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A Personalized and Optimal Approach for Dosing Contrast Material at Coronary Computed Tomography Angiography

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***Abstract*—A method for constructing a personalized contrast medium protocol at contrast enhanced, Coronary CT Angiography (CCTA) is presented. A one compartment pharmacokinetic model is parameterized and identified with a minimal data set from a test-bolus injection. A direct-search optimization is performed to construct a protocol that achieves target enhancement in the cardiac structures. Clinical results demonstrating the method's ability to achieve prospectively chosen image enhancement levels while reducing contrast medium dose are presented.**

I. Introduction

A critical element of all CT Angiography studies is administration of X-Ray absorbing contrast agents by computerized injection systems. To maximize diagnostic performance, however, the scan acquisition should be commensurate with the peak blood-plasma concentration of the contrast bolus in the vessel of interest. As the contrast bolus propagates from the peripheral venous injection site to the central arterial circulation it is dispersed by convective and diffusive processes.

Because the attenuation of the X-Rays is linearly related to the blood-plasma concentration of the contrast bolus, the luminal enhancement pattern of blood vessels directly follows that of the contrast bolus, resulting in a peaked pattern that occurs some time after the end of the contrast injection and whose peak and full width at half maximum (FWHM) are a function of the patient's cardiac dynamics, the injection administration rate, and the volume and concentration of the contrast media[1]. The dosing and delivery method of contrast material per patient rarely considers these pharmacokinetic and cardiovascular conditions of each patient. Typically, every patient receives the same volume of contrast media delivered at the same volumetric flow rate.

A timing bolus injection (10-20 ml prior to the diagnostic scan) is often used in clinical practice to synchronize scan acquisition with the arrival of the contrast bolus. During a timing bolus procedure a single-level scan acquisition is performed for 10-30 seconds, typically at the level of the pulmonary trunk. The scanner operator draws a Region of Interest in a vascular territory such as the ascending aorta (Ao). The scanner software copies the ROI on all the images in the timing bolus data set (see Figure 1). The averaged attenuation level (Hounsfield Units) from each ROI is plotted against the acquisition time to construct a Time Enhancement Curve (TEC). The peak time of the TEC, or the peak time plus an offset, in the aorta is often used as the scan delay between contrast administration and scan acquisition.

To date, scanner manufacturers have not developed software for use in computing personalized contrast injection protocols despite the work of Fleischmann and Mahnken [2],[3] that use an entire TEC from a timing bolus for computing individualized contrast protocols. A practical, clinical constraint for a personalized contrast protocol generation algorithm is it should function on a separate computer or perhaps on the contrast delivery system. It should require a minimum set of manual entry feature data from the timing bolus TEC.

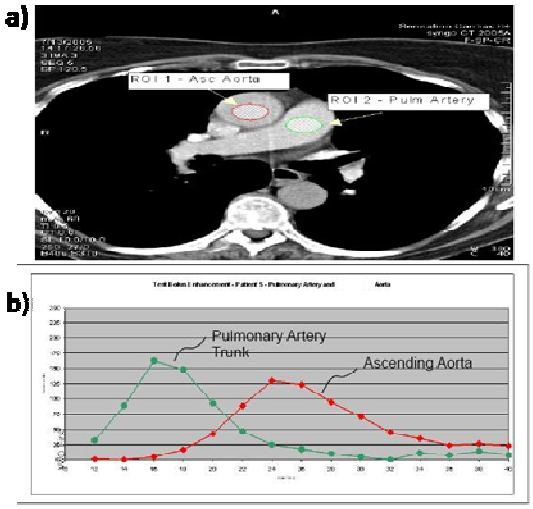

Figure 1 a)Illustration of two ROIs drawn on a test-bolus, axial CT image.b)TECs generated from the data set in Figure 1a.

We present a novel approach for computing personalized, contrast media injection protocols for use at coronary CTA requiring a minimal set of measurements from timing bolus TECs. The algorithm attempts to minimize the dose of contrast material sufficient to achieve specified, image contrast enhancement levels. To our knowledge, our method is the first published algorithm that performs a per-patient optimization using a parameterized model of the drug and patient.

II. Methods

The theoretical basis of this algorithm is a one compartment, open pharmacokinetic model. The

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mathematical model is very similar to one proposed by Dawson and Blomley [4]. Their model was not proposed for use in a per-patient computation paradigm, rather it was presented as a vehicle to explore general principles of contrast medium enhancement.

The input parameters to our PK model are the contrast concentration, flow rate and duration of the injection. We use four point metrics - the time to peak and peak enhancement of two TECs obtained during the timing bolus acquisition to derive estimates of the cardiac output and blood volume. Cardiac output and vascular blood volume are the two key parameters affecting contrast bolus propagation and enhancement at CT Angiography [1, 4].

