

Analytical quantification of aortic valve ¹⁸F-sodium fluoride PET uptake

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Background. Challenges to cardiac PET-CT include patient motion, prolonged image acquisition and a reduction of counts due to gating. We compared two analytical tools, FusionQuant and OsiriX, for quantification of gated cardiac ¹⁸F-sodium fluoride (¹⁸F-fluoride) PET-CT imaging.

Methods. Twenty-seven patients with aortic stenosis were included, 15 of whom underwent repeated imaging 4 weeks apart. Agreement between analytical tools and scan-rescan reproducibility was determined using the Bland–Altman method and Lin’s concordance correlation coefficients (CCC).

Results. Image analysis was faster with FusionQuant [median time (IQR) 7:10 (6:40–8:20) minutes] compared with OsiriX [8:30 (8:00–10:10) minutes, $p = .002$]. Agreement of uptake measurements between programs was excellent, CCC = 0.972 (95% CI 0.949–0.995) for mean tissue-to-background ratio (TBR_{mean}) and 0.981 (95% CI 0.965–0.997) for maximum tissue-to-background ratio (TBR_{max}). Mean noise decreased from 11.7% in the diastolic gate to 6.7% in motion-corrected images ($p = .002$); SNR increased from 25.41 to 41.13 ($p = .0001$). Aortic valve scan-rescan reproducibility for TBR_{max} was improved with FusionQuant using motion correction compared to OsiriX (error $\pm 36\%$ vs $\pm 13\%$, $p < .001$) while reproducibility for TBR_{mean} was similar ($\pm 10\%$ vs $\pm 8\%$ $p = .252$).

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Conclusion. 18F-fluoride PET quantification with FusionQuant and OsiriX is comparable. FusionQuant with motion correction offers advantages with respect to analysis time and reproducibility of TBR_{max} values. (J Nucl Cardiol 2020;27:962–72.)

Key Words: Positron emission tomography • cardiac motion • computed tomography • valvular disease

Abbreviations

PET	Positron emission tomography
CT	Computed tomography
ECG	Electrocardiogram
ROI	Region of interest
SNR	Signal-to-noise ratio
TBR	Tissue-to-background ratio
SUV	Standardized uptake value

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INTRODUCTION

Positron emission tomography (PET) is increasingly utilized in clinical and research settings for myocardial perfusion, coronary plaque and valvular imaging. Given its distinct characteristics, cardiac PET imaging poses unique challenges to the cardiovascular imager that may translate to decreased image quality, inaccurate interpretation and diagnostic uncertainties.¹ Respiratory and gross patient motion, independent movement of the heart during the cardiac cycle, prolonged image acquisition times and the necessity for accurate co-registration at the limits of spatial resolution, all introduce the potential for artifact or variability.

In order to address these issues systematically, the integrated software program FusionQuant (Cedars-Sinai Medical Center, CA, USA) was developed. This analytical tool enables cardiac PET-CT image fusion and co-registration, definition of 2- or 3-dimensional regions of interests (ROI) and measurement of standard uptake values (SUV). Additionally, it allows for interpretation of summed, as well as gated PET images and for integrated cardiac motion correction.^{2–4}

Our aim was to validate FusionQuant and to investigate how it compares to OsiriX (OsiriX Imaging Software, Geneva, Switzerland) used in several previous 18F-sodium fluoride (18F-fluoride) quantification studies (Figure 1).⁵ In particular, we sought to investigate its effect on image interpretation time, signal to noise and scan-rescan reproducibility of mean and maximum tissue-to-background ratio (TBR_{mean} and TBR_{max}).

METHODS

Study Subjects

Participants aged > 50 years with varying degrees of aortic valve calcification were prospectively recruited from the

Edinburgh Heart Centre. Study approval was provided by the Scottish Research Ethics Committee and the Medicines and Healthcare Products Regulatory Authority of the United Kingdom, and the study was performed in accordance with the Declaration of Helsinki. All participants signed written informed consent. A total of 52 scans from 27 consecutive patients who underwent PET-CT scanning between November 2014 and May 2015 were included. This cohort included a group of 15 patients who underwent repeated PET-CT scans on two occasions 4 weeks apart, as reported previously,⁵ and a second group of 12 participants, 11 of whom underwent repeated PET-CT scans approximately 1 year apart.

Image Acquisition

All PET-CT scans were acquired on a hybrid PET-CT scanner (Biograph mCT, Siemens) 60 minutes after administration of 125 MBq intravenous 18F-fluoride. Oral metoprolol 25 mg was administered if resting heart rate was > 65 beats/minutes. An attenuation-correction CT scan centered on the aortic valve was performed before acquisition of 3D PET imaging in list mode using a single 30-minute bed position. Lastly, ECG-gated intravenous contrast-enhanced coronary CT angiography and CT calcium scoring were performed in diastole during held expiration.

