MODEL SIMULATION OF FOREARM HYPERAEMIC REACTIVITY

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ABSTRACT

Forearm hyperaemic reactivity (FHR) has been proposed as a novel noninvasive method for discriminating patients with cardiovascular disease (CVD). However, the modeling functions of FHR require more robust models. The present study was designed to develop quantitative modeling techniques to better estimate the physiology of this model. The fitted time activity curves of the hyperaemic arm of non-CVD participants, using blood and muscle uptake, were obtained in the 2-compartment model with the mean R^2=0.913±0.018. However, for CVD patients, the 2-compartment model yielded a mean R^2=0.844±0.018, so a 3-compartment model was used. This model generated mean R^2 of 0.982±0.002 for non-CVD participants and 0.979±0.002 for CVD patients. It is believed that 3-compartment model provides estimates of the activity in the blood, in the interstitial space or cytoplasm, and in the mitochondria. The 2-compartment model provides good fits for FHR in non-CVD participants but not CVD patients. Alternatively, it would seem that the 3-compartment model provides good fits for both groups. These results should help us optimize the predictive values of the FHR test, infer pathological components of the disease and, ultimately improve the patient risk stratification.

INTRODUCTION

Forearm hyperaemic reactivity (FHR) has been proposed as a novel noninvasive method for discriminating patients with cardiovascular disease (CVD). The approach is based on the intravenous injection of the myocardial perfusion agent Tc-99m-tetrofosmin (Tc-99m) and the simultaneous non-invasive external detection of the tracer ingress and transit into both forearms: the one submitted to reactive hyperemia and the contralateral non-hyperemic one [1, 2]. Initial results from the ratio of the maximal upslope between the arms (termed the relative-uptake-ratio: RUR) was able to significantly predict the presence of disease, with differences in the order of 40-50% between those with and those without CVD. However, the modeling functions of FHR require more robust models. The development of quantitative tracer kinetic modeling techniques holds great potential for noninvasive assessment of physiologic processes in myocardial perfusion imaging using planar scintigraphy [3].

The present study was designed to develop quantitative modeling techniques to better estimate time activity curve distribution in the forearms. Specifically, the contribution of potential physiological compartments such as blood, the interstitial space or cytoplasm, and the mitochondria were assessed.

METHODS

Participants

In total, data from 12 participants recruited from the outpatient clinic of the Department of Nuclear Medicine at the Montreal Heart Institute was used. Patients were defined as either CVD whose risk factors are greater than 5 (3 women and 3 men) or non-CVD whose risk factors are less than 2 (3 women and 3 men) [4]. The study was approved by the ethics committee of the Institute.

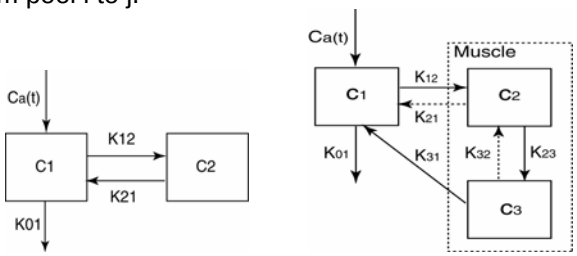
Data acquisition

Forearm hyperaemic reactivity (FHR) was assessed while the patient was seated with both arms extended, hands prone (facing upward) over the top of a standard large field-of-view gamma camera with a low negative high resolution collimator (Scintronix, London, UK). To create the hyperaemic challenge, a blood pressure cuff (Adult First Responders, B&A Instruments, New York) was placed on one arm and inflated to 50 mmHg above systolic blood pressure for 5 minutes, after which it was released. A bolus injection of 0.42 mCi/kg of the radioactive tracer Tc-99m-tetrofosmin (Myoview©, Amersham Health, Princeton, NJ) was introduced into the patient's arm via a small catheter positioned in the bend of the contralateral arm 30 seconds after the cuff was deflated. Dynamic image acquisitions were realized using 128 X 128 matrices at a sampling rate one frame per second [1, 2].

A region of interest (ROI) was drawn over the hyperaemic forearms, limited by the bend of the arm and excluding the wrist. The counts in each ROI were normalized by scan length to obtain the counts pixel^{-1} second^{-1} for a given ROI.

Compartment model

The current study used a 2-compartment model and 3-compart-ment model, as shown in Figure1, to analyze the kinetics of the concentration of the radiotracer in the hyperaemic arm. In Model 1, $c_1(t)$ is loosely considered as Tc-99m concentration in the artery (plus the arterialized vein) represented by the blood time activity curve, and $c_2(t)$ is the concentration in the tissue. In the model 2, $c_1(t)$ is the once again considered to represent the blood, $c_2(t)$ is considered mainly as the concentration in the mitochondrial, and $c_3(t)$ is defined as a third space, which probably represents the interstitial space or the cytosol. The k_{ij} (i,j = 0~3) constants are defined as the rate constants from pool i to j.



