J of Nuclear Medicine Technology, first published online July 30, 2021 as doi:10.2967/jnmt.121.262320

Decay correction for quantitative myocardial PET perfusion in established PET scanners: a potentially overlooked source of errors

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Word Count: manuscript – 2654, references – 266, legends – 1028, total – 3948

Disclosures

Dr. Bober: Bracco - consultant
No other potential conflicts of interest relevant to this article exist.

Short Title: Decay correction and PET

Abbreviations

A_0 – arterial input function
DC - decay correction
MBF – Myocardial blood flow
PET - Positron emission tomography

Abstract

Quantitative myocardial PET perfusion requires decay correction of the dynamic datasets to ensure measured activity reflects true physiology and not radiotracer decay or duration of frame intervals. Decay correction is typically performed by the PET camera system and the exact algorithm is buried within the settings and assumed to be correct for quantitative perfusion data. For quantitative myocardial perfusion, sequential dynamic images should be decay corrected to the activity at the mid time point of the first scan in the sequence. However, there are different decay correction algorithms that can be implemented depending on the needs and expertise of the laboratory. As such, prior to performing quantitative myocardial perfusion, testing the decay correction technique of a camera system should be performed.

Introduction

Quantification of absolute myocardial blood flow (MBF) with Positron Emission Tomography (PET) has become mainstream and is now reimbursed through the Centers for Medicare and Medicaid services. An extensive literature describes the technical requirements for accurate reproducible MBF(*1-4*). An essential but commonly overlooked function is decay correction (DC), particularly for older or refurbished 2D or 3D scanners already in use. Since assumed to be "working" properly for quantification of MBF, the literature offers little information for practical simple testing in order to assess DC of an installed PET scanner or older refurbished scanner under consideration for purchase.

The goals of this manuscript are twofold. First, explain rationale and methods of DC for assessment of MBF. Second, report an easy method to assess DC by technologists without an onsite physicist or technical experts.

Basics of Quantitative Pet Perfusion

Measuring MBF requires 2 primary data: 1) concentration of radiotracer in the arterial blood over time (also known as the "arterial input" (A_o) or "early blood pool phase") and 2) the concentration of radiotracer in the myocardium (M) or "late myocardial phase". For all PET scanners, radionuclides, acquisition protocols, flow models, list mode or binned data, accurate DC of these datasets is essential but often "buried" from the end user and assumed to be correct for MBF studies. Different DC algorithms may be appropriate for different types of imaging (brain, cardiac, oncology), half-life of the radiotracer or questions asked (drug metabolism, scanner performance, MBF)(*5*).

Consequently, each established PET scanner planned for MBF should be checked for correct DC.

Rationale for Decay Correction on Quantification of MBF

Why is DC necessary for accurate and precise quantification of MBF? While the various kinetic models correct for partial volume loss, spillover, extraction and exit from myocardium, in the simplest conceptual form, myocardial blood flow derives from the ratio of myocardial uptake (M) to arterial input (Ao) or $\frac{M}{Ao}$ (*6,7*).

The early phase images (A_0) quantify the change in concentration of radiotracer in the blood pool over time, prior to myocardial extraction, due to dilution by circulating blood and lung volume after iv injection. The late phase quantifies the average concentration of radiotracer trapped in the myocardium (M) after clearance from the blood pool. As a potassium analog, 82Rb in myocardium does not leak out except for severe cell injury wherein intracellular potassium is not maintained. The slow leak of 13N ammonia out of myocardium after initial uptake is accounted for in its flow model. The simplistic inverse relationship between MBF and A_0 shows how erroneous MBF may be due to too high or too low arterial input or myocardial uptake, all of which may be due to incorrect decay correction.

For quantitative perfusion studies, the radiotracer concentrations of A_0 and M should be dictated ***solely by physiology*** and not by the decay of radiotracer, image duration or acquisition parameters (number of frames in an acquisition). If early images are not decay corrected as described in the next section of the manuscript, the downstream impact would lead to erroneously reduced A_0 and thus falsely high MBF. In addition,

there is also a differential impact of incorrect DC between rest and stress dataset thereby causing errors in stress ml/min/g and coronary flow reserve over and above the physiologic effects of cardiac output, heart rate and blood pressure during stress compared to rest.

With the short lived 82Rb with rapid decay over 75 seconds, erroneous decay correction will particularly degrade quantitative data in both early and late phases. Due to the physiologic rapidly changing high blood concentrations of the early phase, A_0 is more prone to cause errors in MBF than the late phase myocardial data. The impact of incorrectly reduced arterial input and late myocardial uptake will yield inaccurate elevation in absolute MBF ranging 10-40%(*1,6,8*).

