Is it Feasible to Use the Commercially Available Autoquantitation Software for the Evaluation of Myocardial Viability on Small-Animal Cardiac F-18 FDG PET Scan?

Kisoo Pahk · Sun Young Oh · Eugene Jeong ·
Sung Ho Lee · Sang Keun Woo · Jung Woo Yu ·
Jae Gol Choe · Gi Jeong Cheon

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Abstract

Purpose To evaluate the reliability of quantitation of myocardial viability on cardiac F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scans with three different methods of visual scoring system, autoquantitation using commercially available autoquantitation software, and infarct-size measurement using histogram-based maximum pixel threshold identification on polar-map in rat hearts.

Methods A myocardial infarct (MI) model was made by left anterior descending artery (LAD) ligation in rat hearts. Eighteen MI rats underwent cardiac FDG-PET-computed tomography (CT) twice within a 4-week interval. Myocardium was partitioned into 20 segments for the comparison, and then we quantitated non-viable myocardium on cardiac FDG PET-CT with three different methods: method A—infarct-size

measurement using histogram-based maximum pixel threshold identification on polar-map; method B—summed MI score (SMS) by a four-point visual scoring system; method C—metabolic non-viable values by commercially available autoquantitation software. Changes of non-viable myocardium on serial PET-CT scans with three different methods were calculated by the change of each parameter. Correlation and reproducibility were evaluated between the different methods. **Results** Infarct-size measurement, visual SMS, and non-viable values by autoquantitation software presented proportional relationship to each other. All the parameters of methods A, B, and C showed relatively good correlation between each other. Among them, infarct-size measurement (method A) and autoquantitation software (method C) showed the best correlation ($r=0.87$, $p<0.001$). When we evaluated the changes of non-viable myocardium on the serial FDG-PET-CT—however, autoquantitation program showed less correlation with the other methods. Visual assessment (method B) and those of infarct size (method A) showed the best correlation ($r=0.54$, $p=0.02$) for the assessment of interval changes. **Conclusions** Commercially available quantitation software could be applied to measure the myocardial viability on small animal cardiac FDG-PET-CT scan. This kind of quantitation showed good correlation with infarct size measurement by histogram-based maximum pixel threshold identification. However, this method showed the weak correlation when applied in the measuring the changes of non-viable myocardium on the serial scans, which means that the caution will be needed to evaluate the changes on the serial monitoring.

K. Pahk · S. Y. Oh · E. Jeong · J. G. Choe (✉) · G. J. Cheon
Department of Nuclear Medicine, Korea University Anam
Hospital, 126-1, Anam-Dong 5-Ga, Seongbuk-Gu,
Seoul 136-705, South Korea
e-mail: choejg@korea.ac.kr

S. H. Lee
Department of Cardiovascular Surgery, Korea University Anam
Hospital, Seoul, South Korea

S. K. Woo · J. W. Yu
Molecular Imaging Research Center, Korea Institute of
Radiological and Medical Sciences, Seoul, South Korea

G. J. Cheon (✉)
Department of Nuclear Medicine, Seoul National University
Hospital, 101 Daehak-Ro, Jongno-Gu,
Seoul 110-744, South Korea
e-mail: larrycheon@gmail.com

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Introduction

Evaluation of the myocardial viability and infarct-size measurement is important for the management of the patients with ischemic heart disease [1, 2]. Nuclear medicine imaging techniques using radiotracers of perfusion or metabolism are known to be valuable for assessing the myocardial viability [3, 4]. Among them, assessment of myocardial glucose metabolism on F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) have been reported as one of the most accurate techniques to evaluate the myocardial viability and infarct-size measurement [5–9].

When we evaluate the myocardium through these modalities using the perfusion and/or metabolic tracers, we can highly depend on observer's views and interpretations. Moreover, visual assessment requires much time for evaluating myocardium with the concerns of low accuracy and reproducibility between intra-observer and inter-observer assessments. Nowadays, there are a few commercially available automatic quantitation programs, which provide consistent measurements of myocardial perfusion and function from the myocardial images [10–12]. Using these quantitation software programs, we can compensate the disadvantages of visual assessments in the routine clinical works. Through the previous studies, commercially available autoquantitation software programs have been presented good reproducibility and correlation with visual assessments in myocardial SPECT using the perfusion tracers [13–16]. Those kinds of software programs have been known to provide good quantitative indexes of wall function as well as perfusion in cardiac SPECT study.

