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Validation of a new automated method for analysis of gated-SPECT images

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Summary

We recently presented a new method for quantification of CArdiac FUnction – denoted CAFU – as the first step in the development of an automated method for integrated interpretation of gated myocardial perfusion single photon emission computed tomography (SPECT) images. The aim of this study was to validate CAFU in the assessment of global and regional function of the left ventricle. Quantitative gated-SPECT (QGS), the most widely used software package for quantification of gated-SPECT images, was used as reference method for the measurements of ejection fraction (EF) and ventricular volumes, and visual analysis by an experienced physician was used as reference method for the measurements of regional wall motion and thickening. Two different groups of consecutive patients referred for myocardial perfusion scintigraphy were studied. Global function was evaluated in 316 patients and regional function in 49 other patients. The studies were performed using a 2-day stress/rest 99 m-Tc-sestamibi protocol. A good correlation was found between EF values from QGS and CAFU (EF CAFU $= 0{\cdot}84$ EF QGS $+ 13$, $r = 0{\cdot}94$), but CAFU values were on average 4 EF points higher than QGS values. With CAFU the segments with normal thickening according to the physician showed significantly higher thickening values (in all parts of the myocardium) compared to the segments classified as having abnormal thickening. In conclusion, this study demonstrates that CAFU can be used to quantify global and regional function in gated-SPECT images. This is an important step in our development of an automated method for integrated interpretation of gated-SPECT myocardial perfusion scintigraphy studies.

Introduction

Clinical interpretation of gated myocardial perfusion single photon emission computed tomography (SPECT) images integrates a visual evaluation of the perfusion of the left ventricle in the rest and the stress images, an assessment of the regional wall motion and thickening in the gated SPECT images, and an analysis of global function expressed as ejection fraction (EF) and left ventricular volumes. Cardiac function assessed from gated-SPECT images have shown to provide useful diagnostic and prognostic information (Go *et al.*, 2004; Travin *et al.*, 2004) and can also assist in the assessment of myocardial perfusion. Normal global and regional function of the left ventricle makes it, for example, less likely that an apparent reduction of uptake in the inferior wall is caused by an infarction. Instead, an attenuation artifact may be the correct interpretation (Johansen *et al.*, 2004).

We recently presented a new method for quantification of cardiac function – denoted CAFU (Lomsky *et al.*, 2005) – as the first step in the development of an automated method for integrated interpretation of gated SPECT images. The innovative approach with CAFU compared to previously presented methods was the use of the active shape algorithm (Richter *et al.*, 2003). With this technique a heart shaped model was used instead of geometrical approximations such as ellipsoid or hybrid cylindric-spheric models. Quantitative measurements by CAFU includes end-diastolic and end-systolic volumes (ESV) as well as EF. We used a digital phantom to simulate gated-SPECT studies for the development and adjustment of CAFU. This approach had the advantage that the true left ventricular volumes were known, but the phantoms represented only ventricles of normal shape without any perfusion defects.

The aim of this study was to validate CAFU in the assessment of global and regional function of the left ventricle using consecutive patient studies. The most widely used software package for quantification of gated-SPECT images, QGS (Germano *et al.*, 1995), was used as reference method for the measurements of EF and ventricular volumes, and visual analysis by an experienced physician served as reference method for the analysis of regional wall motion and thickening.

Methods

Patients

Global function

All patients who during the 6 months period from 15 September 2004 to 14 March 2005, underwent a stress (exercise or adenosine)/gated rest myocardial perfusion scintigraphy at Sahlgrenska University Hospital in Gothenburg were studied. Patients with a complete set of technically sufficient images were included. Only one examination per patient was included. A total of 327 patient studies were included. Eleven studies were excluded because of CAFU failure. The final study group comprized 316 patients, 152 men and 164 women with at mean age of 62 years.

Regional function

All patients who during the period from December 2002 to January 2003, underwent a stress (exercise or adenosine)/gated rest myocardial perfusion scintigraphy at Sahlgrenska University Hospital in Gothenburg were studied. Patients with a complete set of technically sufficient images were included. Only one examination per patient was included. A total of 55 patient studies were included. Six studies were excluded because of CAFU failure. The final study group comprized 49 patients, 26 men and 23 women with at mean age of 64 years.