Understanding PET Scanner Decay Correction

As a thought experiment, imagine a radiotracer X with a half-life (T1/2) approaching infinity. If 185 MBq (5mCi) of X, as measured in a dose calibrator, is placed in a beaker filled with exactly 500 cm^3 of H_20, the concentration of X would be 0.37 MBq/cm^3 (10 $\mu Ci/cm^3$) at T_0. As this imaginary radiotracer's T1/2 is infinite, there is essentially a stable concentration of 0.37 MBq/cm^3 (10 $\mu Ci/cm^3$) over time. For each cm^3, the beaker is emitting 3.70×10^5 disintegrations per second or 0.37 MBq (10 µCi). If this beaker is now placed into an ideal camera system that captures every disintegration and an image acquired over a period of 10 seconds, what is the camera doing? In the first second, in a sample volume of 1 cm^3, the camera receives 3.70×10^5 counts and each second after, receives 3.70×10^5 counts for each second. Therefore, over a period of 10 seconds, the scanner has received 3.7×10^6 counts. Note that the units are

integrated activity multiplied by time (counts/cm^3 x seconds). The total cumulative activity increases over time depending on the counts/second coming from the beaker sample volume. This total cumulative **integrated** activity divided by the total image duration gives the **average** counts/second emitted by the beaker sample volume. In this example, 3.70 × 10^6 counts/cm^3/sec•sec divided by 10 seconds gives the original target concentration of 3.70 × 10^5 counts/sec per cm^3 or 0.37 MBq/cm^3 (10 µCi/cm^3). However, in the real clinical world where decay occurs rapidly, scanners do not capture all disintegrations and biologic processes influence the concentration of radiotracer, how does the camera operate such that the measured activity reflects true activity of the biologic process? The main function of decay correction is to recalculate measured activity for each time frame into values that would have been measured if decay did not occur, thus ensuring accurate arterial and myocardial activity essential for MBF.

The mathematical description of radioactive decay is:

(1) $R(t) = R_i e^{-\lambda t}$

Where $R(t)$ is the amount of radiotracer at time t, R_i is the initial amount of radiotracer at the start of the scanning period and λ is the decay constant of the radiotracer. With regards to quantitative perfusion with PET, there are 2 methodological predicaments that can be deduced from this equation. First, $R(t)$ is not actually measured. As noted above, the PET scanner, accumulates and integrates counts over a time interval. Thus, $R(t) = \int_{t1}^{t2} R(t)dt$ where t_1 and t_2 is the time duration of the scan or frame. Second, $\int_{t1}^{t2} R(t)dt$ is influenced by other factors besides decay, such as myocardial extraction and retention. In other words, the activity of radiotracer in a scanner region of interest

(ROI) will depend on 1) the duration of the time interval 2) decay of the radiotracer and 3) any biologic process that removes or adds radiotracer from the ROI. Hence, in order to accurately measure activity of A_0 and M, decay of the radiotracer must be corrected for the duration of the scanning intervals.

Many PET scanners offer different decay correction options to correct sequential images relative to the activity at some of the point during the scan (*5,9,10*). For dynamic processes and/or imaging PET tracers with half-lives shorter than the acquisition time period, the mid-time point of the first scan is used (5). This correction confirms that any subsequent change in activity in later sequences are due to biologic changes and not due to image duration, interval between images or radiotracer decay. As an example, a beaker containing 470 cm^3 of H_20 is mixed with 30 cm^3 of 370MBq, (10mCi) of 82Rb ($T_{1/2}$ = 76 seconds), yielding 0.74MBq/cm^3 (20 µCi/cm^3) at time zero confirmed with a dose calibrator. If serial images are captured every 20 seconds for 3 frames, each frame, due to decay and calculated using the equation $R(t) = R_i e^{-\lambda t}$, has an actual average concentration of 0.666, 0.562 and 0.470 MBq/cm^3, (18.3, 15.2 and 12.7 µCi/cm^3), respectively. However, the camera system should decay correct frames 2 and 3 using a reference time of 10 seconds into the scan (1/2 the interval of the first frame). Corrected for decay, frames 2 and 3 will have an average concentration of ~ 0.666 MBq/cm^3, (18.3 µCi/cm^3) and all 3 frames should yield nearly identical concentrations, despite the fact that counts/sec and concentrations are decreasing with time. The difference between the concentration at T_0 and the actual measured average concentration of the first frame is due to decay during the 20 second acquisition and lag

time of the first few seconds of the scanner, hence, the rationale for using the mid-time point as the reference(*5*).