Monitoring the myocardial viability and/or non-viability in MI model using an in vivo system is frequently needed in order for the development of new therapeutic modalities. Small animal PET system using FDG can be used for the purpose of assessing the viability and non-viability of the MI heart [17, 18]. For the experiments with small animal cardiac models, however, there were only a few methods available to quantitate the perfusion and/or metabolism of the myocardium. As, in most cases, self-developed quantitative programs with their own algorithm have been used for the small animal models, those software programs had a limited availability for researchers [19, 20]. If we can apply a commercially available quantitation software program to the small animal myocardium, we can easily quantitate the perfusion and metabolic status of the myocardium in experiments. Nonetheless, there were few studies to evaluate the feasibility and reproducibility of commercially available autoquantitation software in cardiac PET scans using small animal models.

In this study, we evaluated the feasibility and reproducibility of the commercially available autoquantitation software programs in quantitating glucose metabolism on

cardiac FDG PET for discriminating viability and non-viability of myocardium in myocardial infarct rat (MI rat) models, based on the different methods of visual assessments and infarct-size measurement using histogram-based maximum pixel threshold identification on a polar map in rat hearts.

Materials and Methods

Myocardial Infarct Rat Modeling

Twenty Sprague–Dawley rats (male, 240–280 g) were used in this study. Myocardial infarct (MI) rat models were made by left anterior descending artery (LAD) ligation in rat hearts. All the rats were anesthetized by 2 % isoflurane while breathing 100 % oxygen with a rodent respirator for the induction of MI disease during the operation. The chest was opened to expose the heart and the left coronary artery (LCA) was permanently ligated on a heating pad. ^{18}F -FDG PET imaging was performed 3 days (first PET) and 4 weeks (second PET) after the induction of MI. Each rat model underwent a preprocedural non-fasting condition provided with enough food and warm environment. All animal studies were performed in accordance with the guidelines for the care and use of laboratory animals at our university with the approval of the animal protection committee.

PET Scans

The PET images were acquired by small animal PET scanner (Inveon; Siemens Preclinical Solutions, Knoxville, TN). PET imaging was performed at 60 min after the administration of 30 MBq of ^{18}F -FDG via tail vein injection. The PET scanner, which has lutetium oxyorthosilicate (LSO) scintillation crystals, was used as a small animal PET scanner and acquired three spans and 31 ring differences through settings of 350–650 keV as an energy window. The acquired list mode data were reconstructed by the ordered subset expectation maximization 2D (OSEM 2D) algorithm with four iterations after being converted into sinogram by the Fourier Rebinning (FORE) method using trigger signal. The PET cardiac images of rats were implemented to adjust the pixel size similarly to the size of actual patient's heart images by multiplying with the scaling factor. Inveon PET images of the cardiac area were converted into DICOM format, which can be read by other image processing software, following rotation and cropping actions. The cardiac area PET image was reoriented to short-axis, horizontal long-axis (HLA) and vertical long-axis (VLA) images and generated as a polar map by the QPS software (Cedars QPS 2008; Cedars-Sinai Medical Center, Los Angeles, CA, USA) which can automatically set the myocardial area (Fig. 1a–c).

Fig. 1 F-18 FDG cardiac PET images in MI rat models. Truncal PET images were acquired at 60 min after the administration of 30 MBq of F-18 FDG. **a,b** PET images were reoriented to short-axis, horizontal long-axis (HLA), and vertical long-axis (VLA) views. **c** Polar map of rat heart was generated using the QGS software

Image Analysis

Myocardium was partitioned into 20 segments, as used in the autoquantitation software program. And then, we quantitated non-viable myocardium on cardiac FDG PET-CT with three different methods: (1) histogram-based maximum pixel threshold identification on a polar-map; (2) visual assessment; (3) autoquantitation using a commercially available software program. Correlation of the metabolic parameters and reproducibility were evaluated between the different methods. We also evaluated the interval changes of non-viability of myocardium on serial PET-CT scans with three different methods by calculating the changes of each metabolic parameter.