Image Reconstruction

PET images were reconstructed in list mode into four gates at 25% intervals of the cardiac cycle using standard iterative ordered-subsets expectation maximization with resolution recovery (256 × 256 matrix size, 2 iterations, 21 subsets, and 5 mm Gaussian smoothing) applying 4 cardiac gates.⁶

Image Analysis

OsiriX method. All scans were analyzed using an OsiriX workstation (OsiriX version 3.5.1 64-bit; OsiriX Imaging Software, Geneva, Switzerland) according to a previously published protocol.^{5,7} The methodology for image analysis used in OsiriX has previously been validated in comparison with alternative techniques. Briefly, for measuring aortic valve uptake, two-dimensional regions of interest were drawn on the *en face* view in the aortic valve plane (by multiplanar reconstruction with 3-mm slice thickness) after anatomically exact co-registration of PET and contrast CT images in the axial, sagittal, and coronal planes using the diastolic gate (50–75% of RR interval). Mean and maximum standard uptake values (SUV) were recorded on each slice, which were then standardized for average blood pool activity

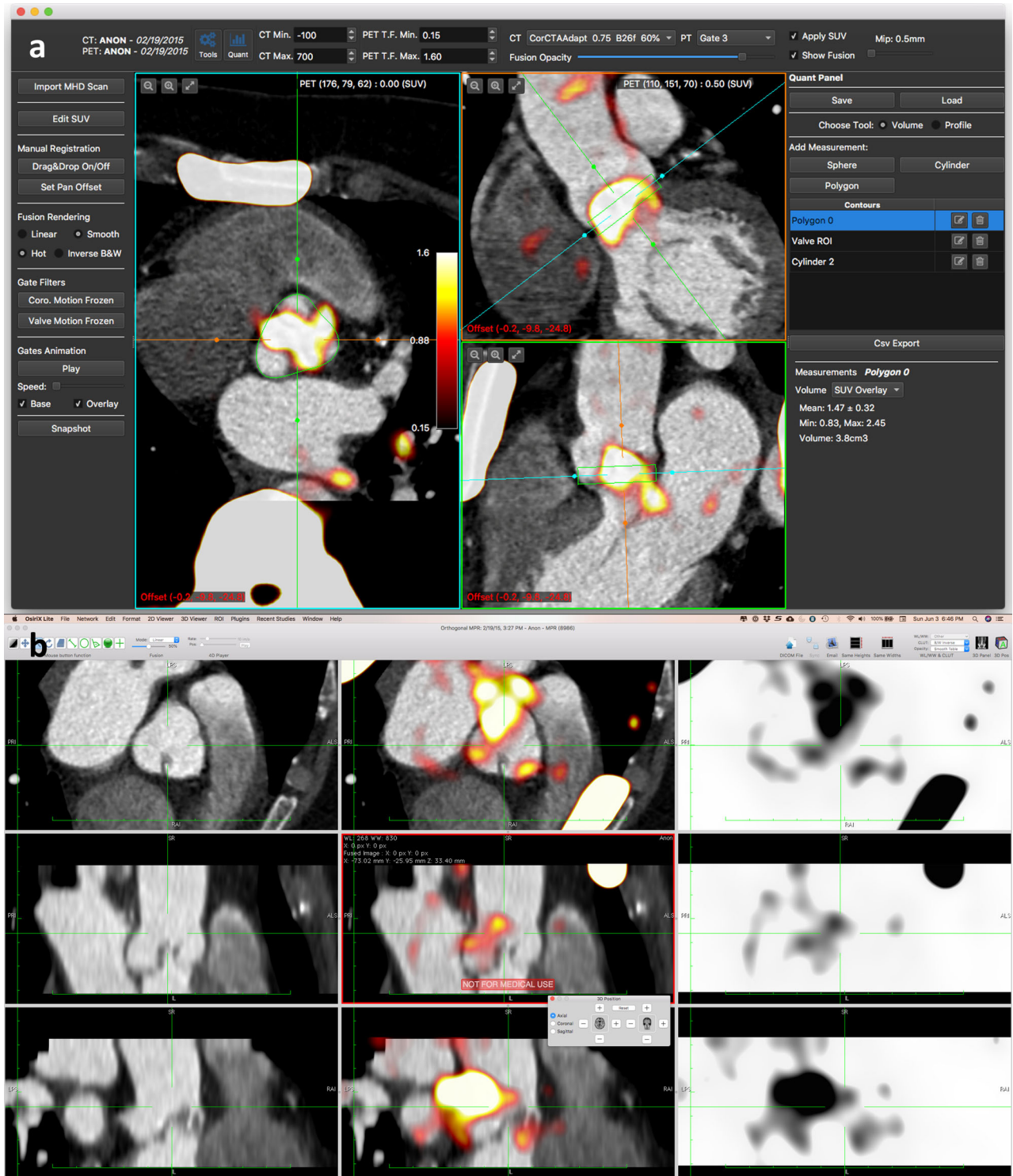


Figure 1. Panel A shows the FusionQuant user interface depicting the aortic valve plane with 18F-fluoride uptake in the aortic valve. Panel B shows misaligned PET and CT images in the OsiriX 2D orthogonal reconstruction images user interface including 3D position tool used to correct co-registration errors in a stepwise fashion.