Gated-SPECT

The gated-SPECT studies were performed using a 2-day stress/rest 99 m Tc-sestamibi protocol. Rest acquisition began about 60 min after the injection of 600 MBq 99 m Tc-sestamibi. Images were acquired with rotating dual-head SPECT cameras equipped with low energy, high-resolution collimators. Acquisition was done with two different cameras, both using circular acquisition and a 64 × 64 matrix applying either 64 projections over 180 degrees for 40 s per projection or 68 projections over 204° for 40 s per projection. The patients were positioned supine on the SPECT table and monitored with a three-lead ECG. The acceptance window was opened to ±20% of the predefined R–R interval except for a very limited number of studies in which a wider acceptance window was used. Other beats were rejected. Each R–R interval was divided into eight equal time intervals. Gated-SPECT acquisition was performed at the same time as ungated routine SPECT acquisition. An automatic motion-correction program was applied in studies showing patient motion during acquisition (Matsumoto *et al.*, 2001).

The gated images were reconstructed using filtered back-projection (Butterworth filter fifth order, cutoff 0·52 cycles cm^{-1}) and reoriented and short-axis images were calculated. No attenuation or scatter correction was used.

QGS

The Cedar-Sinai quantitative gated-SPECT (QGS) program (Germano *et al.*, 1995) was used for comparison to CAFU. The studies from both cameras were processed with the QGS program on the same workstation (Entegra 2·5 workstation, General Electric, USA). This program automatically identifies the epi- and endocardial contours for each of the sets of short axis slices in the cardiac cycle to calculate volume changes. The largest and the smallest left ventricular volumes correspond to the end-diastolic volume (EDV) and the end-systolic volume (ESV), respectively.

Visual analysis of regional function

All studies were classified by an experienced physician as having normal or abnormal wall-motion and thickening. The readings were subjective and done by using a continuous cine loop display of gated data with evaluation of the following nine segments representing the entire left ventricle: basal and apical parts of the anterior, septal, inferior and lateral wall and an apical segment. No quantification program was applied for this analysis of the gated-SPECT images.

CAFU

The CAFU method is based on the active shape algorithm (Richter *et al.*, 2003). The search and delineation of the left ventricle in the gated-SPECT images is based on a heart shaped left ventricular model. In an iterative process, the model is adjusted to optimize the fit with the image data. The model contains 272 landmarks distributed in 17 layers from apex to base with 16 landmarks in each layer. The wall motion measure for each landmark is calculated as the distance normal to the surface of the myocardium between the position of each landmark of the model in the end-systolic and end-diastolic frames. The thickening measure for each landmark is calculated as the ratio between the count value in the end-systolic frame and the count value in the end-diastolic frame for that specific landmark. The thickening values are presented as percentages.

The LV volume is calculated using the endocardial surface and the LV valve plane. This calculation is performed in all frames and the largest volume is defined as the EDV and the smallest is defined as the ESV. The EF is calculated from these volumes. The method has been presented in detail elsewhere (Lomsky *et al.*, 2005).

Statistical analysis

In order to prevent confusion between absolute and relative EF percentages, all EF values are given as EF 'units'. The relationship between CAFU and QGS values was evaluated by correlation and linear regression analyses. Bland–Altman analysis was used as a means of assessing systematic differences between the two methods. The difference among the EF results was shown in absolute EF units, not by percentages of EFs.

The Wilcoxon matched pairs signed rank sum test was used to analyse for differences in regional wall motion and thickening as judged by CAFU versus visual analysis by the experienced physician.

For all tests, $P<0{\cdot}05$ (two tailed) was considered significant.

Results

Global function

The EF values estimated by QGS ranged from 15 to 89 EF points with a mean value of 60. The regression line was calculated as CAFU EF = 0·84 (95% confidence limits 0·81–0·88) QGS EF + 13 (95% confidence limits 11–16), r = 0·94). It differed significantly form the line of identity with regard to slope and intercept. The CAFU EF measurements were on average 4 points higher than the corresponding QGS measurements (median difference 3·6) with 95% limits of agreement from −4 to 14. Figure 1 shows that the largest differences between CAFU EF and QGS EF were found in cases with low EF.