Infarct-Size Measurement (Method A)

We performed infarct-size measurement using histogram-based maximum pixel threshold identification on a polar map of rat hearts. This method has been well known as the absolute threshold method [21, 22]. MI size was defined as the percentage ratio of the area that was under the threshold value

to the entire polar map area. In previous studies, various absolute threshold values had been proposed (50–72 %) [21, 22]. Higuchi et al. [23] and Thomas et al. [21] reported that decreased correlation coefficient was observed when took much lower threshold value in rodent model compared with the human study. In the study of Woo et al. [24], threshold value of 40 % showed the best correlation coefficient in small animal myocardial infarction PET imaging. We set a pre-defined threshold value as 40 %. Then, we calculated the infarct size by using the formula: below the threshold area/total polar map area $\times$ 100 %. We used an open-source image processing program (<http://rsbweb.nih.gov/ij>) to accomplish the infarct-size measurement [25].

Visual Assessment (Method B)

Two experienced nuclear medicine physicians (K.P. and G.J.C.) performed the visual assessments. We used a four-point visual scoring system (0, normal; 1, mildly decreased; 2, moderately decreased; 3, defective) to assess 20 segments of myocardium each (Fig. 2 and Table 1) [16]. Then, we

Fig. 2 Twenty-segment model of the left ventricle

defined summed MI score (SMS) by summation of each segment score to compare each rat. We assumed an infarct segment if scores of more than 2 in each segment. Inter-observer reproducibility was assessed by two examiners and intra-observer reproducibility was also evaluated. We used average values from both SMSs from two examiners in each segment to evaluate the changes of non-viable myocardium.

Autoquantitation Using Commercially Available Software Program (Method C)

PET-CT image was converted to DICOM format and reconstructed to short-axis, horizontal long-axis (HLA), vertical

long-axis (VLA) images and transformed to polar map images with the aid of commercially available autoquantitation software (Cedars QPS 2008; Cedars-Sinai Medical Center, Los Angeles, CA). In each polar maps, software set the maximal pixel count as 100 % and minimal as 0 %. Then all segments were calculated as numerical values. In each segment of rat models, the metabolic non-viable values were calculated by using the formula: $100 - \text{pixel count}$. Then we took average values from summation of all 20 non-viable values of each segment as representative non-viable values of each rat model. In previous studies, Baer et al. [26] and Kitsiou et al. [27] suggested non-viable segments with count of less than 50 % or 65 %, respectively. We assumed the non-viable segments as counting less than 60 % in polar map.

Statistical Analysis

We used Bland-Altman plot to compare measured infarct-size in serial scans by Medcalc software (Medcalc Software, Mariakerke, Belgium) [28]. Agreement between two examiners and reproducibility of repeated examinations in one examiner were evaluated through Cohen's kappa coefficient in visual analysis. And correlations between three methods were analyzed by Spearman's correlation coefficient. A value of $p < 0.05$ was defined as statistically significant. SPSS software (version 17.0) was used for data analysis.

Table 1 Characteristics of rat MI models in each method

Rat model	Infarct-size measurement (%)			Visual assessment (SMS)			Non-viable values by autoquantitation software		
	1st	2nd	Difference	1st	2nd	Difference	1st	2nd	Difference
1	1.4	3.5	2.1	6.5	7.5	1	20.2	19.6	-0.5
2	4.2	7.4	3.3	9.5	11.5	2	20.6	22.1	1.6
3	4.9	7.8	2.9	18.5	17.5	-1	25.6	22.7	-2.9
4	4.7	12.4	7.7	16	17.5	1.5	24	24.8	0.8
5	16.9	8.1	-8.8	31	10	-21	42	29.9	-12.1
6	9.4	9.7	0.4	17	14.5	-2.5	29.7	39.8	10.1
7	3.9	3.7	-0.2	12	11	-1	22.5	28.2	5.7
8	4.1	1.4	-2.7	8.5	5	-3.5	21.4	20.7	-0.7
9	7.2	5.1	-2.2	9	12	3	23.7	29.1	5.5
10	3.6	10.9	7.3	20.5	26	5.5	20.6	30.2	9.6
11	22.5	24.5	2.1	35	26	-9	49.1	41	-8.1
12	2.9	5.4	2.6	21	13.5	-7.5	20.4	29.2	8.8
13	12.9	17.3	4.4	38	24	-14	33.6	45.5	11.9
14	24.4	29.1	4.7	15.5	19	3.5	38.9	47.5	8.6
15	10.4	19.9	9.5	30.5	27.5	-3	46.4	54.6	8.2
16	14.7	9.8	-4.9	24.5	25	0.5	48	31.5	-16.5
17	19.4	24.7	5.4	22	17	-5	41.6	36.1	-5.5
18	21.1	11.6	-9.5	45	27.5	-17.5	29.3	39.1	9.8

