Published in final edited form as:

Nucl Med Commun. 2012 January ; 33(1): 4–13. doi:10.1097/MNM.0b013e32834c13b5.

Combining Dynamic and Electrocardiogram-gated ^{82}Rb -PET for Practical Implementation in the Clinic

George A. Sayre,
185 Berry St. Suite 350, San Francisco, CA 94107

Stephen L. Bacharach, Michael W. Dae, and Youngho Seo

George A. Sayre: george.sayre@ucsf.edu

Abstract

Objectives—For many cardiac clinics, list-mode PET is impractical. Thus, **separate** dynamic and electrocardiogram-gated (ECG-gated) acquisitions are needed to detect harmful stenoses; indicate affected coronary arteries; and estimate stenosis severity. However, physicians usually order gated studies only due to dose, time, and cost limitations and are limited to **detection**. In an effort to remove these limitations, we developed a novel curve-fitting algorithm (ICD) to accurately calculate coronary flow reserve (CFR) from a **combined** dynamic-ECG protocol of length equal to one typical gated scan.

Methods—We shortened several retrospective dynamic studies to simulate shortened dynamic acquisitions of the combined protocol and compared: 1) the accuracy of ICD and a nominal method in extrapolating the complete functional form of arterial input functions (AIFs); and 2) the accuracy of ICD and ICD-AP (ICD with *a posteriori* knowledge of complete-data AIFs) in predicting CFRs.

Results—AIFs predicted by ICD were more accurate than those predicted by the nominal method in 11/12 studies according to the Akaike Information Criterion. CFRs predicted by ICD and ICD-AP were similar to complete-data predictions ($p_{\text{ICD}} = 0.94$ and $p_{\text{ICD-AP}} = 0.91$) and had similar average errors ($e_{\text{ICD}} = 2.82\%$ and $e_{\text{ICD-AP}} = 2.79\%$).

Conclusions—Both ICD and ICD-AP predicted CFR values with sufficient accuracy for the clinic according to a nuclear cardiologist and an expert analyst of PET data. Therefore, by using our method, physicians in cardiac clinics would have access to the necessary amount of information to differentiate between single- and triple- vessel disease for treatment decision-making.

Keywords

nonlinear optimization; nonlinear least squares; PET kinetics analysis; ^{82}Rb -PET

I. Introduction

Coronary artery disease (CAD) is the leading cause of death in the United States for both men and women [1]. Therefore, detecting the presence of CAD is an important endeavor. Obstructive CAD can cause cardiac regions to become ischemic, as a result of reduced blood flow through the associated coronary artery. Myocardial perfusion imaging (MPI) provides visual representations of the atrial and ventricular blood pools and perfusion of the myocardium, and abnormalities observed on the MP images are indicative of ischemic regions and thus, obstructive CAD.

For more than thirty years, single photon emission computed tomography (SPECT) and its predecessor, planar imaging, have been almost exclusively used with ^{201}Tl , $^{99\text{m}}\text{Tc}$ -sestamibi, and $^{99\text{m}}\text{Tc}$ -tetrofosmin for MPI [2]. Despite two major disadvantages, prohibitive cost and complicated logistics, positron emission tomography (PET) can be a reasonable alternative to SPECT for MPI due to several factors, including: improved sensitivity, specificity, and quantitative accuracy, as well as improved evaluation of multi-vessel CAD and obese patients [13]. Furthermore, PET possesses a much better ability to analyze biophysical kinetics, including myocardial blood flow (MBF).

^{82}Rb Positron Emission Tomography (^{82}Rb -PET) has been used to evaluate patients with suspected or known ischemia and CAD [3, 26]. For accurate clinical assessment of MBF, time activity curves (TACs), which are derived from delineated regions in the myocardium, must be compared to arterial input functions (AIFs) using first-order kinetics analyses [4]. Coronary flow reserve (CFR), which is the ratio of MBF with and without physical or pharmacologic stress, has been applied to MPI studies to *detect* and *localize* ischemic regions and stenotic coronary vessels. Specifically, CFR values have been used to: define stenotic vessels [5]; identify triple-vessel CAD [6]; assess severity and risk of stenoses [7]–[9]; detect atherosclerosis before onset of obstructive CAD and detect microvasculature disease [10].

Electrocardiogram-gated (ECG-gated) studies are performed to calculate the left ventricular ejection fraction (LVEF), which is the ratio of stroke volume to end diastolic volume. Unlike CFR, LVEF is not able to localize ischemia and identify stenotic vessels; it is only able to detect the presence of CAD [11]. However, prior detection of CAD (by LVEF) may be used in combination with CFR values to determine the relevance and risk of individual stenoses [9]. Furthermore, we surmise that comparing LVEF values with CFR values may reduce diagnostic uncertainty associated with several modes of CAD.

PET scanners with list-mode capability need only a single acquisition for clinicians to determine LVEF and CFR [12]. However, PET data acquired by list-mode require extra processing time to create and reconstruct dynamic multiframe and ECG-gated volumes [11]. Thus, for scanners at many clinical practices where physics support is inadequate, or those that do not have list-mode capability, dynamic PET acquisitions followed by ECG-gated acquisitions are needed to determine LVEF and CFR. Such a procedure *generally requires twice the dose* and acquisition time as individual dynamic or gated acquisitions and is usually *not implemented in favor of gated-only protocols* [11]. Thus, CFR is not calculated at many clinics and physicians there must formulate diagnoses based upon a suboptimal amount of physiologic information. Perhaps most importantly, *differentiating* between single- and multi- vessel disease can have implications for *treatment*. For example, a study in 2004 by the American Heart Association states that coronary artery bypass grafting (CABG) is the preferred treatment for triple-vessel disease and diffuse disease not amenable to angioplasty [27]. Angioplasty, usually with stenting, is preferred for single vessel disease, because it is less invasive than CABG [28]. Thus, our method may also have bearing on treatment decisions.

In this study, we investigated whether dynamic and ECG-gated studies could be combined into a single protocol of length equal to one typical gated scan. The advantage of such a protocol is that it would afford clinicians the flexibility to order dynamic and ECG-gated studies by minimizing dose, cost, and acquisition time. However, the mutual exclusivity that often exists between dynamic and ECG-gated acquisitions eliminates important frames from the dynamic study. In our validation study of this protocol, uncertainty was estimated by comparing MBF and CFR values calculated from AIFs and TACs with missing frames to MBF and CFR values calculated from AIFs and TACs with all frames. We believe that our

technique, if validated, would enable the *routine* determination of MBF, CFR, and gated LVEF on imaging systems without the capability for list mode processing or acquisition. In this way, complete diagnostic information could be known and treatment decision-making may be improved.

II. Methods

A. Patient Data

Our retrospective analyses using patient data followed an approved institutional review board (IRB) protocol that permits retrospective analyses. The corresponding ^{82}Rb -PET imaging studies were FDA-approved.

B. Acquisition Protocols

In order to calculate left ventricular ejection fraction and coronary flow reserve from a single rest-stress study, ^{82}Rb -PET studies would have to be acquired in list-mode. Given a time-consuming post-processing requirement for physics support, list-mode acquisition is not viable at many clinics. An alternative would be to perform separate rest-stress studies for dynamic and ECG-gated acquisitions, and therefore, inject four doses of ^{82}Rb and two doses of the pharmacologic stress agent such as dipyridimole. The additional cost, dose, and acquisition time of this protocol are severe hindrances to its implementation. The proposed combined PET protocol (Figure 1) to be performed for rest/stress pharmacologic perfusion studies requires half the injections, half the transmission scans, and twenty minutes less acquisition time.

Rest and stress studies are performed sequentially. The transition time between the two can be short because ^{82}Rb decays rapidly. Administration of dipyridimole immediately precedes the second injection of ^{82}Rb and the subsequent dynamic and gated stress acquisitions. The short half-life of ^{82}Rb combined with the high sensitivity of PET relative to SPECT allows a complete rest/stress study to be performed in as little as ½ hour. The proposed protocol was validated using a dynamic protocol with the same total acquisition time (Figure 2).

For the dynamic protocol, each patient underwent two sequential ^{82}Rb studies using UCSF's ECAT HR+ (Siemens Healthcare, Malvern, PA) using dynamic frame mode with nineteen 4-second frames, three 10-second frames, two 20-second frames, four 30-second frames, and three 40-second frames. The acquisition and processing of the transmission and emission scans were clinically optimized to produce high-quality images for visual evaluation by clinical nuclear cardiologists at UCSF. First, the patient was placed upon the PET scanner table so that the heart was within the 15 cm axial field of view. A transmission scan was then performed, using the rotating germanium rod source of the HR+, for approximately four minutes to ensure the patient's position was appropriate. Given satisfactory positioning, a laser line was marked upon the patient's chest for easy, visual guidance.

Following the positioning step, the patient was infused with approximately 1,850 MBq (50 mCi) of ^{82}Rb . Twenty seconds following the initiation of infusion, before the bolus reached the heart, a seven-minute dynamic acquisition was started. The dynamic images were reconstructed using filtered back projection (FBP) with a Hanning filter employing a roll-off that is close to the Nyquist limit. The resulting images were noisy but quantitatively accurate.

The first eighty seconds of the FBP-reconstructed images were summed, weighted with estimated variance, and heavily smoothed using Gaussian blurring with a 7–9 mm FWHM. The user employed the resulting composite images to manually segment the left and right ventricles in each of the six studies (one rest-stress study per patient). These complete-data

AIFs were transformed into incomplete-data AIFs (Figure 3) by first eliminating time points during the transition period (2–4 minutes post-injection) required to switch the detector from dynamic to gated mode. Then, an additional point, averaged over the dynamic frames corresponding to the gated study (4–7 minutes post-injection), was inserted. The resulting incomplete data AIFs simulate the proposed protocol shown in Figure 1, without list-mode acquisition requirement. The count loss incurred when switching from dynamic mode to ECG-gated mode was estimated to be approximately 20% on the HR+.

Following transformation of complete-data (CD) AIFs to incomplete-data (ICD) AIFs, FBP images acquired after 240 seconds post-injection were summed, weighted with estimate variance, and heavily smoothed using Gaussian blurring (7–9 mm FWHM) in PMOD (PMOD Technologies, Zurich, Switzerland) in order to mimic the behavior of ECG-gated images. PMOD was then used to re-orient the heart using the summed image and delineate cardiac segments as defined by the American Heart Association (AHA) [13]. CD TACs were then calculated from selected segments and used to calculate ICD TACs with the same procedure as their AIF counterparts.

C. Arterial Input Function Models

Calculating MBF and CFR from all AHA segments requires accurate determination of left-ventricular AIFs (LV-AIFs) and right-ventricular AIFs (RV-AIFs), because the septal segments contain fractions of both. As such, we had to develop a curve-fitting method that is generalizable to both. First, several functions were used to curve-fit complete-data LV-AIFs and RV-AIFs using a weighted least-squares cost function. Preliminary results showed two such functions, the oft-used triple exponential [14], [15] (Equation 1) and a novel double free-parameter exponential (dFPE), provided the most accurate predictions. The time series (t) in dFPE are exponentiated to account for the two functional behaviors of ^{82}Rb AIFs following their maximum point: a) an initial fast decrease (first term in Equation 2); and b) a gradual decay at later times (second term in Equation 2). These behaviors are present for all measured LV-AIFs and RV-AIFs and can be seen in Figure 3.

$$\text{tripsexp}(t) = P_0 e^{P_1 t} + P_2 e^{P_3 t} + P_4 e^{P_5 t} \quad (1)$$

$$\text{dFPE}(t) = P_0 e^{P_1 t^{P_2}} + P_3 e^{P_4 t^{P_5}} \quad (2)$$

D. Optimization of the AIF Cost Function

The AIF cost function to be optimized (Equation 5) is the goodness-of-fit statistic, which sums weighted differences between measured (decay-corrected) AIFs (AIF_{meas}) and model AIFs ($\text{AIF}_{\text{model}}$) for frames following and including the maximum point. The variance of each frame (σ_i^2) is initially estimated by the ratio of $\text{AIF}_{\text{meas},i}$ to that frame's radioactive decay factor. The radioactive decay factor (DF) is important for accurate parameter estimation, because the rapid decay of ^{82}Rb ($t_{1/2} = 1.273$ minutes) increases the variance at late frames. Finally, after executing several iterations of the optimization function, frame variances were iteratively updated with the current best guess of $\text{AIF}_{\text{model}}$ (instead of AIF_{meas}) to reduce the effect of noise on parameter estimation [15].

$$\chi^2 = \sum_i \frac{1}{\sigma_i^2} (AIF_{meas,i} - AIF_{model,i})^2 \quad (3)$$

When using the triple exponential (tripsexp of Equation 1) as AIF_{model} , the cost function was optimized by executing the Levenberg-Marquardt algorithm [17] numerous times in IDL with Marquardt's mpfitfun [18] across a fine grid of initial guesses for each parameter P_i . This fine-grid exhaustive search was chosen to maximize the accuracy of tripsexp fits so that dFPE fits were compared to an accepted standard.

When using dFPE as AIF_{model} , the cost function used with dFPE was optimized by a variant of the “basin-hopping” algorithm [19] to minimize computation time. Typically, basin-hopping uses gradient descent to find local minima in topological “basins” and simulated annealing [20] (SA) to “hop” between basins to increase the likelihood that the global minimum is found. We decided to use Levenberg-Marquardt (LM) as the local minimizer, because it would ultimately provide better accuracy and repeatability than gradient descent for incomplete-data fits. For clarity, our variation of “basin-hopping” will be referred to as BH-LM (Figure 4) throughout this paper.

The basic function of simulated annealing in BH-LM is to sample initial parameter sets (P_i) from multiple basins in the topology of the weighted-least squares cost function for local minimization by LM (**Step 4 in** Figure 4). Thus, basin hopping samples a local minimum at each iteration, thereby increasing its relative efficiency to stand-alone simulated annealing. The local minimum calculated with BH-LM replaces the prior estimate for global minimum if it has a lower cost (**Step 5 in** Figure 4). Transitions between states (parameter sets) are dictated by a transition probability (P_{trans}) that relates the change in cost function values between initial and final states (ΔE) by a temperature parameter, T (Equation 4/**Step 6 in** Figure 4). Transitions are only made if P_{trans} is greater than a random number sampled from a uniform distribution.

$$P_{trans} = e^{-\Delta E/T} \quad (4)$$

The temperature parameter is initialized such that transitioning between any two two energy states is very likely. (**Step 1 in** Figure 4). This condition ensures that the topology of the cost function is well-sampled over the course of annealing (temperature cooling) and improves the likelihood of finding the global minimum. This likelihood is further strengthened by re-starting the annealing sequence (**Step 8 in** Figure 4) after the P_{trans} distribution hardens after much annealing (Equation 5). The parameter n in Equation 5 represents BH-LM's current iteration since initialization of SA temperature and dFPE average parameters ($\bar{P}_i$) in **Steps 1 and 2** (Figure 4), respectively. Initial guesses (P_i) for LM are then uniformly sampled from a domain (uni_range_i) that is dictated by the temperature in **Step 3** (Figure 4). As the temperature cools (Equation 3/**Step 7 in** Figure 4), it becomes less likely to transition to higher energy states from low energy states. Thus, the global minimum estimate is obtained by finding large topological regions of good estimates at high temperatures and finding very low energy minima in these regions at low temperatures.

$$T_n = \frac{T_0}{\log(n)} \quad (5)$$

E. ^{82}Rb One-Compartment Model

^{82}Rb tracer kinetics (Equation 7) are dictated by the influx of tracer into the myocardium ($K_1 \cdot \text{LV-AIF}$) from the LV lumen, the wash-out of the tracer from the myocardium into the blood pools ($k_2 \cdot \text{TAC}$), and the input functions (LV- and RV-AIFs). Contribution of the blood pools to measured activity in a myocardial segment results from the partial volume effect. Specifically, the activity contributions from LV- and RV-AIFs to a region of interest (ROI) are dictated by their respective volume fractions in that region, V_{LV} and V_{RV} .

$$\text{TAC} = (1 - V_{LV} - V_{RV})K_1 \text{LV} \otimes e^{-k_2 t} + V_{LV} \text{LV} + V_{RV} \text{RV} \quad (7)$$

The influx rate constant (K_1) is the product of blood flow (F) and the fraction of blood extracted into tissue from the blood (E_u). Several models may be applied to estimate E_u , but the most commonly used method was developed by Lortie [22]. In their study, the Renkin-Crone model was adapted to ^{82}Rb kinetics by comparing flow values from $^{13}\text{N-NH}_3$ -PET to K_1 values from ^{82}Rb -PET (Equation 8).

$$E_u = 1 - 0.77 \exp^{-\frac{0.63}{F}} \quad (8)$$

The high degree of non-linearity of Equation 8 is what necessitates very accurate estimation of LV- and RV- AIFs. For example, a three-fold increase in F (from 1.0 to 3.0 mL/g/min) only corresponds to a 1.9x increase in K_1 . Similarly, small errors in AIFs, particularly LV-AIFs, can cause large errors in MBF estimates.

F. Myocardial TACs: Pre-processing and Weight Factors

Weighted least-squares (WLS) estimation produces accurate results when the data is noiseless and the relative weight factors may be estimated precisely [23], [24]. Of course, measured data is rarely without noise and weight factors are difficult to estimate without repeated measurements of the quantity in question. Dynamic ^{82}Rb -PET faces both of these challenges: the measured TACs are noisy (Figure 5); and the relative weights are difficult to estimate without repeated acquisitions, which are not possible. In the absence of repeated measurements, Poisson weights are often used in WLS estimation for several applications, including dynamic PET. However, given the level of noise present in ^{82}Rb TACs (Figure 5), Poisson weights may not accurately reflect the relative variation between measured data points and if so, significantly affect WLS accuracy. Therefore, we decided to use least-squares (LS) regression in kinetics analyses of myocardial blood flow.

Unlike WLS regression, least-squares regression minimizes the sum of squares between measured and modeled data *without* weights. In other words, all measurements are treated as equally important, even if some measurements are less certain (as they are in most PET studies). Therefore, it is important that the overall functional behavior (curve shape) of TACs is captured more accurately for LS estimation than WLS estimation (given proper weights). Functional behavior of TACs, like with AIFs, may be divided into two major regions: large and small variation, which correspond to early and late times, respectively. The region of large variation experiences rapid change in measured activity values (Figure 8) as the corresponding AIFs experience rapid fluctuations. Thus, it is difficult to predict what fraction of the *measured* fluctuations may be attributed to physiologic response or to appreciable noise resulting from high random rates at early times. However, it may be assumed that measured fluctuations at late times are mostly due to noise. Therefore, frame

averaging may be used to reduce variance and delineate more accurate functional behavior. Weighted averaging of late-time frames may be employed, because relative weights (of late-time frames) may be accurately estimated as the product of the decay factor and the frame length ($w_i = DF_i \Delta t_i$) since activity does not vary significantly. Two average frames were calculated using this method for frames between 120s and 240s post-injection and 240s and 420s post-injection, respectively (Figure 5). Inspection of Figure 7 shows this method preserves the expected late-time behavior of ^{82}Rb kinetics and reduces variance.

G. Overview of Validation Methods

The process of validation for this study was two-fold. First, we determined which model, dFPE or tripsexp, best modeled ^{82}Rb AIFs using the Akaike Information Criterion (AIC) and a related quantity, Akaike Model Weights (AMWs) [21]. This analysis was important, because MBF and CFR estimates should be based upon the most physiologically correct AIF model. Second, we examined the degree and type of bias in MBF and CFR estimates with and without an *a posteriori* empirical relationship that approximated the gradual decay behavior of dFPE-modeled AIFs. We hypothesized this relationship would confer additional accuracy and robustness to dFPE-AIF estimates by constraining the problem to observed trends in measured data.

III. Results

A. Complete-Data Fits

Our first step was to compare the accuracy of dFPE-fits of complete data to the established norm (tripsexp). Goodness-of-fit statistics for each model fit of complete-data LV- and RV-AIFs were compiled into Table 1. Patient studies are abbreviated by their number, type of AIF (LV or RV), and type of study (**R**est or **S**tress). Representative dFPE and tripsexp fits of complete-data LV- and RV-AIFs are illustrated in Figure 6.

The goodness-of-fit results in Table I are percentages relative to fits with 100% error in each frame to produce numerical values that are more intuitive. The results in Table appear to show that LV- and RV- AIFs are best modeled by dFPE.

We employed Akaike model weights [21] to validate this qualitative inspection. Akaike model weights (AMWs) are based upon the Akaike Information Criterion (AIC), which balances the effects of sum of squared errors (SSE) with number of fitting parameters to ensure that a given model accurately describes the data (AIF) without over-fitting it. The AMW of model “j” (AMW_j) is the ratio of the relative likelihood of model “j” to the sum of relative likelihoods for all models (Equation 6).

$$AMW_j = \frac{e^{-0.5(AIC_j - \min(AIC))}}{\sum_k e^{-0.5(AIC_k - \min(AIC))}} \quad (6)$$

This quantity may be interpreted as the weight of evidence that model “j” approximates the data best or as the probability that model “j” describes the data best. AMW values calculated for tripsexp and dFPE fits were compiled into Table II. Averaging across the twelve studies yielded an AMW value of 78.08%. This high AMW value, when coupled with our initial qualitative comparison and a better AIC value in 11/12 studies, gives strong evidence that dFPE is the better model for ^{82}Rb LV- and RV- AIFs.

B. Incomplete-data Fits

Though our initial fits of ICD AIFs using dFPE matched their CD counterparts relatively well (Table III), we decided to investigate whether any functional relationships existed between dFPE parameters to incorporate *a posteriori* information into ICD fits. We hypothesized that fits with *a posteriori* knowledge would improve accuracy and act as a constraint/failsafe mechanism if additional dynamic points were lost, *e.g.* due to an operator mismatch between ^{82}Rb injection and acquisition. Investigative emphasis was placed upon parameters P_3 , P_4 , and P_5 , because they control the gradual-decay region and thus may serve to properly constrain incomplete-data AIFs. Specifically, a relationship between P_4 and P_5 would provide the most robust constraint, because slope of the gradual-decay region is more sensitive to their perturbations than those of P_3 . Therefore, we concentrated our data-mining efforts on P_4 and P_5 and extracted a clear relationship between the two for both LV-AIFs and RV-AIFs (Figure 7).

We are confident that this relationship will generalize to patients beyond this initial study for three reasons. First, the squared correlation coefficient (R^2) for the combined dataset is approximately 0.98, meaning that 98% of the variance in AIF_{meas} is accounted for by the regression. In other words, P_4 and P_5 are almost perfectly correlated and the 2% difference likely has a significant noise component. Second, the relationship between P_4 to P_5 is valid for the combined LV- and RV- dataset. Therefore, we may assume that the gradual decay region of LV and RV curves is controlled by the same (or similar) physical processes, which most likely involve tracer dispersion and washout from the myocardium. Third, the simplicity of the P_4 – P_5 relationship minimizes the risk of over-fitting and therefore greatly improves the likelihood of generalization.

The small, but significant, effect of *a posteriori* knowledge on several, but not all, studies is illustrated by a representative example in Figure 8. Specifically, at late times, the LV fit with *a posteriori* knowledge (ICD-AP) better approximates the complete-data fit than the fit without *a posteriori* knowledge (ICD).

Quantitative comparison of goodness-of-fit statistics (GOFS) of ICD-AP fits to ICD fits in relation to CD fits reveals that ICD-AP is more likely to be the better model for fitting incomplete-data AIFs ($\text{AMW}_{\text{ICD-AP}} = 0.578$ and $\text{AMW}_{\text{ICD}} = 0.422$). However, some fits, for example 2-LV-S (Table III), appear to suffer slightly from the application of *a posteriori* knowledge to BH-LM. However, these mismatch cases do not compromise the overall accuracy or precision of ICD-AP and the associated values are actually less extreme than two ICD predictions. Therefore, on average, we might expect ICD-AP to predict MBF values with better accuracy than ICD.

C. Estimation of MBF and CFR

Myocardial blood flow was estimated using the one-compartmental model for ^{82}Rb kinetics in PMOD (PMOD Technologies, Zurich, Switzerland) for several ROIs per patient study. $\text{MBF}_{\text{ICD-AP}}$ and MBF_{ICD} values were compared with MBF_{CD} values to assess bias (Figure 9). The range of calculated flow values is consistent with the expected range for pharmacologic stress studies. High levels of correlation were found to exist between MBF_{CD} and MBF_{ICD} ($R^2=0.99$) and MBF_{CD} and $\text{MBF}_{\text{ICD-AP}}$ ($R^2=0.983$). However, correlation is not necessarily indicative of agreement. For example, two lines with nearly equal slope but different intercepts are highly correlated but have poor agreement. Lack of agreement, or bias, may be assessed for the two ICD techniques by comparing the trendlines of MBF_{ICD} and $\text{MBF}_{\text{ICD-AP}}$ with the line of unity. Visually, $\text{MBF}_{\text{ICD-AP}}$ appears to contain less proportional bias (over/underestimation) than MBF_{ICD} . Comparisons between mean percent error (e) and mean absolute percent error (e_a), which should be nearly equivalent for

techniques exhibiting proportional bias, confirm this finding: $e_{\text{ICD-AP}} = 4.09\%$ and $e_{a,\text{ICD-AP}} = 5.79\%$ while $e_{\text{ICD}} = 7.01\%$ and $e_{a,\text{ICD}} = 7.10\%$.

Constant (systematic) bias and bias dependent on measurement magnitude were assessed from a Bland-Altman plot of the two ICD techniques (Figure 10), and both techniques appear to suffer from the latter to some degree. However, this finding is expected due to the non-linearity of the extraction fraction E_t : MBF estimates for high-flow regions will be more biased than those of low-flow regions for the same LV- and RV-AIFs. Furthermore, the existence of this expected proportional bias means that the two ICD-AP points and one ICD point located outside of the 95% confidence regions, which still retain sufficient accuracy for the clinic, are unlikely to be a cause for concern. Finally, the slopes of the ICD-AP and ICD trendlines confirm the earlier finding regarding proportional bias: the ICD technique systematically overestimates MBF while the ICD-AP technique has minimal proportional bias.

Accurate estimation of MBF is necessary to calculate CFR with clinical accuracy. Because rest and stress studies may be thought of as independent events, it would be intuitive to think that ICD-AP might provide better CFR estimates, because its MBF predictions resulted in a smaller mean absolute percent error (MAPE) and less bias than ICD. However, it was possible that ICD's systematic overestimation of MBF was negated in the $\text{MBF}_{\text{stress}}/\text{MBF}_{\text{rest}}$ ratio. Thus, it was also possible that ICD may produce more accurate CFR values, because ICD-AP is more likely to predict stress-rest pairs with contrasting biases. For example, ICD-AP may overestimate $\text{MBF}_{\text{stress}}$ and underestimate MBF_{rest} while ICD is more likely to overestimate both. Therefore, analysis of the CFR data (Table IV) remained an important step in decision-making.

The results shown in Table 4 indicate that both techniques could be used to accurately calculate CFR. First, each technique predicted CFR values that were not statistically significant from complete-data results according to a paired student t-test: $p_{\text{ICD-AP}} = 0.91$ and $p_{\text{ICD}} = 0.94$. Second, ICD-AP and ICD predicted clinically accurate CFR values according to mean percent error (MPE): $e_{a,\text{ICD-AP}} = 2.79 \pm 10.0\%$, and $e_{a,\text{ICD}} = 2.82 \pm 9.98\%$, respectively. These error ranges indicate that both ICD-AP and ICD will predict CFR values with less than 15% error for 85% of all studies and less than 20% error for 95% of all studies. These ranges were concluded to be sufficiently accurate for the clinic by a nuclear cardiologist and an expert analyst of nuclear medicine data.

IV. Discussion

The question now becomes, can we conclusively state that ICD-AP predicts more accurate CFR values than ICD? The simple answer is no: the techniques produce very similar average (CFR) predictions and are statistically similar ($p = 0.97$). However, we can state that it is likely that ICD-AP will better predict more accurate MBF_{rest} , $\text{MBF}_{\text{stress}}$, and CFR values in rest-stress studies where one of the dynamic acquisitions contain fewer frames that describe the gradual decay region of LV-AIF than seen in this validation study. In such cases, which could result from operator mismatch of ^{82}Rb injection and acquisition start, ICD-AP would act as a failsafe mechanism by augmenting the existing frame values with the P_4 - P_5 functional relationship and predict MBF values more accurately than ICD. For example, if a rest study contained a sufficient number of frames to describe the gradual decay region of LV-AIF and its corresponding stress study did not, then the resulting CFR would be largely inaccurate because ICD would predict an overestimated MBF_{rest} and an underestimated $\text{MBF}_{\text{stress}}$. The $\text{MBF}_{\text{stress}}$ value would be underestimated because the ICD fit would overestimate the amount of tracer present in the LV lumen in the gradual-decay region. Therefore, while we cannot strictly assert that ICD-AP is the better technique, we

can state that ICD-AP should be the technique applied to future trials, because it is better able to minimize procedural errors, if/when they arise.

Additional Applications

Though this investigation was limited to dynamic ^{82}Rb -PET studies with incomplete data, we contend that ICD-AP may have an impact on other dynamic PET applications. First, *ICD-AP may benefit efforts to reduce dose* in cardiac PET studies used to calculate CFR. For example, ^{13}N - NH_3 -PET rest-stress images possess better spatial resolution and contain much less noise (at late times) than images produced from ^{82}Rb -PET. Thus, we can expect AIFs and TACs derived from dynamic ^{13}N - NH_3 -PET scans to be less noisy and less subject to partial volume effects than those derived from dynamic ^{82}Rb scans. As a result, it would seem that reducing ^{13}N - NH_3 dose is possible given that ^{82}Rb -PET scans result in good diagnostic accuracy [3]. We hypothesize that kinetics analysis of ^{13}N - NH_3 -PET images from reduced-dose injections of ^{13}N - NH_3 would benefit from ICD-AP in a manner similar to the ^{82}Rb -PET application presented in this paper. However, in this case, missing information would manifest as a coarser acquisition protocol (to counteract reduced projection counts) instead of missing frames. ICD-AP would then serve to augment this coarse information with *a posteriori* knowledge to preserve nominal-dose CFR prediction accuracy in reduced-dose studies.

In addition, ICD-AP may have some impact on dynamic PET Patlak studies. Typically, AIFs for these studies are acquired via arterial blood sampling, venous blood sampling, or a combination of image-derived points and measured blood points [25]. However, application of ICD-AP may allow researchers and physicians to calculate AIFs purely from images and thus obviate the need for invasive blood sampling. Specifically, the first ten minutes would be used to acquire enough information to describe the two main regions of LV-AIF behavior. The measured LV-AIF would be fitted with ICD-AP using the P_4 - P_5 relationship of the injected tracer and extrapolated out to sixty minutes for Patlak or Logan analysis (depending on the tracer). Specific applications would include: Patlak K_i analysis of head and neck tumors using FDG- or FLT-PET; Patlak K_i analysis of (lower) abdominal tumors with FDG-PET; and Logan analysis of cerebral distribution volume (DV) using ^{15}O - H_2O -PET. Furthermore, ICD-AP (or ICD), may be applied as a means of de-noising AIFs before kinetic analysis given prior validation of the injected tracer.

Implementation at Other Cardiac Clinics

Though additional patient studies are necessary to confirm these initial findings, the results of this feasibility study were positive and were validated as clinically accurate by a nuclear cardiologist and an expert analyst of PET data.

Since this was a feasibility study, the main focus of additional validation should be on repeating this investigation with a larger patient set at UCSF. Given this study is successful, the technique would be made available to other clinics, which would be required to repeat this experiment at their facilities. A main point of these validation studies, particularly at UCSF, would be how ICD and ICD-AP compare over a large patient population. If they are found to be statistically similar, then ICD-AP may not be needed given strict adherence to experimental protocol, especially between injection and acquisition start. However, if they are found to be statistically dissimilar, then the technique with the best agreement should be implemented. If ICD-AP provides better agreement than ICD, then leave-one-out cross-validation should be used to assure that the P_4 - P_5 relationship is valid for large patient populations.

Conclusions

Finally, we understand that we are applying a novel method (ICD-AP) to a problem that is not at the technical forefront of PET studies. However, many cardiac clinics do not have the necessary physics support and resources to acquire in list-mode and are often limited to acquiring gated studies only. With these limitations, physicians must make clinical judgments regarding CAD without knowing *which* coronary vessels are affected by stenosis. Our method was designed to give physicians the flexibility to acquire both dynamic and ECG-gated information without the increased dose, cost, and overhead associated with serial studies. Thus, diagnoses *and* treatment decisions regarding patients at these clinics could be made with more information, less uncertainty, and hopefully, more accuracy.

Acknowledgments

This work was partially supported by NIH/NCI Grant K25 CA114254 (Y.S. and G.S.), NIH/NHLBI Grant R21 HL083073 (G.S. and Y.S.) and the University of California Industry-University Cooperative Research Program Granting dig10174 with Siemens Healthcare (G.S., S.L.B., and Y.S.).

References

1. Wilson WF, et al. Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation*. 1998; 97:1837–1847. [PubMed: 9603539]
2. Beller GA, Watson DD. A welcomed new myocardial perfusion imaging agent for Positron Emission Tomography. *Circulation*. 2009; 119:2299–2301. [PubMed: 19414654]
3. Bateman TM, Heller GV, McGhie AL. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol*. 2006; 13:24–33. [PubMed: 16464714]
4. Morris, E.; Endres, C.; Schmidt, K. *Emission Tomography: The Fundamentals of PET and SPECT*. San Diego: Elsevier; 2004.
5. Yoshinaga K, Katoh C, Noriyasu K. Reduction of coronary flow reserve in areas with and without ischemia on stress perfusion imaging in patients with coronary artery disease: a study using oxygen 15-labeled water PET. *J Nucl Cardiol*. 2003; 10:275–83. [PubMed: 12794626]
6. Parkash R, deKemp RA, Ruddy TD. Potential utility of rubidium 82 PET quantification in patients with 3-vessel coronary artery disease. *J Nucl Cardiol*. 2004; 11:440–9. [PubMed: 15295413]
7. Graf S, Pinch C. Cardiac PET-CT and its Implementation into Clinical Practice. *Imaging Decisions*. 2008; 12:24–31.
8. Dayanikli D, Grambow D, Muzik O. Early detection of abnormal coronary flow reserve in asymptomatic men at high risk for coronary artery disease using positron emission tomography. *Circulation*. 1994; 90:808–17. [PubMed: 8044952]
9. Graf S, Khorsand A, Gwechenberger M. Myocardial perfusion in patients with typical chest pain and normal angiogram. *Eur J Clin Invest*. 2006; 36:326–32. [PubMed: 16634836]
10. Schuijf JD, Poldermans D, Shaw LJ. Diagnostic and prognostic value of non-invasive imaging in known or suspected coronary artery disease. *Eur J Nucl Med Mol Imaging*. 2006; 33:93–104. [PubMed: 16320016]
11. Di Carli MF, Dorbala S, Meserve J. Clinical Myocardial Perfusion PET/CT. *J Nuc Med*. 2007; 48:783–793.
12. Di Carli MF, Dorbala S. Cardiac PET-CT. *J Thorac Imaging*. 2007; 22:101–6. [PubMed: 17325581]
13. Cerqueira MD, Weissman NJ, Dilsizian V. Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart: A Statement for Healthcare Professionals From the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002; 105:539–42. [PubMed: 11815441]
14. Feng D, Huang SC, Wang X. Models for computer simulation studies of input functions for tracer kinetic modeling with positron emission tomography. *Int J Biomed Comput*. 1993; 32:95–110. [PubMed: 8449593]

15. Eberl S, Anayat AR, Fulton RR. Evaluation of two population-based input functions for quantitative neurological FDG PET studies. *Eur J Nucl Med.* 1997; 24:299–304. [PubMed: 9143468]
16. Muzic RF, Chrisitan BT. Evaluation of objective functions for estimation of kinetic parameters. *Med Phys.* 2006; 33:342–353. [PubMed: 16532939]
17. Marquardt DW. An algorithm for least-squares estimation of non-linear parameters. *J Soc Ind Appl Math.* 1963; 11:431–41.
18. Markwardt, CB. Non-linear least square fitting in IDL with MPFIT. *Astronomical Data Analysis Software and Systems XVIII, ASP Conference Series;* 2008. p. 251-254.
19. Wales DJ. Global Optimization by Basin-Hopping and the Lowest Energy Structures of Lennard-Jones Clusters Containing up to 110 Atoms. *J Phys Chem.* 1997; 101:5111–16.
20. Kirkpatrick S. Optimization by simulated annealing: quantitative studies. *J Stat Phys.* 1984; 34:975–86.
21. Wagenmakers EJ, Farrell S. AIC model selection using Akaike weights. *Psychon Bull Rev.* 2004; 11:192–6. [PubMed: 15117008]
22. Lortie M, Beanlands RSB, Yoshinaga K. Quantification of myocardial blood flow with ⁸²Rb dynamic PET imaging. *Eur J Nucl Med.* 2007; 34:1765–74.
23. Carroll, RJ.; Ruppert, D. Transformation and weighting in regression. New York, NY: Chapman & Hall; 1988.
24. Ryan, TP. Modern Regression Methods. New York, NY: John Wiley and Sons, Inc; 1997.
25. Doot RK, Muzi M. Kinetic Analysis of ¹⁸F-Fluoride PET Images of Breast Cancer Bone Metastases. *J Nucl Med.* 2010; 51:521–7. [PubMed: 20237040]
26. Gould KL. Clinical cardiac PET using generator-produced Rb-82: A review. *Cardiovascular and Interventional Radiology.* 1989; 12:245–51. [PubMed: 2514984]
27. Eagle KA, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation.* 2004; 110:340–437.
28. Seung KB, et al. Stents versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease. *The New England Journal of Medicine.* 2008; 358:1781–1792. [PubMed: 18378517]

Fig. 1.

Proposed patient study protocol to acquire CFR and LVEF data in the same amount of time as a typical gated scan.

Fig. 2.
Dynamic protocol used to validate proposed combined protocol.

Fig. 3. Representative complete-data (CD) and incomplete-data (ICD) arterial input functions derived from the left ventricle (LV). CD data represented by lines and ICD represented by triangles (LV).

1. Initialize temperature of simulated annealing
2. Initialize parameter averages $\bar{P}_i$
3. Sample parameters P_i
 - a. $P_i = \bar{P}_i + uni_rand_i * range$
 - b. $-0.5 \leq uni_rand_i < 0.5$
4. Calculate local minimum with Levenberg-Marquardt
5. Local minimum < global minimum?
 - a. Yes: Proceed to Step 7
 - b. No: Proceed to Step 6
6. Accept / reject local minimum as next guess
 - a. Accept: Step 3 with local minimum parameters as $\bar{P}_i$
 - b. Reject: Step 3 with global minimum parameters as $\bar{P}_i$
7. Lower SA "temperature"
8. Acceptance probability distribution check
 - a. "Cold" temperature: Step 1
 - b. "Warm" temperature: Step 3 with global minimum parameters as $\bar{P}_i$

Fig 4.
Basin-hopping algorithm with Levenberg-Marquardt.

Fig. 5.
TAC with significant noise level processed to reduce variability in the “tail” of the curve.

Fig 6.
Representative CD dFPE and tripsexp fits of LV- and RV-AIFs.

Fig 7.
Relationship between P_4 and P_5 for ^{82}Rb AIFs

Fig. 8. Complete-data fits of representative LV- and RV- AIFs compared to incomplete-data fits with and without *a posteriori* knowledge.

Fig. 9. Comparing CD MBF measurements with ICD and ICD-AP MBF measurements. Bias is assessed relative to the line of unity ($MBF_{ICD}=MBF_{CD}$)

Fig. 10. Bland-Altman plot comparing ICD-AP and ICD methods with CD method. 95% confidence boundaries are marked by dashed black lines and dashed grey lines for ICD-AP and ICD, respectively.

TABLE I

Goodness-of-Fit Statistics for dFPE and tripsexp

Patient Study	dFPE	tripsexp
1-LV-R	1.21	1.23
2-LV-R	1.06	0.98
3-LV-R	1.07	1.16
1-LV-S	1.68	2.08
2-LV-S	1.00	2.02
3-LV-S	1.31	1.40
1-RV-R	2.19	3.84
2-RV-R	0.57	1.27
3-RV-R	1.58	2.51
1-RV-S	0.60	2.07
2-RV-S	2.70	2.74
3-RV-S	0.84	0.84

TABLE II

AMW values for dFPE and tripsexp

Patient Study	AMW _{dFPE}	AMW _{tripsexp}
1-LV-R	57.56%	42.44%
2-LV-R	23.62%	76.38%
3-LV-R	77.57%	22.43%
1-LV-S	96.55%	3.45%
2-LV-S	100.00%	0.00%
3-LV-S	73.19%	26.81%
1-RV-R	99.98%	0.02%
2-RV-R	100.00%	0.00%
3-RV-R	99.92%	0.08%
1-RV-S	100.00%	0.00%
2-RV-S	55.12%	44.87%
3-RV-S	53.42%	46.57%

TABLE III

GOFS for ICD and ICD-AP

Patient Study	ICD-AP	ICD
1-LV-R	0.046	0.098
2-LV-R	0.030	0.014
3-LV-R	0.518	1.493
1-LV-S	0.160	0.313
2-LV-S	0.615	0.171
3-LV-S	0.042	0.071
1-RV-R	0.007	0.005
2-RV-R	0.286	0.005
3-RV-R	0.087	0.123
1-RV-S	0.299	0.167
2-RV-S	0.518	1.698
3-RV-S	0.259	0.423

TABLE IV

CFR estimates for each method

CFR_{CD}	CFR_{ICD-AP}	CFR_{ICD}
0.875	0.993	1.067
1.636	1.775	1.726
1.302	1.239	1.223
0.945	0.928	0.941
3.990	4.578	4.432
2.828	3.147	3.346
0.598	0.557	0.582
1.667	1.783	1.723
1.060	1.201	1.084
2.163	1.802	2.030
5.234	5.028	4.669
1.982	1.970	1.933