Left Ventricular Ejection Fraction Analysis in an Equilibrium Cardiac Gated Blood Pool Study: Is the Same Software Package Really Needed to Follow Up the Same Patient?

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ABSTRACT

Objective: To compare the left ventricular ejection fraction (LVEF) estimation using two commercial software packages used in our hospital and factors which may correlate to LVEF result.
Methods: LVEF results using EF analysis (GE Healthcare, Wisconsin, USA) and Syngo MI (Siemens Medical Solution USA Inc., Illinois, USA) in 120 patients were compared. The correlation and difference of LVEF analysis between software packages were evaluated using correlation coefficient and Bland-Altman analysis, respectively. Potential factors for significant difference in LVEF were identified by regression analysis.
Results: The mean LVEF estimated by two software packages were highly correlated (ICC =0.853) and statistically significant ($p<0.001$). Subgroup analysis in each individual software showed slight decrease in correlation of LVEF between software packages (ICC=0.791-0.793), but still had statistical significance ($p<0.001$). Intra- and inter-operator variability assessments showed very high correlation of LVEF obtained from both software packages with statistical significance ($p<0.001$). Factors correlated with significant difference in LVEF were end diastolic area, end systolic count, end systolic area, and background count.
Conclusion: LVEF analysis from GBP study using different software packages is highly correlated with only minimal difference, thus, it may be reasonably interchangeable during follow up without significant clinical impact. However, operators should be aware the importance of precise left ventricular and background region generation to prevent technical errors.

Keywords: LVEF, cardiac gated blood pool, software analysis

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INTRODUCTION

Myocardial function assessment is crucial in management of cancer patients undergoing chemotherapy treatment known to have a cardiotoxicity. The change in left ventricular ejection fraction (LVEF) can early detect functional abnormality long before patients begin suffering from symptomatic heart failure. In patients demonstrating significantly decreased LVEF result, further chemotherapy treatment may be postponed or even stopped. Cardiac gated blood pool study (GBP) usingTc-99m labeled red blood cell has been accepted as a standard, non-invasive technique in LVEF analysis. However, differences

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in software packages used for analysis are one important factor which may lead to variability in LVEF analysis. Results from previous studies recommended the same gamma camera and software should be used in an individual patient throughout the treatment episode to prevent LVEF variations which may result in potential technical errors. Nevertheless, this recommendation cannot be followed in some situations; for example, when equipment is replaced or when the patient is referred to another hospital. Thus, variability in LVEF estimations may be clinically significant and have impact on patient management.

The aim of this study was to compare the LVEF estimation using two commercial software packages used in our division and its clinical impact. We also evaluated reproducibility and correlation of LVEF analysis between these software packages and factors which might have correlated to the LVEF result.

MATERIALS AND METHODS

This study was approved by the Siriraj Institutional Review Board. Retrospective analytical study was done in 120 patients who underwent cardiac gated blood pool study at Division of Nuclear Medicine, Faculty of Medicine Siriraj Hospital during 1 January 2011 to 31 December 2011.The exclusion criteria included patients with age under 18 years, patients with incomplete data acquisition or analysis, patients with severe cardiac arrhythmia and patients with repeated studies. In vivo red blood cell labelling technique was used in all patients. The standard acquisition protocol for GBP study was as follows: 24 frames per cardiac cycle used for processing; matrix size 64 x 64; total count: 5 million; and LAO (best ventricular separation) position was used for LVEF analysis.

Two hundred and ninety-eight GBP studies were done during the enrollment period, and 175 follow up GBP studies were excluded. Only 120 first GBP studies were included in the study and divided into 4 subgroups by the official reported LVEF results to cover wide range in LVEF (≤50% (n=17), 51-60% (n=34), 61-70% (n=35), and >70% (n=34). Stratified randomization was done thereafter. After deleting patients' identification data, the DICOM files of GBP raw data were distributed to two operators with 10-year and 12-year experience in GBP analysis. Both operators were trained for standardization in LVEF analysis prior to conducting this study. Each GBP study was independently analyzed by each operator, two times per each software package with an interval of at least 1 week to avoid recall bias. All GBP data were analyzed using two software packages, EF analysis (GE Healthcare, Wisconsin, USA) and Syngo MI (Siemens Medical Solution USA Inc., Illinois, USA). In both software packages, ROIs of left ventricle and background were generated using automatic edge detection (Figs 1 and 2). The operator could adjust ROI using semiautomatic method if the automatic ROI generation was inappropriate.