Table 2 Reproducibility of visual assessment in MI rat model

a. Inter-observer reproducibility

		Examiner 2				Total
		0	1	2	3	
Examiner 1	0	236	30	3	0	269
	1	61	161	13	3	238
	2	10	56	106	8	180
	3	0	2	4	27	33
Total		307	249	126	38	720

Kappa value=0.63

b. Intra-observer reproducibility in repeated measurements

		Examiner 1, 2nd try				Total
		0	1	2	3	
Examiner 1, 1st try	0	118	18	0	0	136
	1	25	49	24	0	98
	2	0	26	76	1	103
	3	0	0	0	23	23
Total		143	93	100	24	360

Kappa value=0.61

Results

PET Imaging Using Rat MI Model

Eighteen rats were analyzed in this study. Two rats were excluded because they died during the experiments after LAD ligation. No specific complications related to the procedures were noted on 18 rats.

Table 3 Comparison of correlation coefficients between the three different methods

	Method (1st PET image)			Method (2nd PET image)		
	A and B	A and C	B and C	A and B	A and C	B and C
<i>r</i>	0.61	0.87	0.66	0.76	0.81	0.73
<i>p</i> value	0.007	<0.001	0.003	<0.001	<0.001	0.001

Assessment of Non-Viable Myocardium

In infarct-size measurement (method A), measured mean percent infarct size of the first and second PET images were 10.5 % and 11.8 %, respectively. Standard deviations were 7.6 % and 8.1 %, respectively (Table 2 and Fig. 3a). In first PET image, eight rats presented infarct sizes of less than 5 %, two rats presented infarct sizes of 5–10 %, and eight rats presented infarct-sizes of greater than 10 %. In the second PET image, those figures were three, seven, and eight rats, respectively. Twelve rats showed increased infarct size ($4.4 \% \pm 2.7 \%$) and six rats showed decreased infarct size ($4.7 \% \pm 3.8 \%$) during first and second PET images.

In visual assessment (method B), visual scores were acquired from all segments of each rat model. Mean SMSs of the first and second images were 21.1 ± 11.0 , 17 ± 7.5 , respectively (Table 1 and Fig. 3b). Through visual assessment, the kappa value for agreement was 0.63 in inter-observer and 0.61 in intra-observer (Table 2).

Fig. 3 Quantitation of non-viable myocardium by three different methods in first and second PET-scan images. **a** Measured infarct size (%) by histogram-based maximum pixel threshold identification. **b**

Mean summed MI scores (SMS) by visual assessment. **c** Mean non-viable values by autoquantitation software

Fig. 4 Comparison of correlations between the three different methods in the first PET image (a) and second PET image (b)

Fig. 5 Comparison between visual scores and non-viable values by autoquantitation software in each segment (mean with SD)

In autoquantitation software (method C), the values of all segments were calculated in numerical values. The mean non-viable values of the first and second PET images were 31.0 ± 10.6 and 32.8 ± 10.0 , respectively (Table 1 and Fig. 3c).

Correlation Between the Three Different Methods

All the parameters of methods A, B, and C showed relatively good correlation between each other (Table 3, Fig. 4). Among them, infarct-size measurement and quantitative values of the autoquantitation software program showed the best correlation ($r=0.87$, $p<0.001$) compared with the other methods (A and B, $r=0.76$; B and C, $r=0.73$).

Non-Viable Myocardium in Segment-Based Aspect

Among the 360 segments, 123 and 76 were infarct segments by visual assessment and 92 and 87 were non-viable segments by autoquantitation software in both the first and second PET images. As illustrated in Fig. 5, the mean values of non-viable segments by autoquantitation software to each visual score

Table 4 Comparison of correlation coefficients in changes on serial FDG PET-CT between visual score and non-viable values by autoquantitation software in each segment

	Visual score			
	0	1	2	3
<i>r</i>	0.57	0.5	0.44	0.66
<i>p</i> value	<0.05	<0.05	<0.05	<0.05

Fig. 6 Comparison between measured infarct size and non-viable score by autoquantitation software (mean with SD)

were 23.8 ± 11.2 , 34.0 ± 12.2 , 46.4 ± 17.5 , and 59.4 ± 15.4 , respectively.