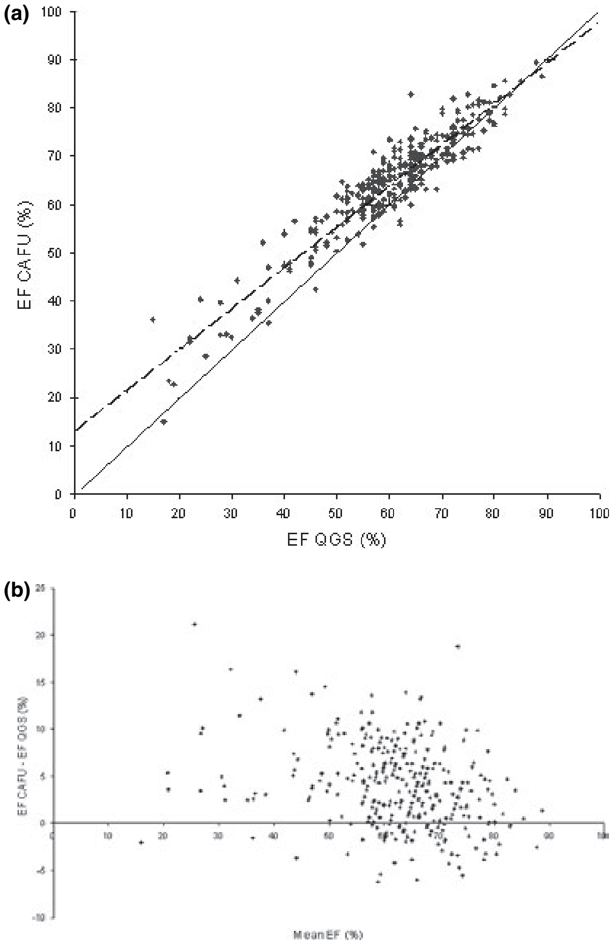

Figure 1 Correlation and regression lines between CAFU and QGS for calculating EF (a). The correlation coefficient was r = 0·94. Bland–Altman plot of the same data (b).

The EDV values estimated by QGS ranged from 39 to 354 ml with a mean value of 99 ml. The regression line was calculated as CAFU EDV = 1·04 (1·02–1·07) QGS EDV + 25 (22–27), r = 0·98). The CAFU EDV measurements were on average 29 ml higher than the corresponding QGS measurements (median difference 28 ml) with 95% limits of agreement from 12 to 55 ml. Figure 2a displays the close correlation with the slope of the regression line close to that of the identity line but with an apparent systematic positive difference. However, the Bland–Altman plot (Fig. 2b) reveals that the differences were larger with larger volumes.

The ESV values estimated by QGS ranged from 5 to 292 ml with a mean value of 44. The regression line was calculated as CAFU ESV = 0·98 (0·96–1·00) QGS ESV + 7 (5·4–7·8), r = 0·98. The CAFU ESV measurements were on average 6 ml higher than the corresponding QGS measurements (median difference 6 ml) with 95% limits of agreement from −8 to 21 ml. The findings for ESV were similar to those of EDV but the systematic differences between CAFU and QGS were smaller (Fig. 3).

Regional function

In seven of nine myocardial regions (not the infero-apical and septal-apical ones), the segments classified by the experienced physician as having normal wall motion showed significantly higher wall motion values as judged by CAFU than the segments classified as having abnormal wall motion (Table 1). The largest motion values for the segments classified as normal were found in the two lateral segments (median 6·8 and 5·9 mm in the basal and apical part, respectively) while the two septal segments showed the least motion (median 3·4 and 3·2 mm in the basal and apical parts, respectively).

In all nine myocardial regions, the segments classified by the experienced physician as having normal thickening showed significantly higher thickening values as judged by CAFU than the segments classified as having abnormal thickening (Table 2). For the segments classified as normal the basal segments showed lower thickening values compared to the apical in all four parts of the myocardium.

Discussion

Main findings

This study demonstrates that CAFU can be used to quantify global and regional function in gated-SPECT images. CAFU measurements of EF, EDV and ESV correlates well with the corresponding measurements calculated by QGS and CAFU quantifications of regional wall motion and thickening agree with the visual analysis of an experienced physician. This is an important step in our development of an automated method for integrated interpretation of gated-SPECT images.