Testing decay correction

In practice, DC can be easily tested using a simple protocol that requires a graduated cylinder, dose calibrator, a 500 cm^3 beaker and a stopwatch. A solution of precise volume and dose of radiotracer is created in the beaker. An aliquot is withdrawn and inserted into a dose calibrator and the beaker position into the scanner. The scanner is started at the same moment the dose calibrator measures activity of the aliquot at T_0. The beaker is then scanned over a duration where a significant amount of decay occurs. For 82Rb, 3.5-7 minutes is adequate, 13N, 10-15 minutes is adequate whereas for 18F, 40-60 minutes is sufficient. The acquisition should allow for several frames to be created over the duration of the scan. For established 2D or 3D scanners acquiring in list mode, the frames can be created after the acquisition however, for non-list mode cameras, the protocol should be prespecified. Most modern 3D scanners correct for decay automatically as data is acquired and likely do not require such testing for decay correction. All images should also be attenuated corrected. After the attenuated corrected frames are created, regions of interest (ROI) are drawn around the radiotracer activity for each frame and the average concentration recorded by the scanner. If decay correction is set up correctly for MBF studies, the average concentration in each frame should be nearly identical and fall within a +/- 3% window from the 1^{st} frame. Furthermore, a ratio of the calculated concentration of first frame (based on the dose calibrator) to the measured concentration can be determined. This ratio should be ~

1.00 +/- 10% if the scanner has accurate time keeping, random, scatter, deadtime corrections and is calibrated correctly for the radiotracer being imaged. If not, further testing of other scanner function or calibration are needed. Distinct protocols for 18F, 13N and 82Rb, that can be performed with one person, in addition to worksheets for 18F, 13N and 82Rb can be found in the online supplemental material.

Case Examples

Figures 1-3 illustrates “beaker tests” performed on an Attrius 2D PET scanner (Positron, Westmont, IL) that demonstrates accurate DC of 18F, 13N and 82Rb in a 500cc beaker with a dose calibrator as the reference standard.

In order to investigate a refurbished 2D camera system where absolute flow values were thought to be erroneous high, a DC beaker test using 18F in a 500 cm^3 was performed. Figure 4 illustrates the results of inaccurate DC by the scanner. To confirm this problem was not unique to the individual camera, a different camera from the same vendor was also tested and yielded similar results. Figure 5 demonstrates the relative and quantitative perfusion data from the refurbished 2D camera using the factory installed incorrect DC algorithm and after the vendor corrected the DC algorithm. The relative images are normal and demonstrate no significant differences between the correct and incorrect DC algorithms. However quantitative perfusion data is ~ 30% higher at rest and ~55% higher at stress with incorrect DC, due to falsely reduced A_0. Besides the obvious difference in MBF values, there are several conclusions that can be made. First, relative perfusion imaging is not impacted and therefore incorrect DC can easily go unnoticed. Second, both sets of MBF values are physiologically plausible

and therefore erroneous MBF values easily can go unnoticed thus skewing site specific "normal" datasets to higher MBF values. Third, prior testing on performances of various camera systems did not specifically confirm correct DC but relied on "routine clinical practice at each institution" (5). Hence, although a camera's performance with regards to peak counts, dead time, scatter and randoms is acceptable for MBF studies, inaccurate DC will still yield erroneous quantitative data. Finally, there is the possibility of clinicians and/or researchers with older refurbished PET cameras with incorrect decay algorithms that are making clinical decisions with erroneous MBF values.

The rationale for alternate decay correction algorithms

The majority of PET cameras are designed and manufactured with a focus on oncologic imaging using low activity of radiotracers (18F and 68Ga) with half-lives significantly longer than the duration of the acquisition. Over the course of a 10-15-minute oncologic acquisition using these isotopes, loss of activity by radionuclide decay is insignificant such that an alternative DC algorithm could be used(*5*). Furthermore, instead of absolute quantification of activity, standard uptake values (SUVs) are used clinically. The SUV is a ratio of the image derived radiotracer concentration to the whole-body concentration of injected dose. Provided calibration time of the injected dose and the start of the acquisition are synchronized, alternative DC algorithms will not impact SUV or non-quantitative data (such as relative perfusion imaging) as whole body and organ specific activities are decaying at the same rate and same start time.

Therefore, unless the end user tests the scanner specifically for DC for MBF studies, alternative DC algorithms could inadvertently be used thereby yielding erroneous MBF.

In fact, alternative DC algorithms will pass routine quality control when systems are designed for long lasting radiotracers such as 18F.

However, non-DC datasets could be exported to software that performs DC as may be used by research laboratories with expertise but is not optimal for primarily clinical services. Finally, in more advanced or research applications, one could apply different DC algorithms based on specific needs since quantitative cardiac imaging is significantly different than oncologic imaging. Half-lives of the approved perfusion tracers are significantly shorter than the duration of the acquisition. Over the course of a myocardial perfusion scan, radiotracer activity decreases ~ 4-fold for 13N and ~64 fold for 82Rb, hence requiring correct DC.

Conclusions

Accurate and precise quantitative myocardial perfusion requires correction for radiotracer decay. Decay correction confirms that changes in activity over the scan duration are due to **physiologic** changes and not due to radiotracer decay, image duration or framing intervals. Testing for correct decay correction is straightforward, can be performed with common instruments found in a standard PET lab by onsite technologists.

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Special thanks to Barbara Siede for medical illustrations.

Figures and Legends

Figure 1

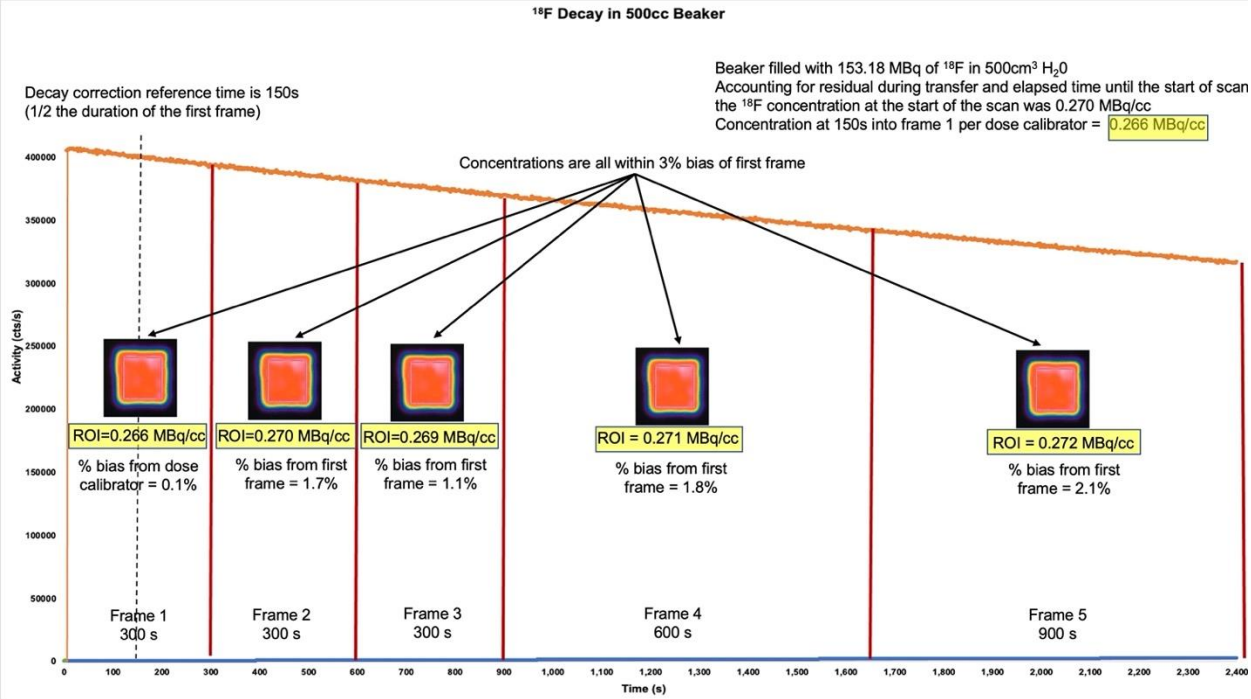


Figure 1 – Decay of 18F in a 500 cm^3 beaker. A detailed 18F protocol ("Fluorine Decay Correction.docx") and worksheet ("F18 Decay Correction Worksheet.xlsx") can be found in the supplemental materials.

With a syringe, 4.14 mCi of 18F was placed a beaker containing precisely 500 cm^3 of H_2O. Accounting for residual activity in the transfer syringe and elapsed time between dose calibrator measurement and the start of the scan, the concentration of 18F at the start of the scan was 7.29 µCi/cm^3. The scanner acquired a 2400 s (40 minutes) list mode acquisition. Twenty-four hours later, after all activity decayed, attenuation scanning was performed and five serial frames were then generated with the intervals of 300s, 300s, 300s, 600s and 900s. Regions of interest (ROI) were placed avoiding the beaker boundaries. The calculation for decay is: $Activity\ at\ time\ t = Initial\ activity\ x\ e^{(-.693\ x\ t\ /(half-life\ of\ radiotracer)}$

Therefore, with the starting activity of 7.29 µCi/cm^3, the expected activity at 150 seconds into the scan (midpoint of the first frame) is 7.180 µCi/cm^3. The half-life of 18F is 6600s.

7.29 µCi/cm^3 x e $^{(-6.93\ x\ 150s/6600s)}$= 7.180 µCi/$cm^3$.

The concentration of ROI of the first frame was 7.186 µCi/cm^3 which is 0.1% bias from the dose calibrator. The concentrations of each subsequent frame are nearly identical to the first frame with biases all within a 3% window.

Based on this test, there are several conclusions:

1) The scanner is decay correcting activity to the mid-time point of the first frame.

2) The scanner also corrects for the duration of each frame giving activity in $\mu Ci/cm^3$.
3) In a biologic system, the only variation in quantitative activity after the first frame would be due to physiologic changes and NOT imaging timing, duration or decay.

Of note, the bias from the dose calibrator of the first frame, also known as the "efficiency" is inconsequential to measurements of MBF as it cancels out in the numerator and denominator of flow equations (6). The bias does inform us if the test was performed with accurate timing, random, scatter and deadtime corrections and also if the camera system has been internally calibrated for the isotope against a standard. If the timing of the beaker decay test was not precise or the camera has not been calibrated, the bias could be significantly different from the dose calibrator however, if decay correction is performed correctly, the bias of the subsequent frames will be uniform.

Figure 2

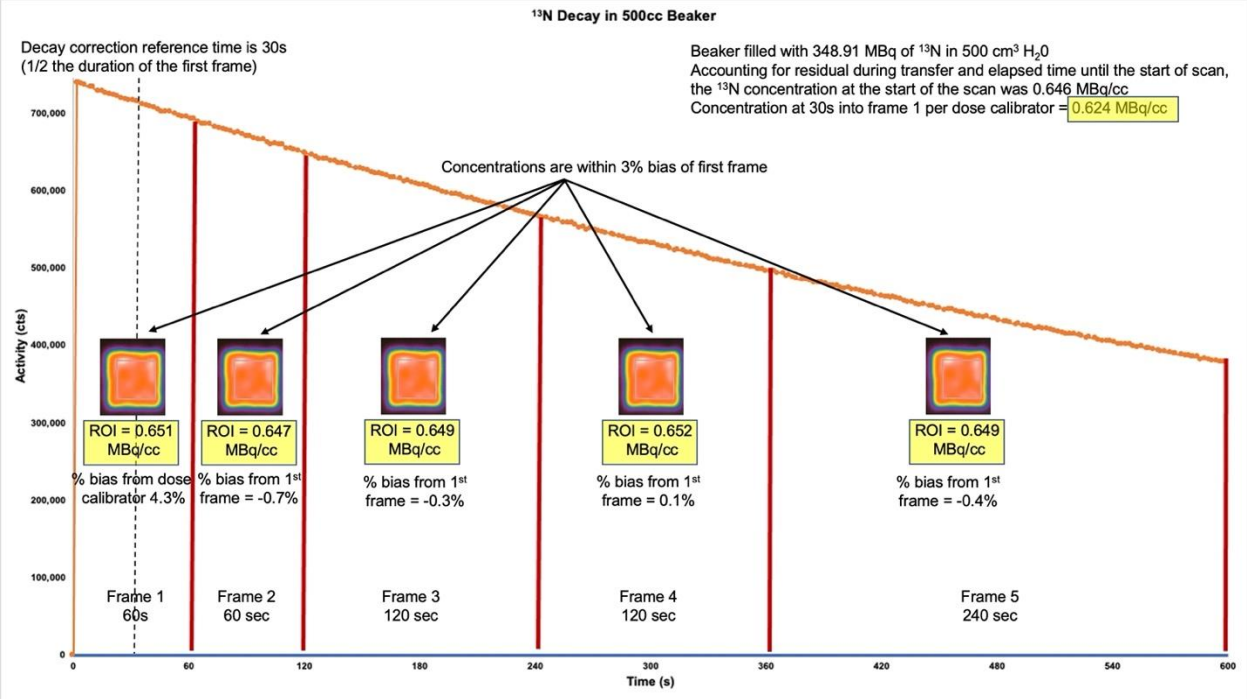


Figure 2 – Decay of 13N in a 500 cm^3 beaker. A detailed 13N protocol ("Nitrogen Decay Correction.docx") and worksheet ("13N Decay Correction Worksheet.xlsx") can be found in the supplemental materials.

Similar to Figure 1, 9.43 mCi of 13N was placed a beaker containing precisely 500 cm^3 of H_2O. The scanner acquired a 600 s (10 minutes) list mode acquisition. Two hours later, after all activity decayed, attenuation scanning was performed and five serial frames were then generated with the intervals of 60s, 60s, 120s, 120s and 240s. Calculations and measurements were performed similarly to Figure 1.

Based on this test, there are several similar conclusions:

1) The scanner is decay correcting activity to the mid-time point of the first frame.
2) The scanner also corrects for the duration of each frame giving activity in $\mu Ci/cm^3$.
3) In a biologic system, the only variation in quantitative activity after the first frame would be due to physiologic changes and NOT imaging timing, duration or decay.

Figure 3

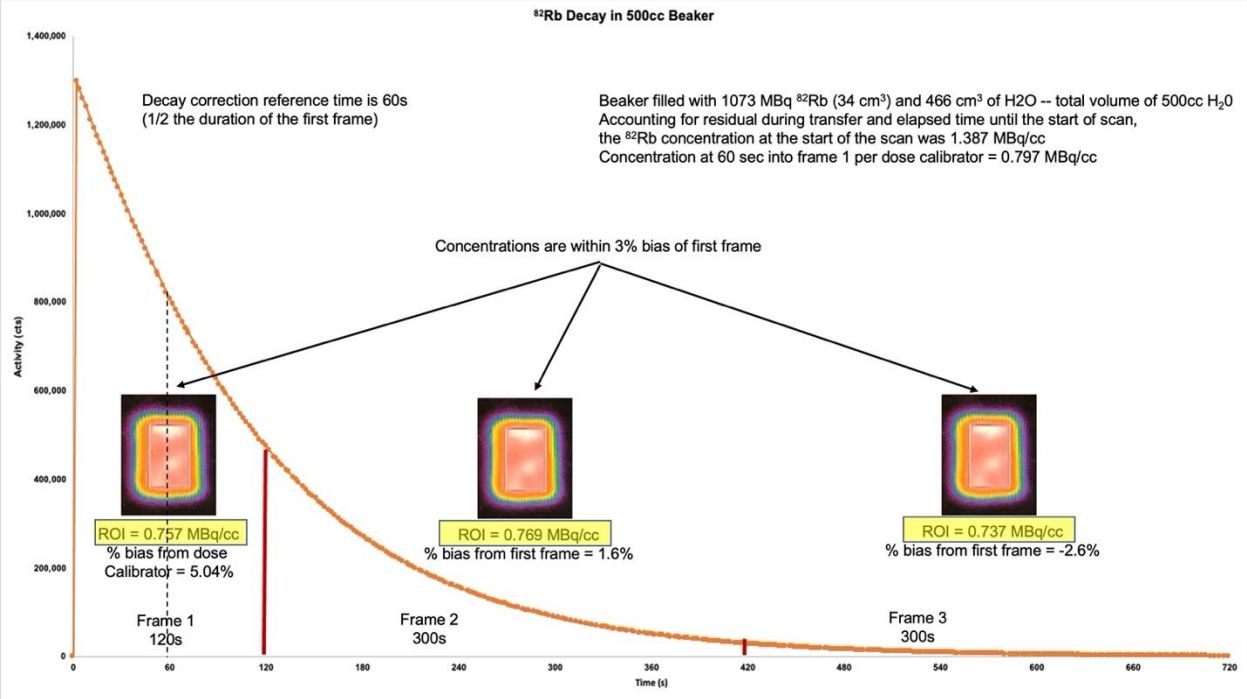
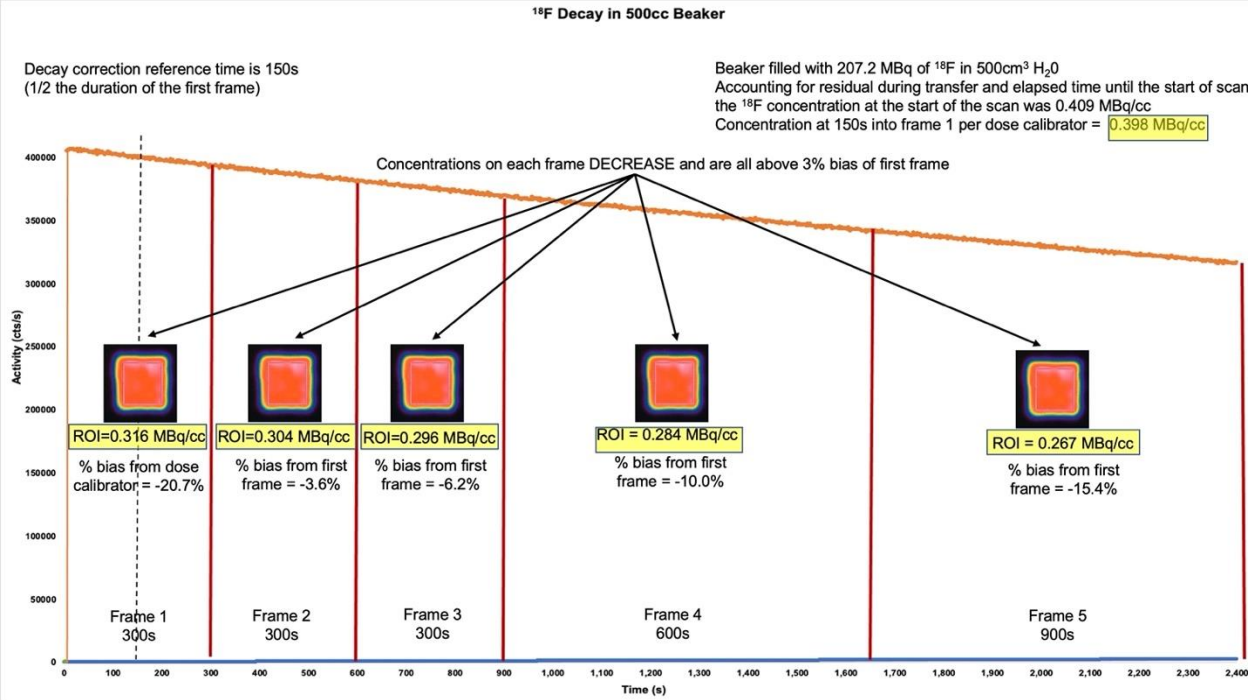


Figure 3 Decay of 82Rb in a 500 cm^3 beaker. A detailed 82Rb protocol ("Rubidium Decay Correction.docx") and worksheet ("82Rb Decay Correction Worksheet.xlsx") can be found in the supplemental materials.

Similar to Figures 1 and 2, 29.0 mCi of 82Rb was placed in a beaker with a total volume precisely 500 cm^3 (H2O plus 82Rb eluate). The scanner acquired a 720 s (12 minutes) list mode acquisition. Ten minutes later, after all activity decayed, attenuation scanning was performed and 3 serial frames were then generated with the intervals of 120s, 300s and 300s. Calculations and measurements were performed similarly to Figure 1. Based on this test, there are several similar conclusions:

1) The scanner is decay correcting activity to the mid-time point of the first frame.
2) The scanner also corrects for the duration of each frame giving activity in $\mu Ci/cm^3$.
3) In a biologic system, the only variation in quantitative activity after the first frame would be due to physiologic changes and NOT imaging timing, duration or decay.

Figure 4



Figures 4

Similar to Figures 1-3, decay beaker testing using 18F was performed on a 2D refurbished PET camera where there was concern for accuracy of MBF data. The scanner acquired 2400 s (40 minutes) list mode acquisition and appropriate attenuation scans were performed. Five serial frames were generated as shown in the figures. As demonstrated in each of the figures, the ROI concentration continues to decrease over time and varying frame durations.

Based on these tests, there are several conclusions:

1. The scanner is not decay correcting activity to the mid-time point of the first frame or correcting for frame duration.
2. Therefore, in a biologic system, the variation in quantitative activity is in part due to inadequate decay correction and/or frame duration which cannot be differentiated from physiologic changes. Therefore, measurement of MBF will not be accurate.