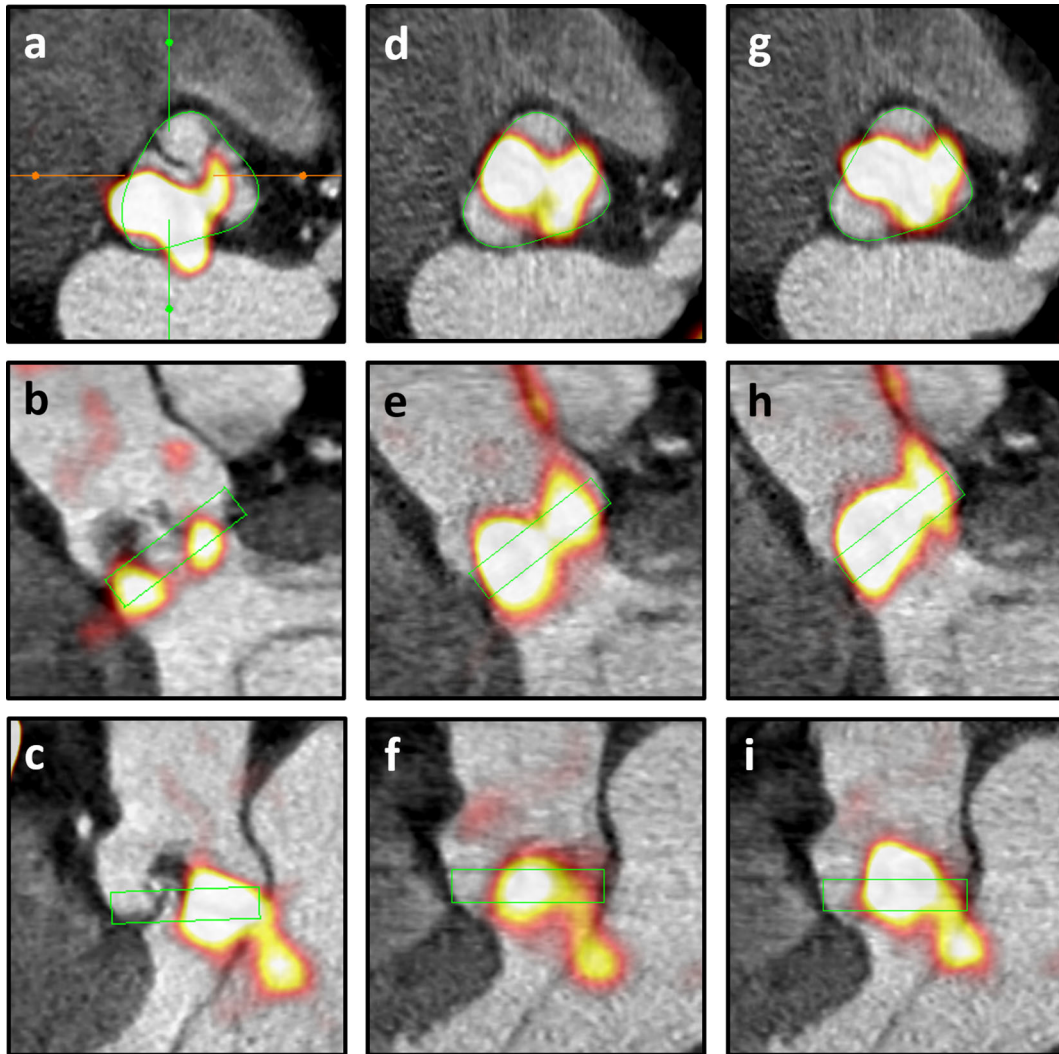


Figure 2. Aortic valve 18F-fluoride analysis with FusionQuant in a patient with aortic stenosis. Region of interest drawn around anatomically exact borders of aortic valve in the valve plane (axial, coronal, and sagittal planes). Panels A, B, and C show misaligned PET and CT images. Through dragging with the mouse, panels (D, E, and F) were achieved. Panels G, H, and I show reduction in PET image noise and improvement in image quality with motion correction.

to generate tissue-to-background ratio (TBR). The “most diseased segment approach” (MDS) was chosen as reference because it has shown favorable reproducibility when compared to an approach using whole valve measurements.⁵ Two contiguous slices with the highest SUV values were averaged in order to generate $SUV_{MDS\text{mean}}$, $SUV_{MDS\text{max}}$ and corresponding TBR_{MDS} values. Blood pool activity was defined as the average of 3 circular regions of interest with 2 cm² area on contiguous slices in the center of the right atrium in the aortic valve plane.

FusionQuant method. All scans were analyzed using FusionQuant (Cedars-Sinai Medical Center, CA, USA). Anatomically exact co-registration of PET and contrast CT images in the axial, sagittal, and coronal planes using the

diastolic gate (50-75% of RR interval) was performed (Figure 2) based upon matching PET tracer uptake in the blood pool of the cardiac chambers and the wall of the ascending aorta with these same structures on the contrast CT angiogram. Correction of image co-registration was done by clicking and dragging the mouse cursor in 3 planes in order to refine alignment in an anatomically exact fashion. ROI definitions were chosen to have similar areas and volumes compared with the most diseased segments approach in OsiriX as follows.⁵ A 3-dimensional polyhedron with parallel congruent bases and 6-mm height was drawn in the aortic valve plane and adjusted in the z-axis to obtain the highest aortic valve SUV_{mean} value. The SUV_{max} value in that position was defined as the highest PET activity inside the polyhedron. The average blood pool uptake was

measured in a cylinder with 8-mm radius and 9-mm height drawn in the center of the right atrium in an *en face* view of the aortic valve. Figure 1 shows a comparison of both user interfaces. Instead of utilizing hybrid PET-CT images obtained during the same imaging session, fusion of PET and CT images acquired at different time points would follow the same protocol without additional processing time.

The manual steps required for image analyses in both software programs are as follows:

OsiriX

1. Open reprocessed series (in order to open 1 diastolic gate only)
2. Create 3D multiplanar reconstruction, align in valve plane
3. Overlay PET and CT series (reorient & fusion)
4. Accurate co-registration (A) 2D orthogonal reconstruction, (B) 3D position tool, manual stepwise alignment (no dragging with mouse possible)

FusionQuant

1. Align in valve plane in main window
2. Accurate co-registration of CTA and PET datasets in three planes by dragging cursor (Figure 2)

Cardiac Motion Correction

Automated correction for cardiac motion was possible only within FusionQuant and this was performed with an anatomically guided registration algorithm according to previously published methods.^{2,3} This algorithm is fully integrated into the FusionQuant software. Briefly, a spherical ROI was drawn to include the entire aortic valve. A non-linear registration algorithm, radially constrained around the aortic valve, was used to align PET images to the diastolic gate. The non-linear registration algorithm was a diffeomorphic, mass-preserving, anatomy-guided demon method that optimizes the global energy between PET frames, with built-in optimization for anatomic data.^{8,9} The motion-corrected gates were then summed to form a motion-free image containing all the PET counts. This approach corrects for motion in the PET data in contrast to the ECG gating employed for the scans analyzed in OsiriX that only considers PET acquired in the diastolic gate and therefore discards approximately 75% of the acquired counts. Analysis time for the motion correction algorithm in FusionQuant is approximately one minute.

Noise and Signal-to-Noise Ratio

Image noise was defined as standard deviation of mean blood pool uptake and expressed in percent. Aortic valve signal-to-noise ratios (SNR) were defined as SUV_{max} divided by image noise and calculated for the diastolic gate and motion-corrected image.

Agreement Between OsiriX and FusionQuant

Agreement of aortic valve 18F-fluoride PET uptake between OsiriX and FusionQuant was assessed for each

method described above. One trained operator (D.M.) performed PET uptake measurements on 23 scans (from 12 consecutive patients) in both analytical tools. Measurements were performed in random and blinded fashion.

Scan-Rescan Reproducibility

Scan-rescan reproducibility of aortic valve 18F-fluoride PET uptake was assessed for each method described above. Two trained operators (T.P. and D.M.) performed PET uptake measurements separately and in a blinded fashion. Scan-rescan reproducibility data obtained with OsiriX on the sub-cohort of 15 individuals who underwent repeated imaging have previously been published.⁵ The main scope of these analyses was to demonstrate differences in error for TBR_{mean} and TBR_{max} (standardized for average blood pool activity) between the two software programs, since variability of SUV is expected based on differences in handling of the radiotracer on different days.

Statistical Analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range), as appropriate. Data were tested for normality with the Shapiro-Wilk test. Comparison of medians was done with the Wilcoxon signed-rank test for paired non-parametric data. Lin's concordance correlation coefficient and the Bland-Altman method were used to compare scan-rescan reproducibility and agreement of PET uptake measurements between methods.¹⁰ For the evaluation of fixed bias, the 95% confidence intervals of mean differences were analyzed. If the limits included zero, we inferred that no fixed bias was present. For the evaluation of proportional bias, a linear regression of mean differences on averages was constructed.¹¹ Comparisons of Bland-Altman 95% limits of agreement were performed using the Pitman-Morgan test. Percent error was defined as $(SD \text{ of mean difference} * 1.96) / \text{overall mean}$. All analyses were performed with STATA 14.2 (StataCorp LP, College Station, TX, USA). Bland-Altman plots were created with Prism 7.0e for Mac OS X (GraphPad Software, La Jolla, CA). A two-tailed $p < .05$ was used to define statistical significance.

RESULTS

Twenty-seven patients were studied, 8 (30%) of whom were women with a median (IQR) age of 71 (66-77) years. Nine patients had mild, 14 moderate and 4 severe aortic stenosis by echocardiography (Table 1).

Analysis Time

Median (IQR) total analysis time for aortic valve and blood pool 18F-fluoride PET uptake, including study import, multiplanar reconstruction in the valve plane, correction of co-registration and delineation of ROIs was 8:30 (8:00-10:10) minutes with OsiriX and

Table 1. Demographics of the study cohort (n = 27)

Age, in years	71 (66–77)
Female sex, n (%)	8 (29.6)
Body mass index (kg/m ²)	28 (26–31)
Mean arterial pressure (mmHg)	100 (94–110)
Current smoker, n (%)	12 (44)
Chest pain, n (%)	6 (22)
Breathlessness, n (%)	10 (37)
Syncope, n (%)	2 (7)
Hypertension, n (%)	21 (78)
Diabetes mellitus, n (%)	5 (19)
CAD, n (%)	13 (48)
ACE inhibitor, n (%)	10 (37)
Angiotensin blocker, n (%)	3 (11)
Beta blocker, n (%)	11 (41)
Statin, n (%)	15 (56)
Aortic valve mean gradient (mmHg)	24 (18–34)

Continuous variables are presented as median (interquartile range)

ACE angiotensin converting enzyme

7:10 (6:40–8:20) minutes with FusionQuant ($p = .002$). This included the motion correction step in FusionQuant.

Agreement Between OsiriX and FusionQuant

18F-fluoride uptake on 23 scans (from 12 consecutive patients, 11 of whom underwent repeat imaging after 1 year) was measured in both software programs by one trained operator. Agreement of 18F-fluoride uptake measurements between OsiriX and FusionQuant was excellent (Table 2 and Figure 3A, B). Fixed bias was detected in the comparison of SUV_{mean} and blood pool uptake, but not SUV_{max} , TBR_{mean} , or TBR_{max} . No evidence of proportional bias was found.

Noise and Signal-to-Noise Ratio

Scan-rescan reproducibility of aortic valve 18F-fluoride uptake was assessed for both FusionQuant and OsiriX in 15 patients who underwent repeated PET-CT scans with a mean (SD) interval between scans of 3.9 (3.3) weeks. After automated motion correction in FusionQuant, mean noise decreased from 11.7% in the diastolic gate to 6.7% in motion-corrected images ($p = .002$), and SNR increased from 25.41 to 41.13 ($p = .0001$) (Table 3).

Scan-Rescan Reproducibility

Scan-rescan reproducibility for TBR_{mean} was excellent using both image analysis software programs, with an error in measurement of $\pm 8\%$ for FusionQuant and $\pm 10\%$ for OsiriX ($p = .252$). However, scan-rescan reproducibility for TBR_{max} values was significantly improved using FusionQuant with motion correction compared to OsiriX (error $\pm 13\%$ vs $\pm 36\%$, respectively; $p < .001$) (Table 3, Figure 3C–F).

DISCUSSION

In this study, we compared 18F-fluoride PET uptake quantification methods using two analytical software programs, OsiriX, a general-purpose medical images viewer used in previous 18F-fluoride PET studies, and FusionQuant, an optimized tool for cardiovascular PET-CT quantification that includes motion correction capabilities. We have shown that the two methods yield comparable results with a high level of agreement. The improved visualization, user interaction, and registration in FusionQuant, 3-dimensional ROI, and cardiac motion correction capability resulted in faster analysis time, decreased noise and improved image quality. FusionQuant's main advantage is the marked improvement in the scan-rescan reproducibility for TBR_{max} values (now comparable to TBR_{mean}), which will enhance the value of this potentially sensitive endpoint in ongoing clinical trials of novel aortic stenosis therapies.

Cardiac 18F-fluoride PET-CT imaging is being increasingly used and validated for several clinical applications. While CT enables quantification of the established calcium burden using calcium scoring techniques, 18F-fluoride PET can measure calcification activity within the cardiovascular system^{12–19} and has been used to investigate coronary atherosclerosis, carotid atherosclerosis, aortic stenosis, and abdominal aortic aneurysm disease.^{7,20–25} Emerging uses include bioprosthetic valve degeneration (NCT02304276)²⁶ and vulnerable plaque detection. Moreover, 18F-fluoride is being used as an exploratory end-point in two ongoing randomized controlled trials to measure the efficacy of novel therapies in patients with aortic stenosis (e.g., SALTIRE 2 NCT02132026,²⁷ BASIK 2 NCT02917525).²⁸ The SALTIRE 2 study (NCT02132026)²⁷ is a randomized placebo-controlled trial that was designed to test whether two drugs commonly used in the treatment of osteoporosis, alendronate, and denosumab, can reduce calcification activity in the valve and slow aortic stenosis progression. While the primary outcome is the change in aortic valve calcium score, participants also undergo repeated

Table 2. Agreement of 18F-fluoride PET uptake measurement between OsiriX and FusionQuant: Mean differences, Bland-Altman 95% limits of agreement and concordance correlation coefficients (CCC) for each analytical method

	Mean difference	95% CI of mean difference	95% Limits of agreement	p for linear regression^a	CCC	95% CI of CCC
Aortic valve SUV _{mean}	– 0.054	– 0.087 to – 0.021	– 0.20 to +0.10	.669	0.971	0.947-0.994
Aortic valve SUV _{max}	– 0.061	– 0.153 to 0.032	– 0.48 to +0.36	.757	0.968	0.942-0.995
Aortic valve TBR _{mean}	– 0.013	– 0.053 to 0.027	– 0.19 to +0.17	.494	0.972	0.949-0.995
Aortic valve TBR _{max}	0.002	– 0.076 to 0.079	– 0.35 to +0.35	.842	0.981	0.965-0.997
Blood pool (right atrium)	– 0.027	– 0.051 to – 0.003	– 0.14 to +0.08	.285	0.964	0.935-0.993

CI, confidence interval

^aLinear regression of mean differences on averages for evaluation of proportional bias

18F-fluoride PET-CT imaging at baseline and after 12 months to determine change in disease activity as a secondary outcome. There is an important need for computer methods to analyze the data from these trials and to optimize reproducibility in measurement of the 18F-fluoride signal. To this end, FusionQuant has been developed as an integrated analytical solution for PET-CT image quantification, allowing accurate co-registration and providing a variety of 2-dimensional and 3-dimensional ROI geometries to quantify tracer uptake in locations with different shapes, such as a cylinder for aortic uptake or a polyhedron for aortic valve uptake. FusionQuant also has the ability to save the image co-registration for later review and additional processing, whereas it has to be repeated each time a study is opened in OsiriX. This feature greatly enhances the efficiency of image analysis which may lead to improved traceability and accountability in the context of clinical trials.

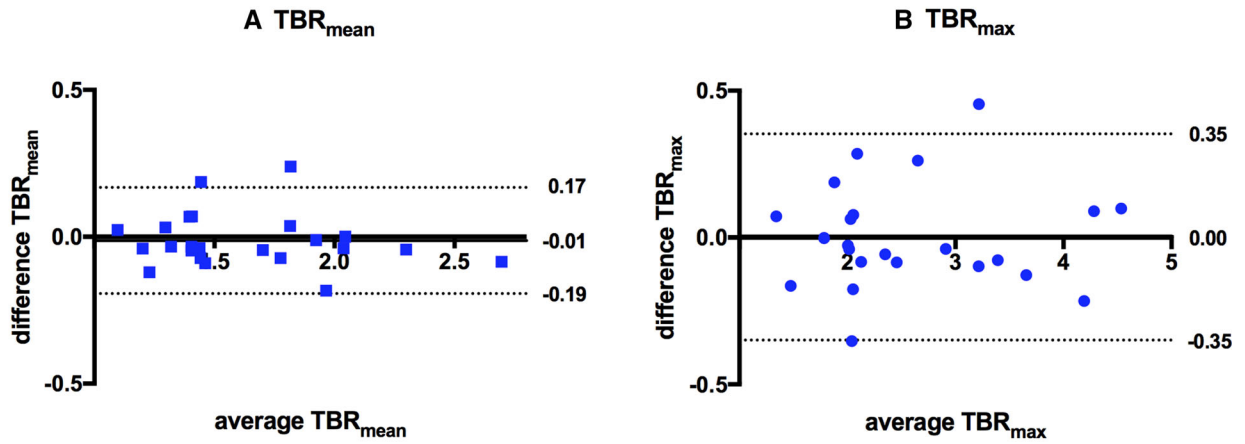
The agreement between FusionQuant and OsiriX was excellent. Although there was evidence of minimal but statistically significant fixed bias for SUV_{mean} and blood pool measurements, we attribute this to the differences in co-registration between the software tools. No fixed bias was detected for SUV_{max} and TBR measurements. Furthermore, as previously reported in a smaller sample,^{1,2} FusionQuant incorporates automated cardiac motion correction using a diffeomorphic mass-preserving image registration algorithm with the third gate (50-75% of RR interval), that here reduced image noise and improved image quality. Although vendors have started to offer cardiac motion correction integrated into the registration,²⁹ such

algorithms are optimized specifically for myocardial imaging and do not perform well for the imaging of other cardiovascular structures.

Our study may also offer guidance on the choice of suitable study endpoints using 18F-fluoride PET imaging. Utilizing SUV values as endpoints may introduce bias given differences in tracer handling at different time points, making TBR values a more stable and attractive outcome due to their standardization for average blood pool activity. A previous study using OsiriX demonstrated the improved scan-rescan reproducibility of TBR_{mean} compared with SUV_{mean} values, although the reproducibility of TBR_{max} values was disappointing.⁵ Here, we confirm that FusionQuant with automated cardiac motion correction not only provides excellent scan-rescan reproducibility for TBR_{mean} values (with a percentage error of just 8%) but also provided a marked improvement in the scan-rescan reproducibility for TBR_{max} values ($\pm 13\%$ vs 36% in OsiriX, $p < .001$). This is important because that level of reproducibility now allows TBR_{max} to be used as an endpoint in ongoing clinical trials of novel aortic stenosis therapy. Given that TBR_{max} values are potentially more sensitive to change than TBR_{mean}, this could be an important advance for the field.

Why would FusionQuant improve the scan-rescan reproducibility of TBR_{max} values? We hypothesize that the degree of variability of TBR_{max} values in OsiriX is mainly due to co-registration errors and the increased signal to noise associated with discarding three quarters of the data for motion correction. The automated motion correction offered by FusionQuant improves upon the