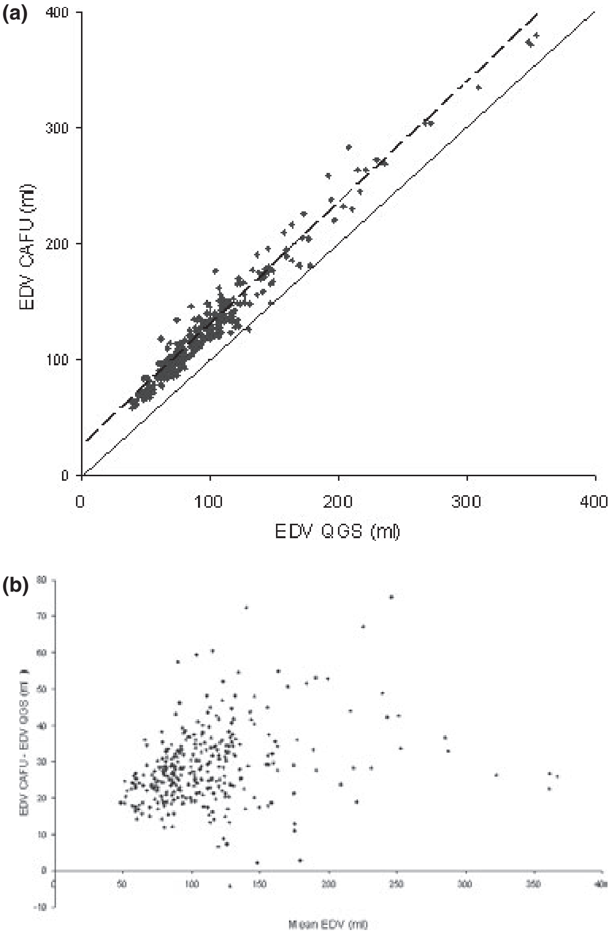

Figure 2 Correlation and regression lines between CAFU and QGS for calculating EDV (a). The correlation coefficient was r = 0·98. Bland–Altman plot of the same data (b).

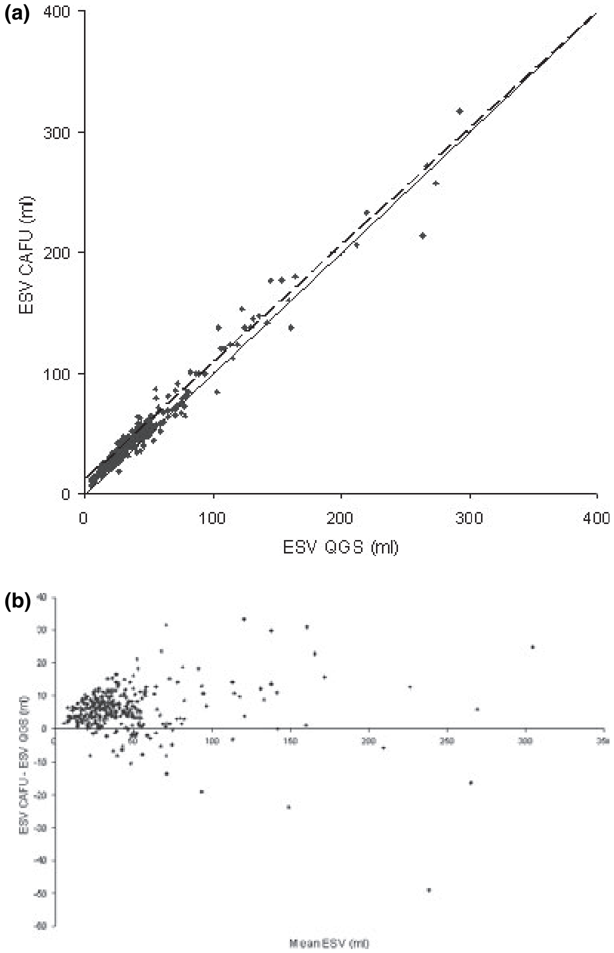

Figure 3 Correlation and regression lines between CAFU and QGS for calculating ESV (a). The correlation coefficient was r = 0·98. Bland–Altman plot of the same data (b).