After data processing was finished, all the following data was recorded including end diastolic count, end diastolic area, end systolic count, end systolic area, background count, background area, ratio LV counts (end diastole count : total frame count), LVEF result and method of ROI generation used.

Sample size (n=120) was calculated using nQuery advisor software (Statistical Solutions Ltd., Ireland) when correlation coefficient of mean

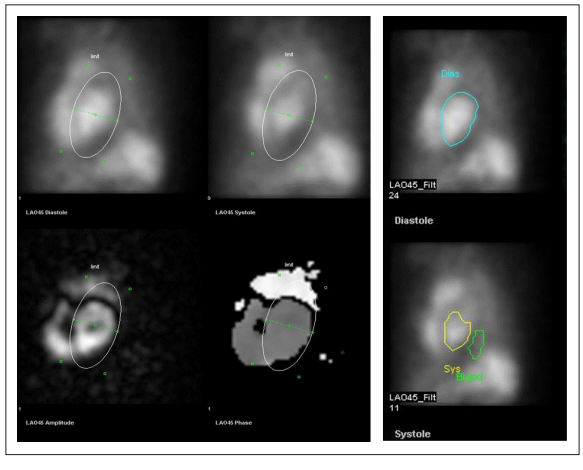

Fig 1. Method of ROIs generation by EF analysis software using automatic edge detection algorithm method. The operator put the draft ROI to cover whole region of left ventricle (left and middle column images), then the computer software automatically draws ROI (right column images) to fit left ventricle in diastole (top), systole and background ROI (bottom).

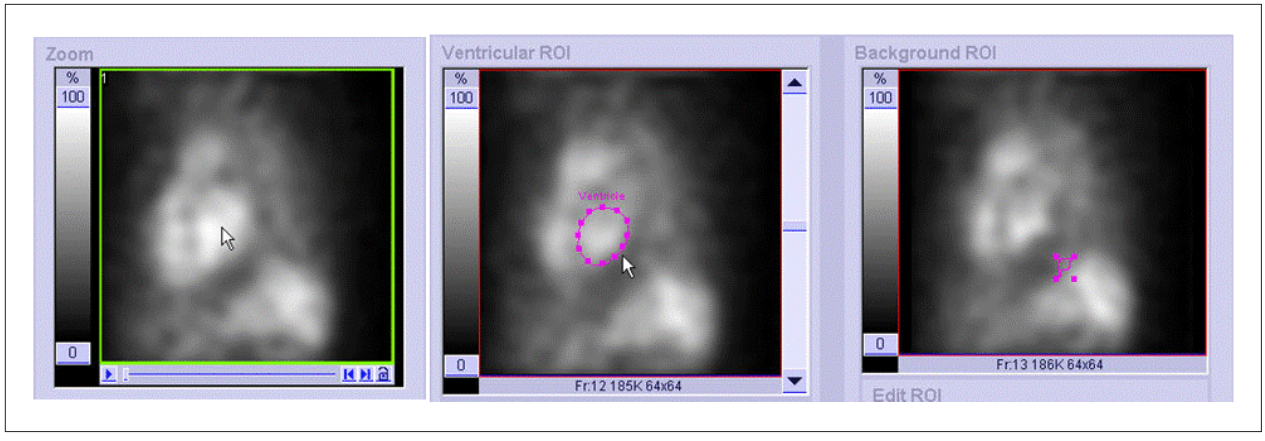

Fig 2. Method of ROIs generation by Syngo MI software using automatic edge detection algorithm method. The operator locates an arrow at the center of left ventricle (left image), then computer software automatically draws ROI to fit left ventricle (middle image) and background ROI (right image).

LVEF results from different software packages in previous reports were 0.95-0.98,[9-10] statistical significance (p value) was 0.05 and correlation coefficient was 0.85 (minimum accepted correlation coefficient was 0.80).

Statistical analysis

All data were analyzed using statistical software package PASW statistics version 18 for Windows (SPSS Inc., Chicago, Illinois, USA) and STATA (StataCorp LP, Texas, USA). The LVEF results between two software packages were compared using Bland-Altman plot. Correlation of LVEF results were evaluated using Pearson correlation coefficient. Intra-operator agreement and inter-operator agreement were evaluated using intraclass correlation coefficient (ICC). Factors which were considered to have effect on different LVEF results were evaluated using multivariate regression analysis.