Figure 5

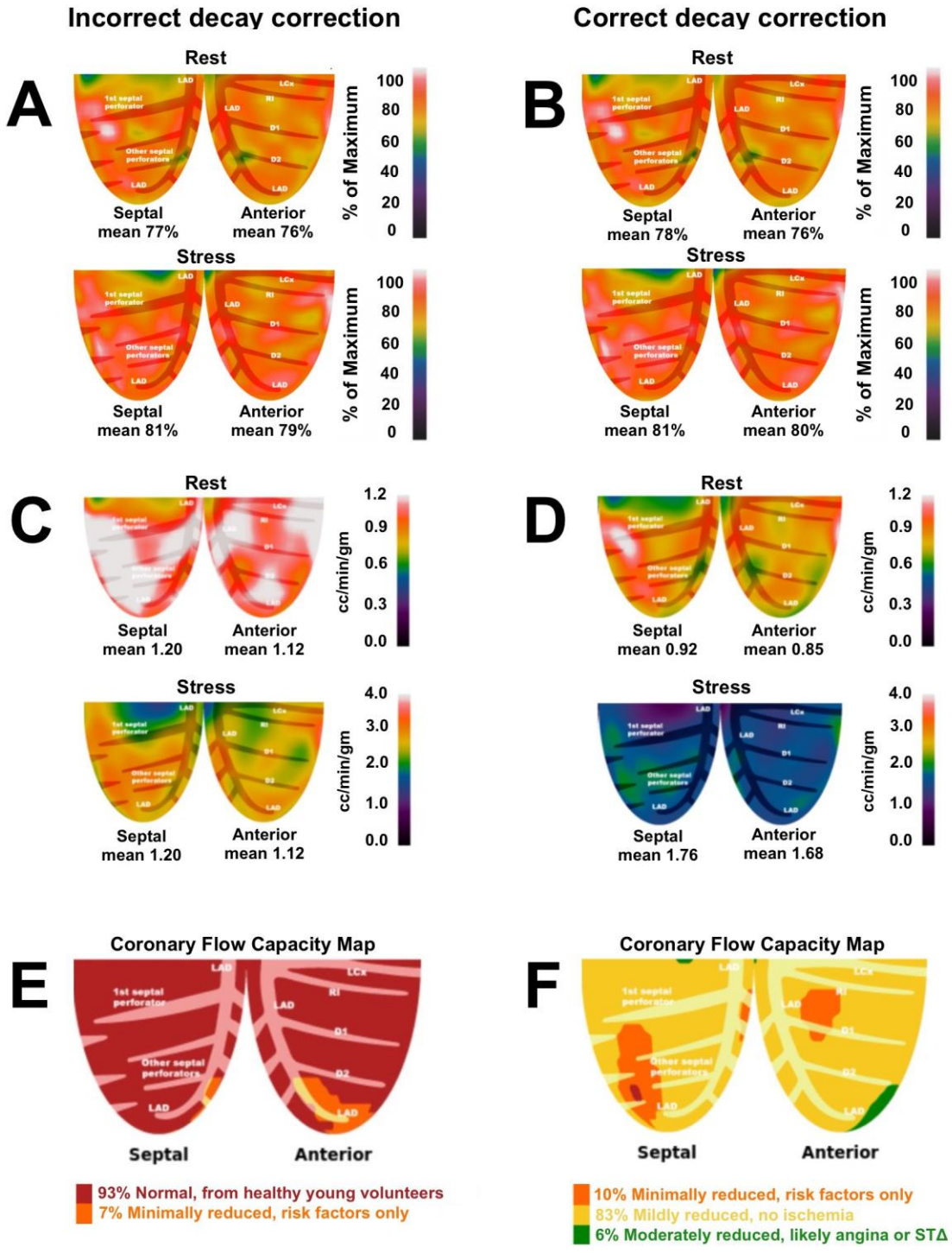


Figure 5 demonstrates relative and quantitative perfusion data of the LAD territory obtained from a refurbished 2D/3D PET system where decay correction (DC), as part of

the default settings within the camera, was performed incorrectly (left column). After recognition of the error, the DC algorithm was corrected, and the study reprocessed. Figures A and B represent rest and stress relative perfusion images, respectively. Both sets of relative images (incorrect and correct DC) are normal and appear nearly identical. Figures C and D demonstrate inaccurate and accurate DC of rest and stress absolute perfusion in cc/min/g, respectively. With correct DC, rest and stress MBF are ~ 30% and ~55% lower, respectively.

Figures E and F demonstrate the coronary flow capacity (CFC) maps derived by the integration of absolute flow metrics of the incorrect and correct DC datasets, respectively. With incorrect DC, CFC maps suggest physiology consistent with healthy volunteers without risk factors. However, with correct DC, CFC maps are consistent with mild diffuse epicardial disease for which medical therapy is appropriate. Based on CFC maps, treatment would possibly be different based on the absolute perfusion metrics.

Graphical Abstract