A direct search minimization is performed to identify values of injection duration and flow rate that minimize a cost function.

A. Pharmacokinetic Model

Equation (1) describes the distribution of contrast material in the central blood compartment resulting from injection into a peripheral injection site. The origin, $t=0$, corresponds to the time at which the contrast material arrives in the region of interest. In (1), Q_{inj} [ml/s] is the injection flow rate, T_{inj} [s] is the injection duration, Q_{CO} is the cardiac output [ml/s], V_B is the blood volume between the injection site and measurement point [ml], C_i is the concentration of the stock contrast medium, and C_o is the blood concentration of the agent at time t.

$$C_o(t) = \begin{cases} \frac{Q_{inj}}{Q_{co}} C_i \left(1 - e^{\frac{-Q_{CO}}{V_B} t} \right) & t \le T_{inj} \\ C_o(T_{inj}) e^{\frac{-Q_{CO}}{V_B}(t - T_{inj})} & t > T_{inj} \end{cases} \qquad (1)$$

A TEC measured in the ascending aorta from a timing bolus injection is annotated as $s_{AO}(t)$ [HU]. $s_{PA}(t)$ is the TEC measured in the pulmonary artery trunk. T_{inj} is the injection duration.. K_{HU_mgI} is the conversion factor relating HU to concentration of Iodine *in vivo* at the measurement location. There is a linear relationship between a TEC and the blood-contrast concentration [mgI/ml]:

$$C_{AO}(t) = \frac{s_{AO}(t)}{K_{HU\_mgI}}$$
$$C_{PA}(t) = \frac{s_{PA}(t)}{K_{HU\_mgI}} \qquad (2)$$

We use 27.1 HU/(mgI/ml) as the default value for K_{HU_mgI}, and near the range (21-26 HU/(mgI/ml)) published by several investigators [5-7]. Our value was computed by a calibration experiment prior to clinical experiments.

B. Parameter Estimation

To use our governing model for patient-specific diagnostic protocol generation, estimates of cardiac output (Q_{CO}) and blood volume between the injection site and measurement point (V_B) are necessary.

Because we are only considering a limited number of point metrics (such as the time of peak contrast enhancement) from the timing bolus TECs instead of the entire curves, there is only one data point on each concentration curve available, and the system is underdetermined. We approximate acquiring two points on a single curve by combining the data points on the individual curves from each structure, which is valid given a set of simplifying assumptions.

First, we assume the blood volumes are the same in both compartments so the concentration is equivalent to the amount of iodine in the compartment (otherwise, the system is still underdetermined with two equations and three unknowns). Second, we restrict the system to two single compartments where the peak enhancements and times to peak are measured. The contrast is injected, flows into the pulmonary artery, flows into the ascending aorta, and then flows out. Loss of iodine in an intermediate compartment (such as the lungs) is ignored. This is a similar treatment as Harris and Heath give in [8] when describing a technique to measure blood volume using dye dilution. The simplified model yields $C_o(t)$ curves similar to those shown in Figure 2.

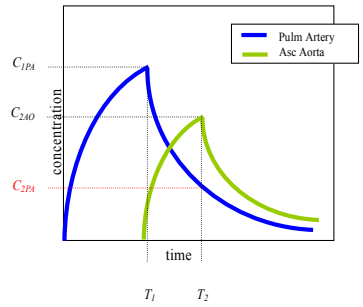

Figure 2 Sample concentration curves resulting from a small or "test" bolus injection, where times to peak and peak enhancements are labeled.

The available measurements from the 2 TECs are C_{1PA}, T_1 (peak time of C_{PA}), C_{2AO}, and T_2 (peak time of C_{AO}). We assume that the maximum value of each concentration curve is $C(T_{inj})$. At $t=T_1$, $C_{1PA}*V_B$ milligrams of iodine are present in the pulmonary artery. The total mass of contrast in the pulmonary artery at T_1 is less than the amount in the test bolus because some has already flowed into the ascending aorta. At $t=T_2$, $C_{2AO}*V_B$ milligrams of iodine are present in the ascending aorta. The peak in the ascending aorta curve at T_2, C_{2AO}, is less than the pulmonary artery peak because a portion of the bolus is still in the previous compartment. Therefore, the magnitude of C_{2PA} can be approximated by the difference in peaks:

$$C_{2PA} \approx C_{1PA} - C_{2AO} \tag{3}$$

The peak of the pulmonary artery curve is defined by:

$$C_{1PA} = \frac{Q_{inj}}{Q_{CO}} C_i \left(1 - e^{\frac{-Q_{CO}}{V_B} T_1} \right) \tag{4}$$