RESULTS

There were 295 patients who under went GBP study during 1 January 2011 to 31 December 2011. Twenty-eight patients who under went multiple GBP studies during this period were excluded. Then 120 patients (LVEF 20%-85%) were randomized and included in the study. All these patients had GBP data acquisition as previously described, with total count of 5,000,000, mean frame time was 33.47 seconds (SD 5.57, range 24-52) and mean accepted beats was 676.74 (SD 208.551, range 341-1,479).

In terms of ROI generation method, operator 1 used automatic region generation in all patients (100%) using EF analysis software and in 118 patients (98.3%) using Syngo MI software. Operator 2 also used automatic method in all patients (100%) using EF analysis software and in 116 patients (96.7%) using Syngo MI software. The rest of patients needed manual adjustment of ROI to correctly fit left ventricle, or to reposition background ROI which included blood pool structures.

Correlation of LVEF results between software packages

The mean LVEF result using EF analysis software was 62.07% (SD 10.867) and median was 63% (range 20%-82%), while mean LVEF result using Syngo MI software was 63.83% (SD 11.030) and median was 65.4% (range 26%-85%). High agreement of LVEF results between these software packages was shown (ICC = 0.853, 95% CI 0.795-0.895), which was statistically significant ($p<0.001$). The correlation of mean LVEF results between both software packages has been shown in Fig 3.

Slightly lower agreement of mean LVEF results between software packages analyzed by operator 1 (ICC = 0.791, 95% CI 0.713, 0.850) and operator 2 (ICC =0.793, 95% CI 0.716, 0.851) were observed, both of which showed substantial agreement, but still had statistical significance ($p<0.001$).

Intra-operator variability

In operator 1, there was very high agreement between LVEF results within each software package (ICC = 0.976, 95% CI = 0.966-0.983) and 0.931 (95%CI = 0.903-0.951) using EF analysis and Syngo MI software, respectively. In operator 2, very high agreement between LVEF results was also observed within each software package. The ICC in operator 2 was 0.982 (95% CI 0.974 -0.987) using EF analysis and slightly decreased using Syngo MI (ICC =0.880, 95% = 0.832-0.915) (Table 1). Moreover, the correlation of LVEF results analysed by the same operator using the different software package were highly correlated. (Fig 4)

Inter-operator variability

Using EF analysis software, there was very high agreement of LVEF results between both operators (ICC = 0.964, 95% CI 0.949-0.975). A slightdecrease in agreement of LVEF results between both operators using Syngo MI software was observed (ICC = 0.886, 95% CI 0.841-0.919). However, all of these were within almost perfect agreement and of statistical significance ($p<0.001$) (Table 1).

Difference in LVEF results using two software packages

The LVEF results using EF analysis software were significantly lower than that of Syngo MI software ($p = 0.007$). Mean LVEF using EF analysis software was 62.07%, which was slightly lower (mean 1.76%) as compared to that of 63.83% when using Syngo MI software (Fig 5). This significance might have resulted from data from 2 patients that was scattered far out of the -2SD line, while the majority of the patients were within the 2SD line. In these 2 patients, there were relatively low LV count ratios causing failure in automatic ROI tracking using Syngo MI software, thus, manual ROI adjustment was needed which might partly explain the discrepancy in LVEF results.

Difference in mean LVEF results between these software packages analyzed by each operator were also evaluated (Fig 6). The difference in mean LVEF from EF analysis software as com-

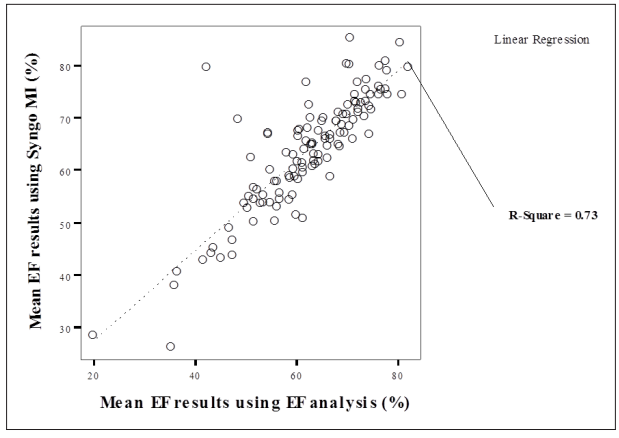

Fig 3. Correlation between mean LVEF results obtained from EF analysis software (X axis) and Syngo MI software (Y axis).