Agreement OsiriX vs. FusionQuant



Scan-rescan reproducibility

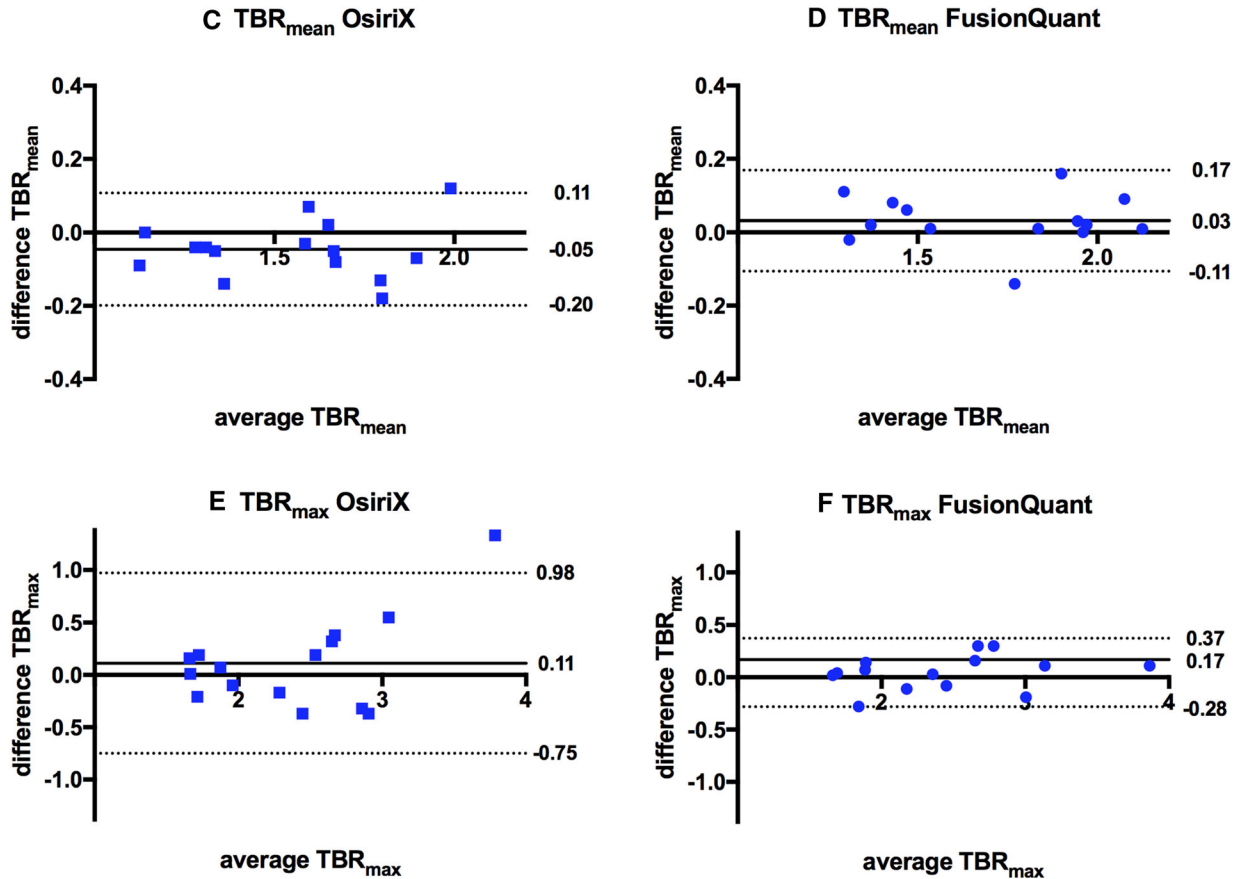


Figure 3. First row: Agreement between OsiriX and FusionQuant: Bland–Altman plots comparing 18F-fluoride uptake measurements in OsiriX vs FusionQuant, (A) aortic valve TBR_{mean}, (B) aortic valve TBR_{max}; Second and third row: Bland–Altman plots showing scan-rescan reproducibility for (C) aortic valve TBR_{mean} in OsiriX, (D) aortic valve TBR_{mean} in FusionQuant, (E) aortic valve TBR_{max} in OsiriX, (F) aortic valve TBR_{max} in FusionQuant (with motion correction).

Table 3. Scan-rescan reproducibility of 18F-fluoride PET uptake for OsiriX and FusionQuant among 15 patients: Bland-Altman 95% limits of agreement, concordance correlation coefficients and percentage errors for each technique and software program

	Overall mean	Difference		95% Limits of agreement	p	CCC	% Error
		Mean	SD				
SUV_{mean}							
OsiriX ^a	1.662	0.043	0.292	− 0.528 to 0.615	.007	0.727	34
FusionQuant	1.795	0.087	0.194	− 0.292 to 0.467		0.863	21
FusionQuant with motion correction ^b	1.801	0.074	0.207	− 0.332 to 0.481	.023*	0.856	23
TBR_{mean}							
OsiriX ^a	1.546	− 0.046	0.078	− 0.199 to 0.107	.252	0.946	10
FusionQuant	1.711	0.040	0.072	− 0.101 to 0.181		0.963	8
FusionQuant with motion correction ^b	1.716	0.031	0.070	− 0.106 to 0.169	.130*	0.967	8
SUV_{max}							
OsiriX ^a	2.528	0.275	0.632	− 0.964 to 1.513	< .001	0.483	49
FusionQuant	2.647	0.160	0.326	− 0.479 to 0.799		0.865	24
FusionQuant with motion correction ^b	2.527	0.110	0.316	− 0.509 to 0.729	< .001*	0.857	25
TBR_{max}							
OsiriX ^a	2.385	0.111	0.439	− 0.750 to 0.971	.024	0.768	36
FusionQuant	2.555	0.071	0.321	− 0.558 to 0.699		0.898	25
FusionQuant with motion correction ^b	2.437	0.044	0.167	− 0.283 to 0.372	< .001*	0.964	13

CCC, Lin’s concordance correlation coefficient; *SUV_{mean}*, mean standardized uptake value; *SUV_{max}*, maximum standardized uptake value; *TBR_{mean}*, mean tissue-to-background ratio; *TBR_{max}*, maximum tissue-to-background ratio

*p value for comparison with OsiriX

^aData for OsiriX from ⁵

^bMotion correction presented in 14 patients due to ECG gating error in one PET acquisition

latter while image co-registration is more user-friendly for the former. Finally, FusionQuant does not require reslicing of the data in the plane of the valve, which may be subject to error.

We observed that analysis time was significantly faster in FusionQuant compared with OsiriX. This is largely because FusionQuant was developed as a dedicated standalone software tool for viewing fused PET-CT images and quantifying PET uptake. The main improvement in analysis time is owing to the easier “drag and drop” mechanism for improving co-registration of the fused images.

This study has limitations. Cardiac CT angiograms are performed during end-expiration while PET acquisition occurs throughout the respiratory cycle, which may add a source of misregistration. While gating to one-fourth of the cardiac cycle does confer a substantial improvement in noise and image quality, the necessary prolongation of scan time may lead to increase in other

sources of motion. Further conceivable gains may be achieved by implementing correction for respiratory and patient motion, as well as for partial-volume effects.³⁰ Future software iterations may implement these options.

CONCLUSION

18F-fluoride PET uptake quantification with FusionQuant and OsiriX yield comparable results. However, FusionQuant with integrated motion-correction results in faster processing, reduced noise, and improved inter-observer reproducibility for *TBR_{max}* values.

NEW KNOWLEDGE GAINED

Cardiac 18F-fluoride uptake quantification with FusionQuant and OsiriX was comparable, although analysis time, operator, and scan-rescan reproducibility

were improved with FusionQuant. Integrated motion-correction techniques lead to decreased noise and improved image quality.

Disclosure

The authors have indicated that they have no financial conflict of interest.

Author contribution

DM, MKD, JK, DD, DEN, MRD, and PJS participated in conception and design of the study; DM, MKD, SC, JK, TAP, and FECMP were actively involved in collecting data and data analysis; DM, MRK, and PJS drafted the manuscript; all authors gave final approval of the submitted manuscript.

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