The expression for C_{2PA} on the downslope is then:

$$C_{2PA} \approx C_{1PA} - C_{2AO} = C_{1PA} \left(e^{\frac{-Q_{CO}}{V_B}(T_2 - T_1)} \right) \tag{5}$$

and solving for V_B in (5) yields:

$$\hat{V}_B = \frac{-(T_2 - T_1) Q_{CO}}{\log\left(\frac{C_{1PA} - C_{2AO}}{C_{1PA}} \right)} \tag{6}$$

We can now isolate Q_{CO}:

$$\hat{Q}_{CO} = \frac{Q_{inj}}{C_{1PA}} C_i \left(1 - \left(\frac{C_{1PA} - C_{2AO}}{C_{1PA}} \right)^{\frac{T_1}{T_2 - T_1}} \right) \tag{7}$$

C. Optimization and Protocol Generation

Two parameters must be set by the clinician: the desired peak concentration and the target concentration. The target concentration is defined as the concentration at the start and end of the scan window. In our model, $C_{LH\text{-}Peak}$ occurs T_{inj1} seconds after the contrast arrives in the left heart (T_{LH_arr}) (see Figure 3).

The scan begins at T_{start}, on an unknown point on the upslope of the left heart concentration curve. It is the task of the protocol generation algorithm to determine the scan start time in relation to the predicted contrast enhancement profiles. The scan ends ΔT seconds later, where ΔT is the diagnostic, CT scan duration and falls on the downslope of the LH enhancement curve. The scan duration is a function of the scan length, heart-rate and other parameters of the imaging procedure.

To compute a protocol resulting in contrast concentration (and therefore contrast enhancement) of C_{Target} throughout the scan duration, we construct a cost function that penalizes the peak and target enhancements. The volume of contrast material is the product of the administration flow rate, Q_{inj} and the duration of the injection, T_{inj}.So, if we determine values of the duration and flow rate at which the cost function is minimized, we are computing a minimum volume sufficient to satisfy the clinical targets. We search

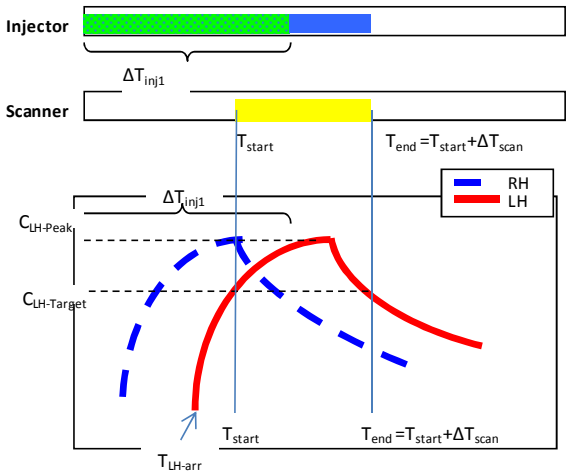

Figure 3 Relative timing and interrelationship among the injection protocol, the CT scan, and the enhancement of contrast *in vivo*. RH = Right Heart structures, LH = Left Heart structures (including coronary arteries).

for the parameters T_{inj} and Q_{inj} that minimize the cost function in (8):

$$Q^*_{inj}, T^*_{inj} = \underset{Q_{inj}, T_{inj}}{\arg\min} \left(\begin{vmatrix} CP_{Desired} - C_{\text{Peak}} \end{vmatrix} + \begin{vmatrix} CT_{Desired} - C_{\text{Target}} \end{vmatrix} \right) \tag{8}$$

where $CP_{Desired}$ and $CT_{Desired}$ are the desired peak and target enhancement in the left heart structures. To find Q^*_{inj} and T^*_{inj}, the error function must be defined in terms of Q_{inj}, T_{inj}, and identified parameters. This is already true by definition for C_{Peak}:

$$C_{Peak} = \frac{Q_{inj}}{Q_{CO}} C_i \left(1 - e^{\frac{-\hat{Q}_{CO}}{\hat{V}_B} T_{inj}} \right) \tag{9}$$

The value of C_{Target} on the upslope is also a function of T_{start}, the unknown time at which the scan begins:

$$C_{Target} = \frac{Q_{inj}}{Q_{CO}} C_i \left(1 - e^{\frac{-\hat{Q}_{CO}}{\hat{V}_B} T_{start}} \right) \tag{10}$$

On the downslope, C_{Target} is the concentration at the end of the scan, which is a function of C_{Peak} and T_{start} (assuming the scan duration, ