Original Article

A practical background correction method for an immediately repeated first-pass radionuclide angiography

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Abstract

Background: A satisfactory bolus injection is essential for a successful first-pass radionuclide angiography (FPRNA). Rescheduling the FPRNA study is usually needed due to high background interference caused by an unsatisfactory bolus injection. We developed a protocol to correct the pre-existing background activity subsequent to immediately repeating the study.

Methods: Seventy-four consecutive patients who had their bone scan and FPRNA scheduled on the same day were included for analysis. The initial 51 cases constituted the "validation-only" group. In the other 23 cases, the "validation plus clearance constants" group, a 5-min dynamic acquisition was performed during the 5-min equilibrium to obtain the background clearance curve and the clearance constants. For all included 74 cases ejection fraction (EF) analysis was proceeded using the images from the first injection, second injection, and second injection with the corrected background to yield EF1, EF2, and EF2′, respectively. EF2 and EF2′ were then compared to the ejection fraction without background interference, the EF1.

Results: For the LV, the mean difference between the EF1 and the uncorrected EF2 (|LVEF1-LVEF2| in mean ± SD) was 3.1 ± 2.0% and the difference between the EF1 and the corrected EF2′ (|LVEF1-LVEF2′|) was 1.6 ± 2.1%, while the mean differences for RV are 2.2 ± 1.9% and 1.8 ± 1.8%, respectively. A significant difference ($p < 0.05$) was observed between the uncorrected and the corrected data for both the LV and RV.

Conclusion: In FPRNA, when a bolus injection is immediately readministered, both LVEF and RVEF can be underestimated. With our correction method, the results are superior to those without correction.

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Keywords: Background correction; Background interference; Background subtraction; Ejection fraction; First-pass radionuclide angiography; Image processing

1. Introduction

Despite many nuclear medicine techniques for evaluation of heart function such as gated myocardial perfusion scan, gated cardiac blood pool imaging, and gated cardiac positron emission tomography, first-pass radionuclide angiography (FPRNA) remains the simplest and the least expensive method. It provides rapid evaluation of both right and left ventricular ejection fractions (RVEF and LVEF), ventricular wall motion of the imaging plane, and quantification of the left-to-right shunt.

In FPRNA, a satisfactory bolus injection is crucial for a good quality study and accurate results. If the bolus is unsatisfactory, guidelines indicate that the image should not be analyzed further, and the study should be repeated on another day to avoid background interference from the failed injection.[1-3] It is well known that an incorrect background selection may result in inaccurate ejection fractions (EF) in a single-injection FPRNA, but to the best of our knowledge, there has not been a study

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discussing the impact of a pre-existing background on the RVEF and LVEF.[4]

However, even with experienced hand and very careful procedure, failure of bolus injection happens at an incidence rate, with conservative estimation at, around 3−5%, that is, almost an every-day-event in a high throughput laboratory with 20−30 cases of FPRNA a day. Rescheduling the study on another day not only causes inconveniences both to the patients and the clinicians but also causes a delay in diagnosis and treatment. Repeating study immediately avoids these inconveniences but the issue of the pre-existing background interference needs to be handled properly.

The purpose of our study is two-fold: first, to determine the effect of a pre-existing background on an ejection fraction if a study is repeated immediately after the first injection and second, to assess whether the EFs can be corrected with our technologically advanced background correction method.

2. Methods

2.1. Patient population

Consecutive patients, who had their bone scan and FPRNA study scheduled on the same day, referred to our department by the clinicians were eligible. We prospectively included these patients from August 14, 2012, to July 16, 2013. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital. All included patients were well informed about the study and completed a written informed consent.

We explained our study protocol to a total of 117 patients and 83 patients agreed to participate in the study. Fifty-five patients were in the "validation-only" group and the other 28 patients were in the "validation plus clearance constants" group (Fig. 1).

A total of nine patients' data was excluded due to prolonged superior vena cava mean transit time (SMTT) (four patients), prolonged pulmonary mean transit time (PMTT) (three patients), and inadequate data acquisition (two patients). This made the actual patient number in the "validation-only" group to be 51 and the patient number in the "validation plus clearance constants" group to be 23 (Fig. 1).

The SMTT and PMTT are important quality control (QC) indexes in an FPRNA which respectively guarantee a successful bolus injection and concentrated pulmonary transit. Acceptable transit times, i.e. SMTT less than 4 s and PMTT less than 8 s, constitute the basis of an accurate EF results. With prolonged SMTT and/or PMTT, the temporal separation of the RV phase and LV phase is lost and the accuracy of the LVEF and RVEF will be hampered. Therefore, those cases with prolonged QC indexes were excluded.

2.2. First-pass radionuclide angiography acquisition

A single head gamma camera (Siemens Symbia E ®, single head) with a low-energy, all-purpose collimator is used for FPRNA studies. Patients are in a supine position with the detector positioned in the right anterior oblique 30° on the anterior chest of the patient. A bolus injection of 370 MBq (10 mCi) of Tc-99m MDP was given through a 21-gauge venous cannula in the external jugular vein or the anterior cubital vein if the neck veins are difficult to access. Data acquisition for a total of 60 s in a frame mode with a frame time of 0.05 s was started immediately after injection.

2.3. Validation of the correction method

The 83 patients involved in this part of the study were constituted by the 55 patients in the "validation-only" group and the other 28 patients in the "validation plus clearance constants" group, received a total dose of 740 MBq (20 mCi) of Tc-99m MDP that was split into two doses, 370 MBq (10 mCi) each, to accommodate two FPRNA studies per patient without hampering the patients' imaging quality or increasing the patients' radiation burden. The split doses were highly concentrated with their volume less than one milliliter, which is essential to facilitate bolus injection. A 1-min dynamic acquisition was done after a bolus injection of the first dose of 370 MBq (10 mCi) of Tc-99m MDP. The acquisition parameters were described in section 2.2. This was followed by a 5-min rest period for the 55 patients in "validation-only" group having no data acquisition during the 5-min rest period (protocol A) and the remaining 28 patients in the "validation plus clearance constants" group having data acquisition using frame mode at a rate of 10 s per frame for a total of 5 min (protocol B). The purpose of the 5-min data acquisition was explained later in section 2.4. Then, in both groups, a 30-s static frame was obtained for background correction. The second dose of 370 MBq (10 mCi) of Tc-99m MDP was given via the same intravenous cannula and followed by another 1-min dynamic acquisition with the same parameters as the acquisition after the first dose of 10 mCi Tc-99m MDP. A schematic summary of the study design was in Fig. 1.

2.4. Obtaining average clearance constants

Because activity changes with time and changes differently in each ROI, after the first injection, a single 30-s static frame at 5 min post first injection cannot represent the exact background distribution during the second injection phase. So, we replaced the 5-min rest period with a 5-min dynamic acquisition with a frame time of 10 s in 28 cases leaving the other 55 cases with no data acquisition during the 5-min rest period (Fig. 1).

Time-activity curves (TAC) for the LV, the right ventricle (RV) and the pericardiac background regions of interest (ROI) from the 5-min acquisition were derived and fitted with simple exponential clearance functions to get the average clearance constants for the RV ROI, the LV ROI, and the pericardiac background ROIs.

2.5. Background correction and ejection fraction analysis

All images, including the FPRNAs and bone scans, were reviewed to exclude overt tracer infiltration and no overt infiltration was noted in all included 74 cases. Background
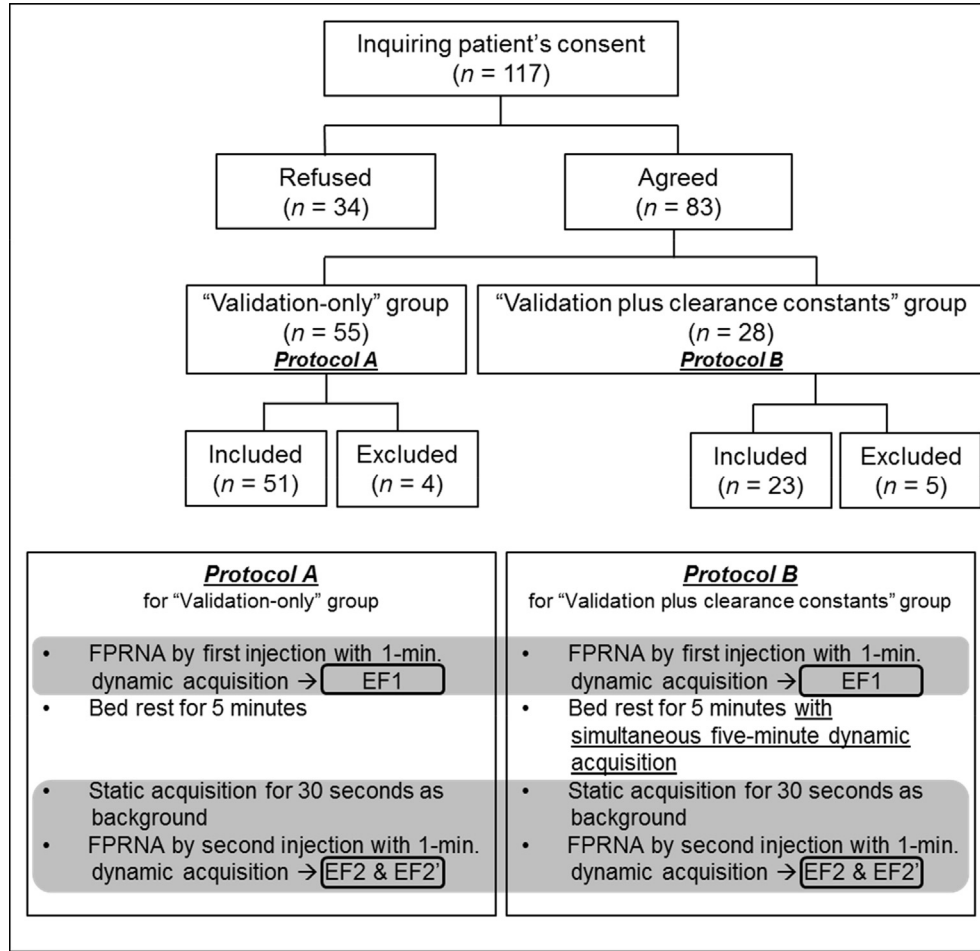
Fig. 1. Patient population inclusion and study protocol. Protocol A was applied to 55 patients and protocol B was applied to 28 patients. The same procedures in the two protocols were shadowed in grey boxes. The only difference between protocol A and B was that, in addition to bed rest for 5 min in protocol A, a 5-min dynamic acquisition during the 5-min bed rest was added between the two FPRNA procedures in protocol B as underlined above. The FPRNA by the first injection yielded EF1 while the FPRNA by the second injection yielded EF2 (uncorrected) and EF2′ (corrected).

correction and ejection fraction analysis then proceeded. The RV and the LV background activity in the 30-s static frame were extrapolated with the average clearance constants mentioned in section 2.4 according to the time interval between the 30-s static frame and the second injection. The temporally extrapolated static image was used as a pre-existing background and subtracted from the second injection dynamic image on the basis of the entire RV ROI and LV ROI instead of subtraction pixel by pixel. An illustrated study protocol using an example case was in Fig. 2.

Further ejection fraction analysis results were derived using the images from the first injection, the second injection, and the background corrected images to yield EF1, EF2, and EF2′, respectively. The ROIs were drawn manually by three experienced operators, who have more than 30 years of experience processing FPRNA images. Each operator was blind to the results of the other.

2.6. Statistical analysis

A single-tail paired Student's t-test was used to determine the difference between EF1 and EF2, and also the difference between |EF1-EF2|, and |EF1-EF2′|. Correlation analysis was performed by using Pearson's correlation coefficient to demonstrate the inter-operator and intra-operator EF results. The agreement of inter-operator and intra-operator results were analyzed using the Bland-Altman difference plot to report upper and lower limits of agreement (LOA).

3. Results

In this study, the overall failure rate of FPRNA was 10.8% which was attributable to failed bolus injection (4.8%), prolonged pulmonary transit related to patient's underlying pathophysiology (3.6%) and other technical issues (2.4%) and these failed FPRNA were not included for further statistical analysis.

After excluding these ineligible cases, a total of 74 patients' data was used for analysis, including 51 patients in the "validation-only" group and 23 patients in the "validation plus clearance constants" group. The demographic data of the 74 patients was summarized in Table 1.

The average clearance constants, T½, from the 23 patients of the validation-plus clearance constants group were
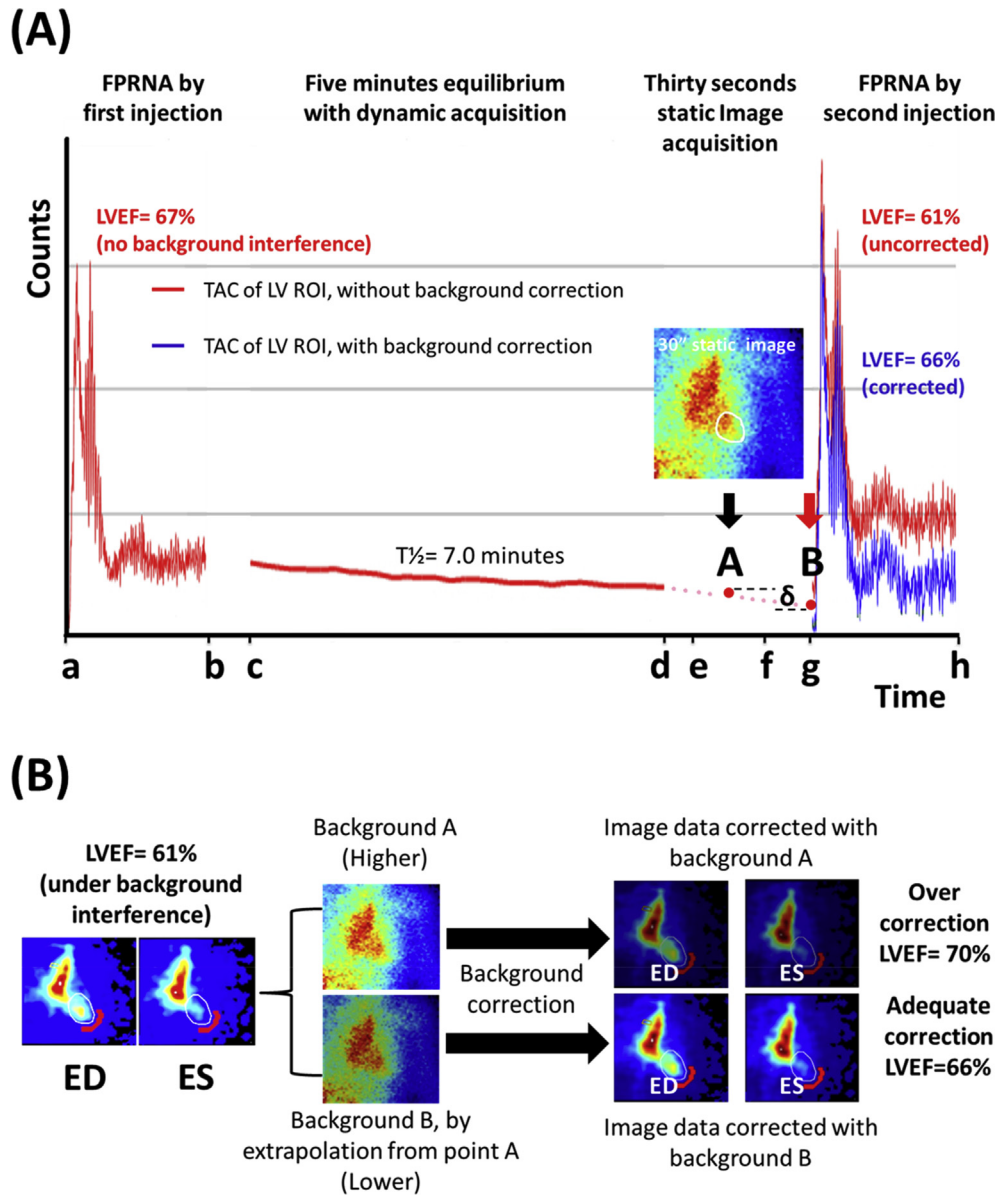
Fig. 2. Illustrated study protocol using an example case from the "validation plus clearance constants" group. (A) Time activity curve (TAC) of the LV ROI through the whole time course where time point a represents the start time of acquisition of the first FPRNA, b: the end of the first FPRNA acquisition, which would be 60 s after time a, c: the start time of the dynamic acquisition during the 5 min equilibrium phase, d: the end of the 5-min dynamic acquisition, which would be 300 s after time c, e: the start time of the 30-s static acquisition, f: the end of the 30-s static acquisition, g: the start time of acquisition of the second FPRNA, h: the end of the second FPRNA acquisition, which would be 60 s after time g; period bc, de and fg were variable but short time intervals which last around ten to 20 s for necessary technique operation between each acquisition. The LV ROI in the 30-s static image obtained after the 5-min dynamic acquisition gave an average count rate during that 30 s and its value could be viewed as the count rate at the time point in the middle of the 30 s (in unit of kcts/0.05 s), point A. And it was theoretically very close to the 5-min clearance curve extrapolated (the pink dotted line) to the middle point of period ef. We initially tried to use that data (background A) to perform background correction. However, the second FPRNA actually started at time g where the actual background was B, there was a decrease (δ) in the background from A to B because background clearance in LV ROI obviously did not reach equilibrium at time d and it kept going between period dg. Therefore, to approach the actual background B at time g, the TAC of the LV ROI from the 5-min acquisition was fitted with simple exponential clearance functions (not shown) to get the average clearance constant for the LV ROI, T½ of LV ROI. Then, the background A was extrapolated using the clearance constant to approximate the actual background B at the start time of the second FPRNA, time g. And the background correction was performed with that approximation rather than using the background A. The uncorrected TAC of the LV ROI was shown in red, giving the uncorrected LVEF of second FPRNA 61%, and the background-corrected TAC of the LV ROI was shown in blue, giving the corrected LVEF 66%, which was closer to the value, 67%, from the first injection without background interference. (B) The image data from the second injection was under the background interference from the first injection and the resulted LVEF 61% was underestimated as compared with the value without interference, 67%. If the background was corrected using the static image obtained during period ef, which represents a higher background level (background A), it would result in an overcorrection, giving a biased LVEF, 70% in this case. If the 30-s image was manipulated by extrapolation to approach the actual background B at time g, the corrected LVEF was 66%, a result better than the uncorrected LVEF or the overcorrected LVEF.

Table 1
Study groups and data acquisition characteristics.

Mean ± SD	All patients	Decay constant group	p
No. of patients	74	23	N/A
Age (y)	62.4 ± 12.5	58.7 ± 12.5	0.22
Female	58.1%	69.6%	0.23
Height (cm)	159.1 ± 9.1	158.2 ± 7.1	0.63
Weight (kg)	62.3 ± 12.8	58.6 ± 11.3	0.22
Total count 1	624.6 ± 136.3	737.1 ± 134.1	<0.005
Total count 2	1000.4 ± 185.0	1105.8 ± 189.0	0.02
SMTT1 (sec)	2.7 ± 1.2	2.7 ± 0.8	0.83
PMTT1 (sec)	5.9 ± 1.3	5.7 ± 0.8	0.67
SMTT2 (sec)	2.9 ± 1.5	2.8 ± 1.1	0.72
PMTT2 (sec)	6.6 ± 1.4	6.6 ± 1.1	0.90

SD = standard deviation; Total count 1 = total counts in the 60-s acquisition from the first injection; Total count 2 = total counts in the 60-s acquisition from the second injection; SMTT1 = superior vena cava (SVC) mean transit time in the first injection; PMTT1 = pulmonary mean transit time in the first injection; SMTT2 = SVC mean transit time in the second injection; PMTT2 = pulmonary mean transit time in the second injection.

(mean ± SD) 7.0 ± 0.8 min for LV ROI, 6.5 ± 0.7 min for RV ROI, 40.5 ± 18.7 min for LV pericardiac ROI, 12.2 ± 4.4 min for RV pericardiac ROI.

The mean LVEF1, LVEF2, and LVEF2′ were 57.6%, 55.0%, and 58.1%. The mean RVEF1, RVEF2, and RVEF2′ were 46.6%, 45.3%, and 46.7%. The standard deviations were listed in Table 2. A statistically significant underestimation of EF was observed for both LVEF and RVEF if an FPRNA was repeated immediately with the second injection without background correction ($p < 0.05$, Table 2). The differences between |EF1-EF2| and |EF1-EF2′| for LV and RV were also

shown in Table 2, which indicated that, in both LV and RV, the corrected EFs were closer to the original EFs with statistical significance ($p < 0.05$).

The overall intra-operator correlation coefficients for both LVEF and RVEF were 0.98 and the overall intra-operator agreement analysis disclosed the đ ± SD were −0.2 ± 1.6 for LVEF and 0.2 ± 1.5 for RVEF (Table 3). The overall inter-operator correlation coefficients for both LVEF and RVEF were 0.94 and the overall inter-operator agreement analysis disclosed the đ ± SD were −0.1 ± 2.9 for LVEF and 0.4 ± 2.4 for RVEF (Table 4). Bland-Altman difference plots for the overall intra-operator agreement were presented in Fig. 3 (LVEF) and Fig. 4 (RVEF) and those for the overall inter-operator agreement were presented in Fig. 5 (LVEF) and Fig. 6 (RVEF).

4. Discussion

Nuclear medicine functional studies to report numerical results are thought to be influenced by the retained tracer from an immediate previous study so that it is usually not recommended to repeat study immediately if the existing activity is high.[5–8] A repeated study on an alternative day is usually needed because of the unsatisfactory image quality caused by poor tracer injection. A repeated examination scheduled on an alternative day can cause inconvenience and delayed treatment for patients. The literature indicates that repeating the study immediately may skew the study results due to high background activity.[9] However, there is almost no literature discussing how much the influence of the background activity

Table 2
The background-uncorrected and corrected EFs.

Mean ± SD	EF1	EF2	EF2′	|EF1-EF2|	|EF1-EF2′|	p1	p2
LVEF (%)	57.6 ± 9.0	55.0 ± 8.6	58.1 ± 8.9	3.1 ± 2.0	1.6 ± 2.1	<0.005	<0.005
RVEF (%)	46.6 ± 7.4	45.3 ± 6.7	46.7 ± 6.8	2.2 ± 1.9	1.8 ± 1.8	<0.005	0.019

EF1: the EF without background interference, EF2: the EF with background interference, before background correction, EF2′: the EF with background interference, after background correction, p1: the p-value of difference between EF1 and EF2; p2: the p-value of difference between |EF1-EF2| and |EF1-EF2′|.

Table 3
Intra-operator correlation and agreement analysis.

Intra-operator correlation analysis

Correlation coefficient (r)	Operator 1	Operator 2	Operator 3	Overall
LVEF 1p v.s. 2p	0.99	0.98	0.98	0.98
RVEF 1p v.s. 2p	0.99	0.97	0.98	0.98

Intra-operator agreement analysis

(đ, SD) (Lower/UpperLOA)	Operator 1	Operator 2	Operator 3	Overall
LVEF 1p v.s. 2p				
(đ, SD)	(−0.2, 1.2)	(−0.4, 1.7)	(0.1, 1.7)	(−0.2, 1.6)
(đ − 1.96 SD, đ + 1.96 SD)	(−2.7, 2.2)	(−3.6, 2.8)	(−3.2, 3.4)	(−3.2, 2.9)
RVEF 1p v.s. 2p				
(đ, SD)	(0.1, 1.1)	(−0.1, 1.8)	(0.5, 1.6)	(0.2, 1.5)
(đ − 1.96 SD, đ + 1.96 SD)	(−2.1, 2.2)	(−3.6, 3.5)	(−2.5, 3.6)	(−2.8, 3.2)

1p: first time process, 2p: second time process, LOA = limit of agreement, đ = difference between EFs by the first time process and the second time process, SD = the standard deviation of đ.

Table 4
Inter-operator correlation and agreement analysis.

Inter-operator correlation analysis

Correlation coefficient (r)	LVEF1	LVEF2	LVEF2′	LV Overall	RVEF1	RVEF2	RVEF2′	RV Overall
Operator 1 & 2	0.95	0.94	0.94	0.94	0.96	0.95	0.94	0.95
Operator 1 & 3	0.98	0.97	0.97	0.97	0.96	0.94	0.94	0.95
Operator 2 & 3	0.96	0.94	0.94	0.94	0.95	0.93	0.94	0.94
Overall	0.95	0.94	0.94	0.94	0.95	0.93	0.93	0.94

Inter-operator agreement analysis

(đ, SD) (Lower/UpperLOA)	LVEF1	LVEF2	LVEF2′	LV Overall	RVEF1	RVEF2	RVEF2′	RV Overall
Operator 1 & 2								
(đ, SD)	(1.6, 2.8)	(1.6, 3.0)	(1.3, 3.1)	(1.5, 2.9)	(1.2, 2.1)	(1.3, 2.2)	(1.0, 2.5)	(1.2, 2.3)
(đ − 1.96 SD, đ + 1.96 SD)	(−3.9, 7.0)	(−4.3, 7.4)	(−4.7, 7.3)	(−4.3, 7.2)	(−2.9, 5.3)	(−3.0, 5.6)	(−3.8, 5.9)	(−3.2, 5.6)
Operator 1 & 3								
(đ, SD)	(0.5, 2.0)	(−0.2, 2.0)	(−0.6, 2.2)	(−0.1, 2.1)	(0.8, 2.2)	(0.5, 2.3)	(0.4, 2.3)	(0.5, 2.2)
(đ − 1.96 SD, đ + 1.96 SD)	(−3.5, 4.4)	(−4.1, 3.7)	(−4.9, 3.8)	(−4.2, 4.0)	(−3.5, 5.1)	(−3.9, 4.9)	(−4.1, 4.9)	(−3.9, 5.0)
Operator 2 & 3								
(đ, SD)	(−1.1, 2.6)	(−1.8, 2.9)	(−1.9, 3.0)	(−1.2, 2.7)	(−0.4, 2.4)	(−0.8, 2.5)	(−0.7, 2.5)	(−0.6, 2.4)
(đ − 1.96 SD, đ + 1.96 SD)	(−6.2, 4.0)	(−7.5, 3.9)	(−7.8, 4.0)	(−6.4, 4.0)	(−5.1, 4.3)	(−5.6, 4.0)	(−5.5, 4.2)	(−5.3, 4.2)
Overall								
(đ, SD)	(0.3, 2.7)	(−0.2, 3.0)	(−0.4, 3.1)	(−0.1, 2.9)	(0.5, 2.3)	(0.3, 2.4)	(0.3, 2.5)	(0.4, 2.4)
(đ − 1.96 SD, đ + 1.96 SD)	(−4.9, 5.6)	(−6.0, 5.7)	(−6.3, 5.6)	(−5.8, 5.7)	(−4.0, 5.1)	(−4.5, 5.1)	(−4.7, 5.2)	(−4.4, 5.1)

1p: first time process, 2p: second time process, LOA = limit of agreement, đ = difference between EFs by two different operators, SD = the standard deviation of đ.

will be, and whether the influence can be corrected by image processing. These were the questions that we tried to answer by the study.

The terminology of background correction and background subtraction are interchangeable in many published articles, however, to avoid causing confusion, we define the terminology of background correction differently than background subtraction in this discussion. Simply, we use the term background subtraction when referring to a routine FPRNA and the term background correction when referring to an immediately repeated FPRNA. The theoretical basis of FPRNA to evaluate ejection fraction is that ventricular TAC can approximate ventricular volume as it varies throughout the cardiac cycle.[1]

And in ejection fraction analysis of FPRNA, a "background subtraction" is conducted as the equation listed below,

$$\frac{(EDcount - BKG) - (EScount - BKG)}{EDcount - BKG} = EF$$

where BKG represents the background subtracted in this equation and in our further discussion, EDcount represents end-diastolic count and EScount represents end-systolic count.

As has been well-established, without background subtraction, ejection fraction by FPRNA has a poorer correlation with ejection fraction by contrast angiography than that with background subtraction.[10] Many approaches for background subtraction have been proposed and compared in the
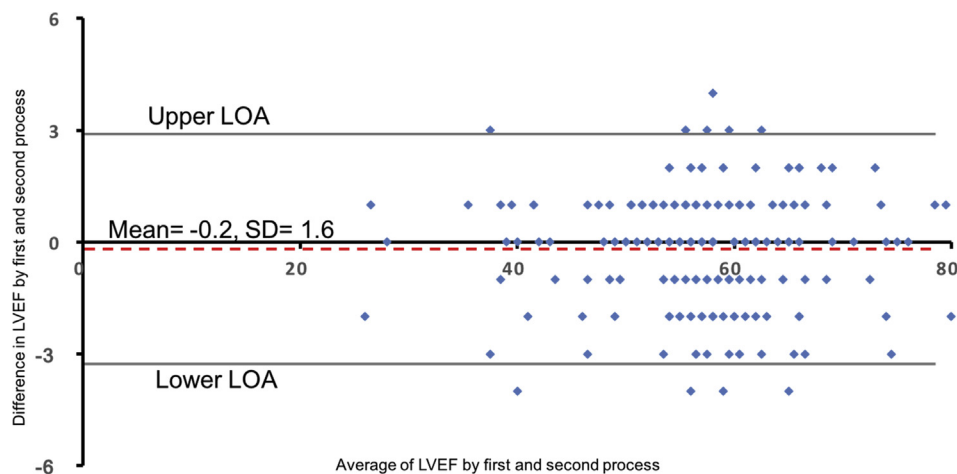

Fig. 3. Overall intra-operator agreement analysis for LVEF: Bland-Altman difference plot. Mean: mean of the difference in LVEF by the first and the second process, LOA: limit of agreement, Upper LOA: Mean + 1.96 SD, Lower LOA: Mean − 1.96 SD.
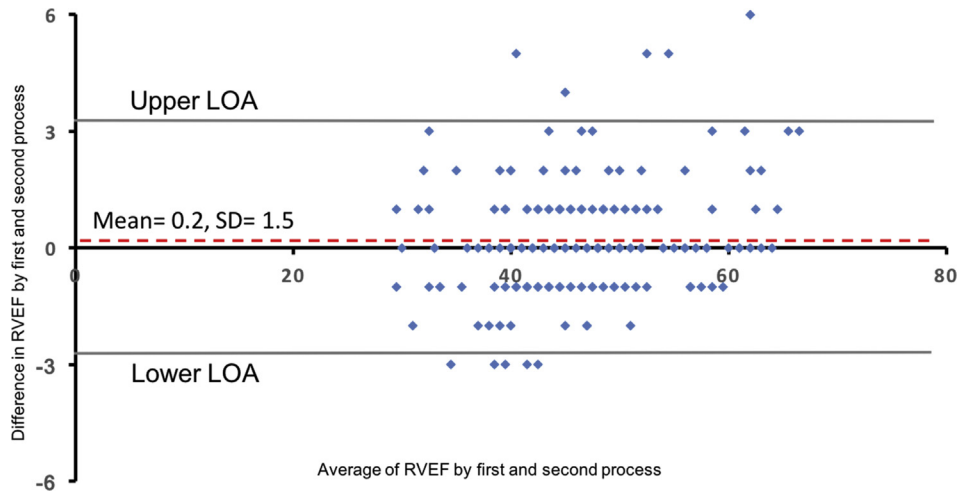
Fig. 4. Overall intra-operator agreement analysis for RVEF: Bland-Altman difference plot. Mean: mean of the difference in RVEF by the first and the second process, LOA: limit of agreement, Upper LOA: Mean + 1.96 SD, Lower LOA: Mean − 1.96 SD.
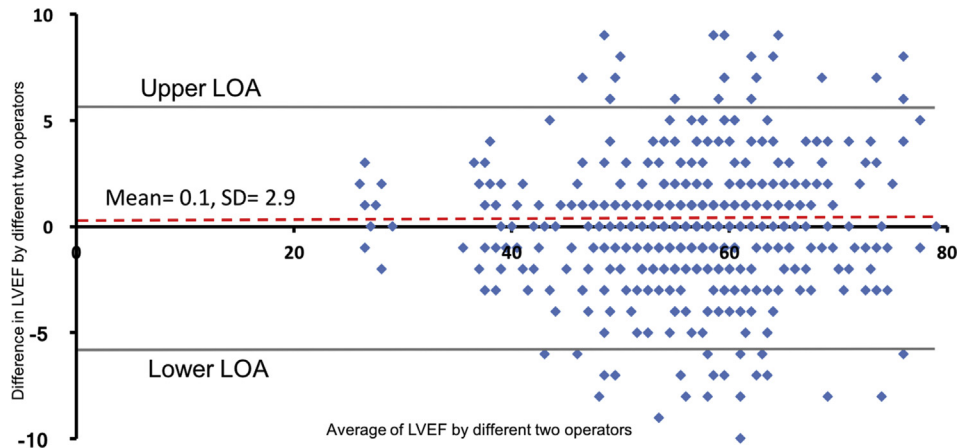

Fig. 5. Overall inter-operator agreement analysis for LVEF: Bland-Altman difference plot. Mean: mean of the difference in LVEF by two different operators from operator 1, 2 and 3, LOA: limit of agreement, Upper LOA: Mean + 1.96 SD, Lower LOA: Mean − 1.96 SD.
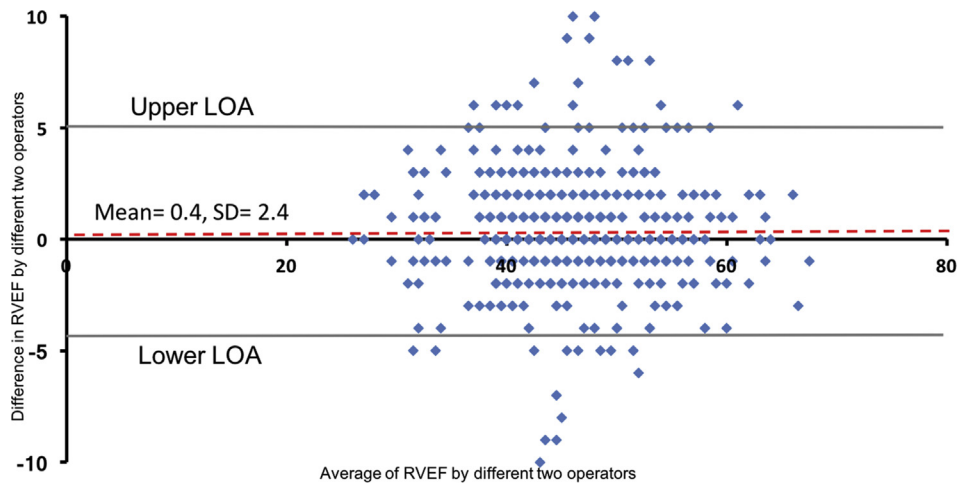

Fig. 6. Overall inter-operator agreement analysis for RVEF: Bland-Altman difference plot. Mean: mean of the difference in RVEF by two different operators from operator 1, 2 and 3, LOA: limit of agreement, Upper LOA: Mean + 1.96 SD, Lower LOA: Mean − 1.96 SD.
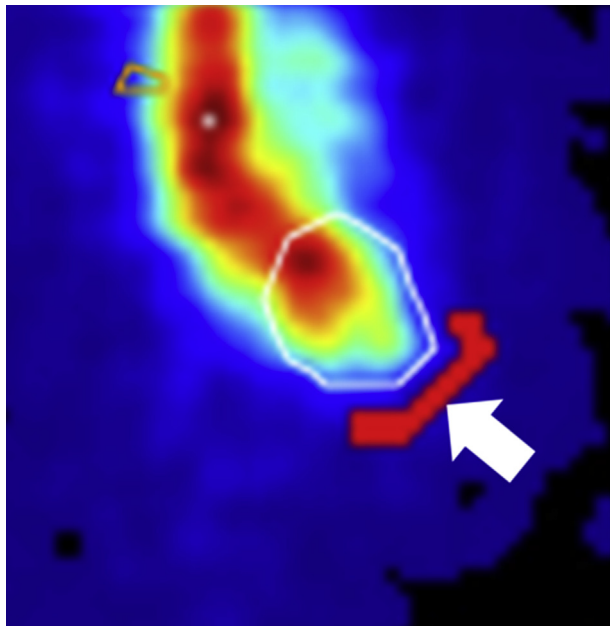
Fig. 7. The pericardiac horseshoe-shaped ROI. The horseshoe ROI (arrow) generated automatically by the software close to the manually-drawn left ventricle ROI is used for background subtraction in our routine FPRNA studies.

literature.[10–13] In brief, there are two mainstream methods to estimate the BKG that needs to be subtracted: pericardiac ROI method and intracardiac subtraction method.[11] In the pericardiac method, the BKG is obtained from a ring-shaped or horseshoe-shaped ROI surrounding the ventricle and a time−activity curve is derived for background subtraction. In the intracardiac method, the BKG is obtained from the ROI of the ventricle. In our hospital, the pericardiac method has been applied for decades and the background represented with a pericardiac horseshoe-shaped ROI generated automatically by proprietary software (Fig. 7).[14]

With our routine background subtraction method by the horseshoe-shaped ROI, the BKG representation will be inadequate in an immediately repeated study, so a "background correction" is needed. In other words, after the background correction, the corrected raw data can be processed by further routine analysis and the BKG representation, by the routine pericardiac horse-shoe method, will be adequate.

In an FPRNA study without infiltrated injection, the BKG is contributed by two parts, the residual activity in the superimposed anatomical structure (i.e., the left hilum in the RAO 30° acquisition) and the Compton scatter background from the injected dose.[12] Then, BKG = BKGs + BKGc, where BKGs represents structure background and BKGc represents Compton scatter background. With our routine automatic pericardiac horse-shoe method, the BKG subtracted is mainly BKGc, a substantial and measurable portion of BKG.[12] The background contributed by the superimposed anatomical structure, BKGs, will not be measured because the sampling pericardiac area does not include the superimposed left hilum. So, the above equation in our routine study is actually:

$$\frac{(EDcount - BKGc) - (EScount - BKGc)}{EDcount - BKGc} = EF$$

However, in a study with an infiltrated first injection and immediate repeat with a second dose, the composition of the BKG is more complicated. Included in the composition is a superimposed anatomical structure background (BKGs), Compton scatter background (BKGc, from both first dose and second dose), and the luminal activity in the ventricle from the first injection (BKGi). Therefore BKG = BKGs + BKGc + BKGi. And if using our routine automatic pericardiac horse-shoe method to perform background subtraction, the exact BKG includes BKGi, and thereby the equation should be:

$$\frac{[EDcount - (BKGc + BKGi)] - [EScount - (BKGc + BKGi)]}{EDcount - (BKGc + BKGi)}$$
$$= EF$$

But the BKGi is not measured in the pericardiac horse-shoe ROI, and that results in an underestimation of the background. Therefore, in the pericardiac method, the LVEF and RVEF would be underestimated due to an underestimation of the BKG if the study is repeated immediately.[4,15] Unfortunately, the scale of this underestimation is seldom reported in the literature.[9]

To our knowledge, this is the first study to discuss the degree of impact of a pre-existing background activity on the EF in an FPRNA. In our study design, we simulated an infiltration by using a non-infiltrated first dose. The worst EF underestimation is, intuitively, therefore established because in a real infiltration, the dose entering the blood pool is less than a full dose and the EF underestimation is not as severe as that caused by a full dose. According to our data of the yet corrected second injection study, most results revealed underestimation in both LVEF and RVEF, i.e. most EF1 > EF2, which was consistent with our expectation as discussed previously. The average underestimation of the LVEF is 2.6% and of the RVEF is 1.4% (Table 2). The most severe underestimation in LVEF is up to 8% in two cases, in whom the LVEF1/LVEF2 were 59%/51% in one case and 56%/48% in the other case.

In a few cases, EF overestimation was also noted according to yet corrected second injection data. Whether the reason for this unexpected overestimation was test-retest variation warrants further investigation. However, no matter the reason for this overestimation was test-retest variation or not and no matter the correction percentage points was larger than the test-retest variation or not, our proposed protocol is still worth its salt if its correction is effective and validated. It is because, in any measurement, there are two sources of error, which are systemic error and random error. The test-retest variation is a random error and the interference of a pre-existing background is a systemic error. The two types of error are independent and the impacts of these errors are addictive one on another. If the systemic error is correctable, it should be corrected as much as possible and that was exactly what we tried to do in this study and that also was the basis of the clinical impact of the proposed correction protocol.

In 55 patients of all included 83 patients, the first injection and the second injection were separated by a 5-min rest period for the better equilibrium of the first dose and a static 30-s frame was obtained before the second injection. It is worth to explain why we set a 5-min-interval between the twice injections. After the first dose of the radiotracer, a complete equilibrium to a steady state was desired since the goal of this study was to correct the background resulting from the first dose. Therefore, a long-enough time interval between the two injections is undoubtedly needed. But a time interval of a too-long period, ex: several hours, would not be allowed because it makes patients inconvenient and also makes the motive of this study lost. So, we chose 5 min as the time interval between the two injections because in general condition, it takes around 1 min for a complete cycle of systemic circulation and hence a 5-min time interval gives four to five cycles of the systemic circulation. But the preliminary analysis revealed the background correction results were not satisfactory when using that static frame to correct the background from the first dose. We found that it was most likely due to the distribution of the first injection dose had not reached equilibrium 5 min after injection. In other words, the clearance of the tracer activity in different ROIs keeps going between the time interval of the 30-s static frame and the second injection, as illustrated in Fig. 2(A). Therefore, the 30-s static frame cannot represent the actual background when the second FPRNA was started. Hence, a 5-min dynamic acquisition during the 5-min rest period was performed in the other 28 patients to obtain clearance constants in different ROIs.

The intra-operator correlation and agreement analysis results are listed in Table 3 and the inter-operator correlation and agreement are analyzed in Table 4. The good intra-operator and inter-operator correlation and agreement indicate the three operators are well-trained and experienced.

There is a limitation in our study. The corrected EF will not be right if the reinjection is too far beyond 5 min after the first injection. This is because the ventricular background was obtained by extrapolating the 5-min static acquisition with the clearance constants derived from the 23 cases in the "validation plus clearance constants" group as discussed previously. If the time interval between two injections is much longer than 5 min, the ventricular background calculated by extrapolation could be distorted and result in an inaccurate background correction.

The results of this study are very illuminating because we proved the feasibility of background correction in a nuclear medicine study with a pre-existing background. The corrected results are very close to the results without background interference. The same correction model may also be applied in other numerical studies in nuclear medicine (e.g., glomerular filtration rate study and gamma camera based effective renal plasma flow measurement) to avoid the inconvenience of repeating a study in an infiltrated injection. More investigations are needed for broader application of the background correction method.

In conclusion, when a bolus injection is immediately readministered in FPRNA, both LVEF and RVEF can be underestimated. In this research, we found that with our correction method, the EF results are superior to those without correction for both the left ventricle and the right ventricle.

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