In interval changes between the first and second images, we evaluated the correlation coefficient between visual score and non-viable values by autoquantitation software in each segment (Table 4). Among them, segments of visual score 3 showed the best correlation ($r=0.66$, $p<0.05$) compared with the other visual scores (0, $r=0.57$; 1, $r=0.50$; 2, $r=0.44$).

Non-Viable Myocardium in Ventricle-Based Aspect

There was proportional relation between infarct size and non-viable scores by autoquantitation software. As illustrated on Fig. 6, the mean non-viable scores to infarct size were 22.2 ± 2.7 , 28.6 ± 5.5 , and 40.5 ± 8.1 , respectively.

We evaluated the changes of non-viable myocardium on the serial FDG PET scans with different three methods. In infarct-size measurement, the mean difference between the two images was -1.3 on Bland-Altman plots. As illustrated on Fig. 7a, the 95 % CIs for the difference were -11.7 and 9.1 , respectively. Standard deviation was 5.3 .

In visual assessment, the mean difference between the two images was 3.8 , and on Bland-Altman plots and 95 % CIs for

Fig. 7 Bland-Altman plots on interval changes. **a** Interval changes of infarct-size measurement. **b** Interval changes of visual assessment. **c** Interval changes of autoquantitation software

the difference were, respectively, -10.8 and 18.3 with a standard deviation of 7.4 (Fig. 7b). In autoquantitation software, the mean difference between the two images was -1.9 on Bland-Altman plots and 95 % CIs for the difference were -18.2 and 14.4 with a standard deviation of 8.3 (Fig 7c).

Table 5 Comparison of correlation coefficients in changes of non-viable myocardium on serial FDG PET-CT

	Method		
	A and B	A and C	B and C
r	0.54	0.23	0.06
p -value	0.02	0.35	0.81

Correlation Between the Three Different Methods of Interval Changes During the Test (first PET Image) and Retest (second PET Image)

Serial changes of non-viable myocardium measurement of autoquantitation software showed relatively weak correlation with other values by infarct-size measurement and visual assessment (Table 5). Among the different three methods, we found meaningful correlation of the interval changes during the test and retest between the methods of infarct-size measurement and visual assessment ($r=0.54$, $p=0.02$).

We set different cut-off values (30, 40, 50, 60, 70, 80, and 90) of viability in the autoquantitation software to assess the effect of different cut-off on correlation of interval changes of serial monitoring with infarct-size measurement. That is to say, for example, if we assumed cut-off value of 70, the values greater than or equal to 70 were regarded as 70 by the autoquantitation software. Then, we obtained the metabolic non-viable values by subtracting from 70 of all segments. However, we could not find a meaningful difference of correlation using different cut-off values between autoquantitation software and infarct-size measurement (Fig. 8).

Correlation of Non-Viable Myocardium by Autoquantitation Software Between Defect-Severity Subgroups

In the segment-based approach, we assumed a minor defect segment as having a visual score of 0 or 1, and a severe defect as having a visual score of 2 and more. Among 360 segments,

Fig. 8 Correlation coefficient between method A and C at different cut-off values

237 were mildly defective segments, and 123 were severely defective segments. Between the two groups, the mild-defect group showed better correlation with autoquantitation software ($r=0.60$, $p<0.05$) than the severe-defect group ($r=0.32$, $p<0.05$).

In the ventricle-based approach, we defined the minor-defect group as less than 10 % and the severe-defect group as 10 % or more in infarct size by measurement. Ten rats were in the minor-defect group and eight rats in the severe-defect group. Both groups presented weak correlation coefficients (minor-defect group, $r=0.26$, $p=0.41$; severe-defect group, $r=0.31$, $p=0.28$).

Correlation of Non-Viable Myocardium by Autoquantitation Software Between Subgroups of Anatomical Regions

We classified subgroups by anatomical regions of 20 segments in each rat model. Then, we compared the correlation between visual scores and non-viable values on autoquantitation software in cross-sectional image (Table 6a) and serial FDG PET scans (Table 6b) according to different subgroups. In cross-sectional image, all the anatomical regions showed good correlation except the apex region. In serial FDG scans, the anterior and lateral wall showed the best correlation with viability changes ($r=0.51$, $p<0.05$) than the other regions.

Discussion

In this study, we tried to evaluate the feasibility and reproducibility of a commercially available autoquantitation software program in evaluating viability and non-viability of myocardium on FDG-PET imaging using small-animal MI models.