The results show a good correlation between EF, EDV and ESV values calculated by QGS and CAFU, but the CAFU values were on average 4% higher in EF, 29 ml higher in EDV and 6 ml higher in ESV compared to QGS. Similar findings have been presented previously in comparisons between different software packages for quantification of gated-SPECT. Nakajima *et al.* (2001) compared the four software packages QGS, Emory Cardiac Toolbox (ECTb), 4D-MSPECT and pFAST and they found good correlations between QGS, ECTb and 4D-MSPECT for EF (r = 0·91–0·95). The corresponding correlation coefficients for pFAST compared with the three other methods were lower (r = 0·80–0·89). The correlations between EDV values from QGS, ECTb and 4D-MSPECT were also very good (r = 0·96–0·98), while the corresponding correlation coefficients for pFAST compared with the other methods were lower (r = 0·89–0·94). Although, they found good correlations between the software packages they also found different characteristics of the packages. For example, they found a significant underestimation of volumes by QGS and 4D-MSPECT and an overestimation by pFAST for smaller hearts compared to a mathematic phantom.

Lum & Coel (2003) presented also high correlation coefficients for EF (r = 0·91–0·93) and very high correlation coefficients for EDV (r = 0·98–0·99) when comparing results between QGS, ECTb and 4D-MSPECT. Schaefer *et al.* (2005) found rather high correlation coefficients for EF when comparing results between QGS, ECTb and 4D-MSPECT (0·88–0·92). Bland–Altman limits for EF when comparing QGS with ECTb and 4D-MSPECT were −22–3 and −16–4 ml, respectively, and for ECTb versus 4D-MSPECT −18–10 ml. Correlation coefficients for EDV and ESV when comparing results between QGS, ECTb and 4D-MSPECT were also high (r = 0·95–0·97). Bland–Altman limits for EDV when comparing QGS with ECTb and 4D-MSPECT were −35–14 and −32–19 ml, respectively, and for ECTb versus 4D-MSPECT −27–20 ml. Bland–Altman limits for ESV, when comparing QGS with ECTb and 4D-MSPECT were −15–29 and −16–24 ml, respectively, and for ECTb versus 4D-MSPECT −16–22 ml. The results of our comparison between CAFU and QGS are thus in the same range as previously published results comparing QGS, ECTb, 4D-MSPECT and pFAST.

Table 1 Regional wall motion (in mm) in segments visually classified as normal or abnormal.

	Normal		Abnormal		
Segment	***n***	**Median range**	***n***	**Median range**	***P*-value**
Antero-basal	41	5·4 −2·8–8·4	8	3·7 −3·2–5·9	P = 0·004
Antero-apical	40	4·0 −3·4–7·7	9	1·1 −2·7–5·4	P<0·001
Septal-basal	37	3·4 0·4–8·4	12	1·7 −2·3–7·3	P = 0·048
Septal-apical	35	3·2 0·1–8·6	14	3·5 −4·1–4·7	P = 0·24
Infero-basal	41	4·4 0·8–18·6	8	3·0 0·0–7·5	P = 0·034
Infero-apical	42	4·4 0·3–17·5	7	3·8 −1·0–6·9	P>0·30
Latero-basal	40	6·8 −3·0–12·7	9	3·4 0·1–6·7	P<0·001
Latero-apical	40	5·9 −0·3–10·7	9	2·4 −2·2–5·5	P<0·001
Apical	36	4·0 −1·4–7·7	13	1·2 −6·7–4·4	P<0·001

Table 2 Regional wall thickening (in %) in segments visually classified as normal or abnormal.

	Normal		Abnormal		
Segment	***n***	**Median range**	***n***	**Median range**	***P*-value**
Antero-basal	41	32 −12–121	8	9 0–36	P = 0·001
Antero-apical	39	40 7–110	10	5 −17–47	P<0·001
Septal-basal	36	32 −12–104	13	20 0–69	P = 0·031
Septal-apical	39	48 16–100	10	14 −16–45	P<0·001
Infero-basal	38	42 2–95	11	10 −5–34	P<0·001
Infero-apical	39	43 15–95	10	8 0–36	P<0·001
Latero-basal	43	36 −6–102	6	14 0–27	P = 0·003
Latero-apical	46	41 6–98	3	11 0–17	P = 0·004
Apical	36	36 18–114	13	14 −8–32	P<0·001