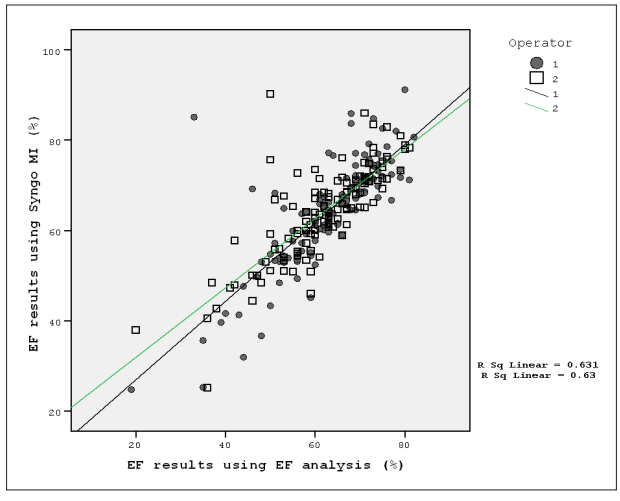

Fig 4. Scatter plot of correlation between LVEF results using different software package; EF analysis (X axis) and Syngo MI (Y axis), analysed by operator 1 (circle) and operator 2 (box).

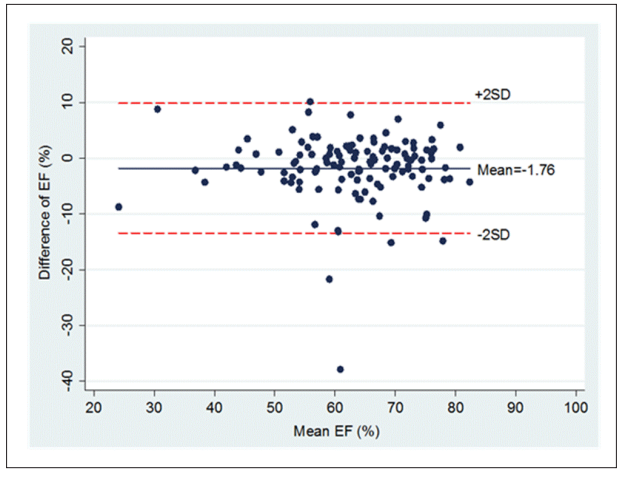

Fig 5. Bland-Altman plot of difference in mean LVEF result between the two software packages (GE analysis-Syngo MI).

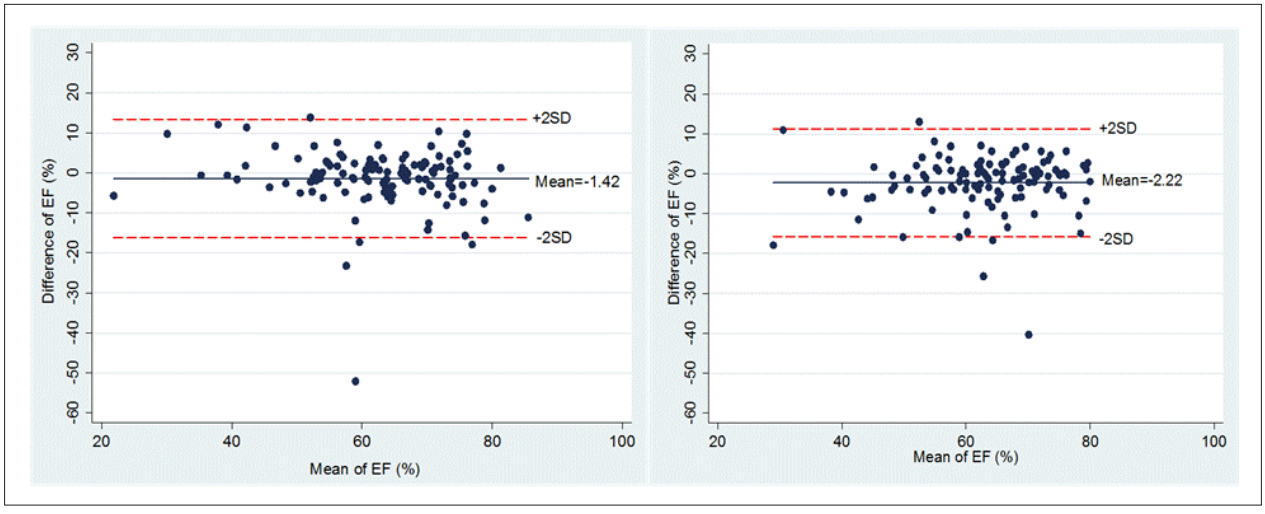

Fig 6. Bland-Altman plot of difference in mean LVEF results between the two software packages (EF analysis-Syngo MI) in operator 1 (left) and operator 2 (right).

TABLE 1. Intra-operator variability and inter-operator variability ofLVEF results analyzed by two software packages.

Variability	ICC (95% CI)					
	EF analysis	P value	Syngo MI	P value	EF analysis vs Syngo MI	P value
Intra-operator						
Operator 1	0.976 (0.966,0.983)	< 0.001	0.931 (0.903-0.951)	<0.001	0.883(0.833,0.919)	<0.001
Operator 2	0.982 (0.974,0.987)	<0.001	0.880 (0.832,0.915)	<0.001	0.885(0.835,0.920)	<0.001
Inter-operator	0.964 (0.949,0.975)	<0.001	0.886 (0.841,0.919)	<0.001	0.853 (0.795,0.895)	<0.001

pared to Syngo MI software was -1.42 EF unit (SD 7.56, 95% limit of agreement -16.24-13.41) and -2.22 EF unit (SD 6.90, 95% limit of agreement-15.74, 11.29) in operator 1 and operator 2, respectively. These differences in mean LVEF were minimal, but statistically significant in both operators (p = 0.034 and 0.002, respectively).

Effect of ROI area and count statistic parameters on LVEF result

There was statistically significant differences (p<0.05) in almost all ROI areas and count statistic parameters between the two software packages, except for total frame count and ratio LV count (Table 2).

The correlations between significant differences in LVEF (>2 SD) using different software packages and these parameters were evaluated by regression analysis. Different LVEF result using two software packages showed significant correlation with difference in end diastolic area (p<0.001), end systolic count (p<0.001), end systolic area (p=0.025), and background count (p<0.001), while there was no such correlation between difference in LVEF result and other parameters including end diastolic count, background area, frame count and ratio LV count (p = 0.099-0.756).

Clinical significance of LVEF difference using different software packages

Of 120 patients, eleven patients (9.2%) showed changes in LVEF results of more than 10% when different software packages were used. Manual ROI adjustment was needed in two out of these eleven patients. In this group of 11 patients, only differences in end diastolic area (p<0.001), end systolic count (p=0.001), background count (p<0.001) and background area (p=0.022) were significantly correlated with differences in LVEF

TABLE 2. ROI counts and area (pixel) obtained from EF analysis and Syngo MI softwares when Diff. GE-SM = difference in count/area (pixel) between EF analysis and Syngo MI.

Parameters	Mean (SD)		Mean Diff.	P value	95%CI
	EF analysis	Syngo MI	GE- SM (SD)		(upper, lower)
End diastolic count	17670.25 (9144.58)	15677.32 (5064.23)	1992.92 (7734.72)	0.006	594.81, 3391.03
End systolic count	7799.31 (3427.65)	7083.68 (3350.40)	715.64 (999.37)	<0.001	534.99, 896.28
Background count (average)	64.44 (12.12)	47.01 (10.25)	17.44 (8.12)	<0.001	15.97, 18.90
Total frame count	201276.12 (25405.62)	198128.49 (27007.25)	3147.63 (29873.99)	0.251	-2252.32, 8547.58
Count ratio	.0976 (0.0656)	0.0942 (0.0604)	0.0034 (0.078)	0.636	-0.01069, 0.01743
End diastolic area	128.82 (31.29)	115.75 (32.34)	13.06 (9.30)	<0.001	11.38, 14.74
End systolic area	69.16 (24.54)	62.56 (23.06)	6.61 (8.79)	<0.001	5.02, 8.19
Background area	42.48 (5.71)	10.46 (2.64)	32.01 (5.36)	<0.001	31.04, 32.98

results. However, the small number of this subgroup might be too low to analyse the factors.

Another clinical significance of LVEF change is when LVEF results fall into different range groups. In this study, three patients (2.5%) had LVEF change from abnormal group (≤ 50%) to normal group (>50%) when analyzed by different software package. The LVEF changes in these patients were from 42% to 80%, 48% to 70% and 50% to 54% using EF analysis software and Syngo MI software, respectively. Similar change was found in both operators in 2 patients. In another case, change in LVEF range group was found in operator 1 (from 46% to 69%), but not in operator 2 (from 56% to 73%), although a large difference in LVEF (17%) was still found.

DISCUSSION

Assessment of cardiac function is essential in management of cancer patients undergoing treatment with chemotherapeutic agents.[1,2] The change in cardiac function, determined by changing LVEF, usually precedes clinical symptoms of heart failure and can alert to early diagnosis of cardiotoxicity. Decrease in LVEF more than 10% from baseline, or when LVEF approaches 50% in patients whose baseline LVEF was higher than 50% or when LVEF approaches 30% in those with baseline LVEF less than 50%, suggest clinically significant cardiotoxicity and cessation of chemotherapeutic treatment is recommended.[3]

Cardiac gated blood pool study using Tc-99m labeled red blood cell has been accepted as a standard technique to assess LVEF due to its simplicity, high accuracy and very high reproducibility.[4] Although recent published articles reported advantages of MRI or GBP SPECT over planar GBP technique, these newer techniques still have some limitations, such as high cost, prolonged processing time and lack of availability.[5,6] Therefore, planar GBP is still the method of choice in assessment of cardiac function prior to, during and follow up after chemotherapy in most cancer patients. Although LVEF estimation obtained from GBP study has high reproducibility, technical errors may occur due to many factors during image acquisition and processing.[7] Previous studies have found high correlation of LVEF estimation using different software packages, but significant difference among software packages still exist.[8-10]

From this study we found very high correlation of LVEF results using different software packages. Although statistically significant differences in LVEF were found, the mean difference was minimal (1.76 EF unit), so these software packages may be used interchangeably without significant clinical impact. However, there were about 9% of patients who had significant EF differences, particularly when manual ROI adjustment was used. Thus, careful review of data analysis detail in every patient is still essential for prevention of possible technical errors.

The previous study by Skrypniuk, *et al* in 63 centers in UK using 10 different software packages found the overall SD of mean LVEF was 7.9% with the mean global LVEF with random error between 3.4%-7.6% and concluded that different software packages had significant effect in LVEF estimation.[9] A similar study by Bailey, *et al* in Australia and New Zealand using the same dataset used in the UK study in 22 centers found very high correlation of mean LVEF estimated by 6 different software packages.[10] The correlation of mean LVEF in the ANZ study was higher than in our study, although the mean differences of LVEF among software packages in both studies were higher than in our study (2.2%[9] and 5.09%[10] vs 1.76%). Wider range of LVEF differences in both studies may be explained by the greater number of software packages. However, much fewer datasets (n = 12) were included in their study as compared to our study (n = 120), as well as lower variation of global LVEF (42% to 55%) as compared to our study (20%-85%). Greater variability in LVEF estimation in studies with a mean LVEF less than 40% has been reported,[10] and this may partly explain the discrepancy in LVEF estimation in our study.

Another study by Hiscock, *et al*[11] to assess the variability of LVEF results among 9 different software packages used in 11 hospitals found good agreement between systems (Cronbach's alpha = 0.982), but the mean difference of LVEF among software packages (approximately 7.6%) were higher than in our study. In their study, no significant difference between the variability was found in each operator using EF analysis software package (1.26%-3.1%), which was similar to our results. However, significant differences of LVEF estimation between operators were shown and they concluded it was probably due to differences in ROI adjustment.

Studies with poor counting statistics encounter difficulty with detecting left ventricular wall, and may increase variability of LVEF analysis.[9,11] The regression analysis found only differences in end systolic count and background count significantly correlated with differences in LVEF results. Thus, operators should pay careful attention in ROI determination, especially background ROI which may overlay on high blood pool organs, such as spleen, and lead to falsely high background activity causing error in LVEF estimation.

Discrepancies seen between software packages were possibly influenced by variability in semi-automatic edge tracking and background correction methods, although the effect of ROI generation method on LVEF was marginal.[9,11] The semi-automatic method allows the operator to reposition or resize the region, which depends on the operator and may increase error causing variability in LVEF estimation. In our study, semi-automatic adjustment was needed in only 4 patients (3.3%) when using Syngo MI software with significantly effect only on background area pixels without significant correlation with differences in LVEF (>2 SD). Therefore, the size of background ROI, unless there is blood pool structure included, may have no impact.

In this study, only small number of patients showed clinically significant change in LVEF using different software packages. Although we are not against the recommendation to use the same software to evaluate LVEF in the same individual, this recommendation may be impossible in the real practice, so changing software during follow up is reasonable. Details of previous GBP study, especially ROI of LV and background, should be reviewed in order to prevent technical error in LVEF analysis.

CONCLUSION

LVEF analysis from GBP study using different software packages has very high correlation

with only minimal differences, thus, it may be reasonably interchanged during follow up without significant clinical impact. However, a small number of patients may have clinically significant LVEF difference with changing software. Therefore, operators should be aware of the importance of precise left ventricular and background region generation to prevent technical errors.

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