Our data showed that autoquantitation software had a proportional relationship with visual assessment and infarct-size measurement (Figs. 5 and 6). The three different methods—infarct-

size measurement, visual analysis, and autoquantitation software—showed relatively good correlation with each other. Furthermore, it also presented the best correlation with infarct size measurement (method A) than visual assessment (Table 3). We also found good agreement between the two nuclear medicine physicians and good reproducibility in repeated measurement on visual analysis. That means we could get reproducible results from visual assessment without an aid of quantitation program, although we did not perform the reproducibility test for the less-experienced personnel. However, this kind of visual assessment took a lot of time and was a highly laborious job. Also, there are many concerns about the subjectivity and lack of reproducibility for the visual assessments that would take place in every test. Therefore, it may be possible to use autoquantitation software to evaluate viability and non-viability of myocardium. With this autoquantitation method, it can reduce the extra-time to analyze viability of myocardium and provide consistent measurements to researchers.

In this current study, autoquantitation software implied some limitation on evaluating the apex region of viable and non-viable myocardium on FDG PET images. In regional comparison, the apex region showed the worst correlation than the other regions using autoquantitation software and other methods in cross-sectional and serial monitoring (Table 6). This finding could be a result of algorithmic problem in autoquantitation software. It was frequently reported in a myocardial perfusion study that apical thinning with a partial volume effect can occur in cardiac perfusion imaging [23]. Furthermore, perfusion blackout in the apex may be a confounding factor in autoquantitation software [29]. That is to say, perfusion at the apex in a polar-map image is dependent on the operator's exact selection of the apex and base of the left ventricle in oblique slices. If the selection is beyond the actual region, decreased perfusion can occur in image processing [30]. Autoquantitation software also showed limitation on evaluating serial changes of viable and non-viable myocardium on FDG PET images, compared with the cross-sectional evaluation. Algorithmic limitation of autoquantitation could also affect the non-viability assessment on the serial monitoring. Operator-dependent selection of the region-of-interest (ROI), partial volume effect of the myocardium, and normalization of the maximum pixel count within the ROI rather than the absolute quantitation could affect the serial monitoring the myocardial viability.

In our data, autoquantitation software showed better correlation with other methods among the segments of mild defects rather than severe defects in both cross-sectional and serial monitoring of the non-viable myocardium. We could speculate several reasons to that kind of limitation. Firstly, in auto-quantitative process, Cedars QPS software set the maximal pixel count as 100 % and minimal as 0 % in each polar map. In other words, the presented numbers are relatively distributed values from each polar map. Due to this

Table 6 Comparison of correlation coefficients of non-viable myocardium and interval changes according to different anatomical regions

	Anatomical regions				
	Apex	Anterior	Septum	Inferior	Lateral
a. Correlation Coefficients of Non-viable Myocardium according to Different Anatomical Regions					
<i>r</i>	0.28	0.70	0.64	0.61	0.78
<i>p</i> -value	0.10	<0.05	<0.05	<0.05	<0.05
b. Correlation Coefficients of Interval Changes of Non-viable Myocardium according to Different Anatomical Regions					
<i>r</i>	0.05	0.51	0.50	0.46	0.51
<i>p</i> -value	0.78	<0.05	<0.05	<0.05	<0.05

reason, we could postulate that commercially available autoquantitation software was not yet fully suitable for the evaluation of changes in myocardial viability in serial monitoring. Secondly, we used two-dimensional (2D) polar maps in methods A and C. This 2D polar map could not fully reflect the true defects in the myocardium, because of the partial volume effect of nontransmural defects [31]. Furthermore, when we transformed the 3D heart into a 2D model, spatial distortions and loss of data occurred during the process [32–35]. Consequently, these reasons made autoquantitation software difficult to apply in serial monitoring of myocardium. In the study of Itti et al. [36], they insisted that voxel-based 3D technique presented more reliable results, compared with 2-dimensional polar maps in quantitation of serial changes in myocardium.

In conclusion, it was possible to use commercially available quantitation software to measure the viability and non-viability of myocardium on small animal cardiac FDG PET scans, cross-sectionally. Autoquantitation software could reduce workload of the time-consuming and laborious quantitation process. However, caution should be needed to evaluate the apex regions and changes of myocardial viability on the serial FDG PET monitoring when using the commercially available autoquantitation software programs.

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