software was found. This type of variability was also found in patients with normal perfusion. Variability in this analysis may therefore influence the clinical interpretation and lead to false conclusions.

The reproducibility of the calculated LVEF between different operators was very high, even in patients with large apical defects and low LVEF. The variability in definition of alignment axes between the operators, even if the axes were slightly misaligned, had no major effect on LVEF.

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