Model 1 Model 2

Figure 1:Compartment models used for fitting kinetics of radiotracers in the forearm. *Model 1*, 2-compartment model; *Model 2,* 3-compartment model.

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The two models are only crude approximations of the more complex biological system [5-9]. Our main purpose is to derive reasonable curve distributions in the blood and tissue. There are many applications of kinetic modeling techniques providing improved understanding of more complex dynamic processes [7-12]. Generally, tracer kinetic modeling requires the measurements of the tracer time activity curves in both plasma and tissue to estimate the physiological parameters, i.e. to fit the parameters of certain compartment models as the model input and output functions, respectively. However, our measured activity time curves, using the scintigraphy, represent the cross contamination of the true tissue activity, venous return and blood activity. The scintigraphy cannot support the complex modeling analysis because it lacks absolute quantification of radioactivity concentration (planar imaging) or has insufficient temporal resolution [6]. To solve this problem, the dynamic time activity curve was decomposed into vascular and tissue compartments which was represented by c_1 and c_2 in the Model 1. In the actual curve, the latter segment of the curve seems gradually stable which was assumed to be a muscle uptake compartment c_2. This curved was simulated by using equation 1 in the Model 1 [6]. The input function $c_a(t)$ is assumed to be $A(t-\tau)e^{-\lambda(t-\tau)}$, where λ is the fraction remaining of Tc-99m, A is amplitude (count/second).

$$c_2(t) = \begin{cases} 0 & if\ t < \tau \\ (A_1(t-\tau) - A_2 - A_3)e^{-\lambda(t-\tau)} + A_2 e^{-\lambda_1(t-\tau)} & \\ + A_3 e^{-\lambda_2(t-\tau)} & if\ t > \tau \end{cases} \quad (1)$$

In the equation 1, λ_1, λ_2 are eigenvalues of the model; A_1, A_2 and A_3 are coefficient constants; τ is the timing delay constant.

After substracting compartment c_2, the remaining part of the actual curve (c_1) was fitted by the gamma function. The sum (c(t)) of the fitted curve c_1 and c_2 was compared with the actual curve, to derive a R^2 to estimate the goodness of fit.

In Model 2, the compartment c_3(t) was simulated as $\sum_{i=1}^{3} A_i e^{-\lambda_i t} \otimes c_a(t)$. The combination of the time activity curve c(t) = c_1(t) + c_2(t) + c_3(t) was calculated and compared to the actual curve obtained. Once again R^2 was calculated to estimate the goodness of fit. All fit processes used the non-linear least squares (NLS) method to minimize the objective function. All data were created from proprietary software which used Matlab as a base program.

RESULTS & DISCUSSION

Data from all of the participants were tested by using both Model 1 and Model 2. Examples of the obtained curves from the 2-compartment model are presented

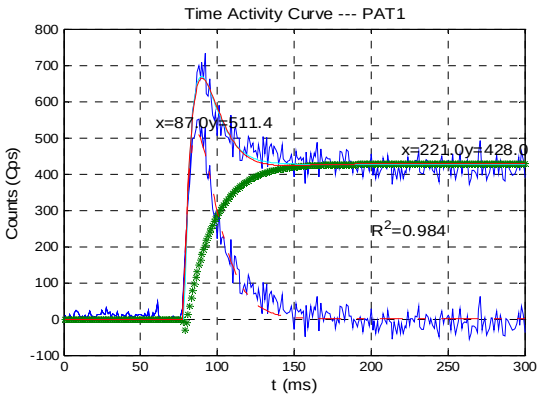


Figure 2: The curves generated from Model 1 for a participant without CVD.

in Figures 2 and 3. The dashed curve reflects compartment c_1, blood uptake, and the stared curve represents compartment c_2, tissue uptake. The curve on the top c(t) is the total uptake ($c_1(t) + c_2(t)$), which fits the actual curve obtained from the scintigraph. Figure 2 is from a non-CVD patient and reflects a good fit (R^2 = .98). In contrast, Figure 3 is from a CVD patient, where the fit is moderate (R^2 = .79).