In a survey of the literature, we found eight studies comparing ventricular volumes and EF by QGS based on eight-interval gated SPECT examinations to the corresponding measurements with cardiac magnetic resonance imaging. In all studies, QGS underestimated EF. A total of 306 patients were included in the eight studies and the average underestimation by QGS was 6·5%. The underestimation of EF in the different studies were 7·4 (Schaefer *et al.*, 2005), 4 (Persson *et al.*, 2005), 6·6 (Thorley *et al.*, 2003), 7·4 (Lipke *et al.*, 2004), 8 (Faber *et al.*, 2001), 2·8 (Tadamura *et al.*, 1999a), 2·9 (Tadamura *et al.*, 1999b) and 10% (Vaduganathan *et al.*, 1999). Considering the results of these studies it seems likely that it is favorable for CAFU to calculate higher rather than lower EF values compared to QGS.

The differences between QGS and CAFU can be explained by differences in algorithms. The CAFU differ from QGS in that it is based on a heart shaped model, in which the thickness of the left ventricular wall is not set to a fixed value but estimated from the images. Furthermore, with CAFU the delineation of the mid-myocardial surface in each frame is made separately, i.e., no constraints regarding left ventricular basal motion are included. Ficaro *et al.* (2003) compared EF estimations by QGS and 4D-MSPECT and showed that a constrained basal plane can at least partly explain why QGS presents lower EF values. These methodological differences may be the cause why CAFU calculated larger EF, EDV and ESV. The present study was, however, not designed to show whether CAFU or QGS were closest to the true values.

The CAFU values of wall thickening in the group of segments classified as normal by the experienced physician were higher in apical segments than the basal segments. The normal motion values were highest in the lateral wall and lowest in the septal wall. These findings are in agreement with Sharir *et al.* (2001) who presented an evaluation of QGS. Shen *et al.* (1999) also reported greater wall thickening in the apical than the basal parts of the left ventricle.

Study limitation

The gold standards used in this study were measurements obtained from the same gated-SPECT images that were analysed by CAFU. The differences between our gold standards and the absolute truth regarding ventricular function must be recognized. However, in this phase of the development of an automated method for integrated interpretation of gated-SPECT images we felt that this type of validation was quite fair. There were two advantages with the design of this study. First, it was possible to include a relatively large patient group compared to studies using independent gold standard methods such as cardiac magnetic resonance imaging, echocardiography, contrast ventriculography, gated blood-pool imaging, or first pass radionuclide angiography. The eight studies mentioned above comparing ventricular volumes and EF by QGS and with corresponding measurements obtained by cardiac magnetic resonance imaging included a total of 306 patients, i.e., fewer patients than in our study. Second, the differences between CAFU and the gold standards depended mainly on differences in methodology since exactly the same acquisitions were analysed.

In method comparison studies of this kind, acquisitions with test and reference method are often made at different times, e.g. in succession or on separate days. Sometimes the studies are done during different conditions as is the case of Faber *et al.*

(2001). In this study, the gated-SPECT images were compared to cardiac magnetic resonance imaging at rest, the acquisitions were done within 48 h interval. The gated-SPECT acquisitions were done 15 min after a treadmill exercise test, when hemodynamics probably not were in steady state. Thus, confounders due to differences in time or other experimental divergences are quite frequent. With our design we could avoid this, and we chose QGS as reference because it is the most widely used and validated program.

Clinical implications

Perfusion data from stress and rest gated-SPECT studies were successfully used as input to artificial neural networks created for interpretation of myocardial perfusion images. We plan to use the quantitative global and regional LV function data, acquired simultaneously with the perfusion data, as input to the neural networks in order to further improve the automated interpretation of gated-SPECT perfusion images. The validation of the quantitative data presented in this study is a step in this development.

Conclusions

This study demonstrated that CAFU can be used to quantify global and regional function in gated-SPECT images. The CAFU quantifications of left ventricular function agreed well with corresponding quantitative values obtained by QGS and with the subjective judgments of an experienced physician. This method of quantification will be one cornerstone of an automated method for integrated interpretation of gated-SPECT images.

Acknowledgments

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