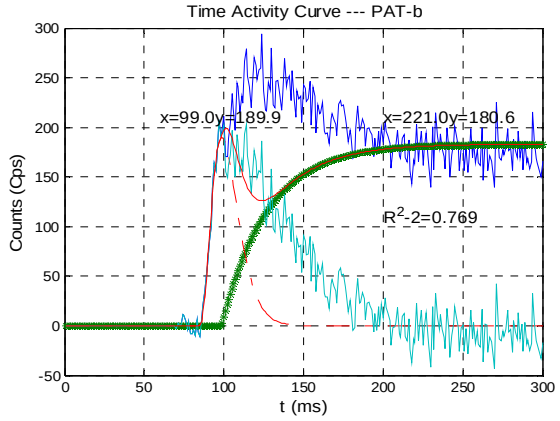
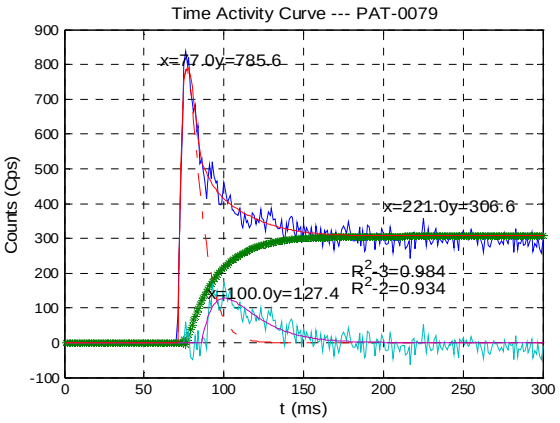
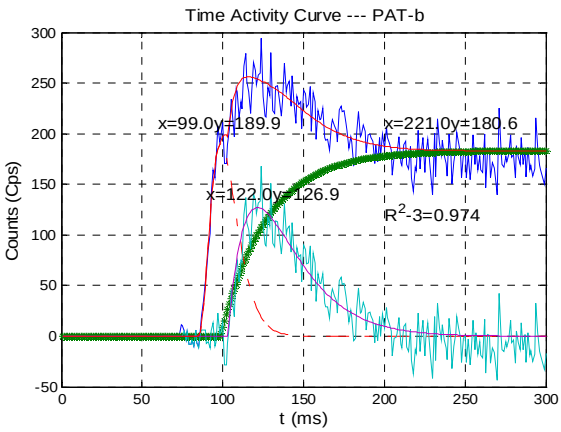


Figure 3 The curves generated from Model 1 for a patient with CVD



(a)



(b)

Figure 4: The fitted curve results for Model 2 in (a) a participant without CVD, and (b) a patient with CVD.

Figure 4 provides 2 examples of curves generated from Model 2. As with Figures 2 and 3, the dashed curve represents compartment c_1, the blood uptake. The stared curve is thought to reflect the uptake of Tc-99m in the mitochondria. The fitted curve on the bottom that is defined as the third space is believed to relate to the interstitial or cytosolic space. Tc-99m-tetrofosmin is known to be retained by the mitochondria of muscle cells by a mechanism which is dependent on the mitochondrial membrane potential[5]. Therefore, the third space is hypothesized to be related to mitochondrial dysfunction. Its size might provide more information of mitochondrial mechanism. The curve on the top is the sum of curve $c_1(t)$, $c_2(t)$ and $c_3(3)$, which fits the actual curve obtained from the scintigraph.

Table 1 shows the mean ± SD, and the value of t-test for Model 1 and Model 2 in participants with (CVD) and without (non-CVD) CVD. In addition, the relative error E_R^2 of R^2 (defined as, (R^2 (Model 2) - R^2 (Model 1)) / R^2 (Model 2) * 100%) is also reported.

Table1: The results of R^2 for Model 1 and Model 2 in CVD and Non-CVD participants.

Parameter	*CVD (n=6)*	*Non-CVD (n=6)*	*t*	*p*
Model1				
Mean R^2 ± SD	0.844±0.018	0.913±0.018	2.68	<0.02
Model2				
Mean R^2 ± SD	0.979±0.002	0.982±0.002	0.96	<0.36
Model 1&2				
E_R^2 (%)	13.8 ± 2.1	7.1 ± 1.3	2.7	<0.02

CONCLUSION

In this study, we found that the 2-compartment model provided a good fit for FHR in non-CVD participants. However, it did not provide as good a fit for CVD patients. The 3-compartment model can be used to account for the presence of a transient uptake component for both CVD and non-CVD participants and seems to have a good fit. Further, utilization of E_R^2 may provide a means to discriminate between those with and without CVD. However, further work is needed to confirm this clinical utility.

Ultimately, these results should help us optimize the predictive values of the FHR test, explore the pathological components of the disease, and eventually, improve patient risk stratification.

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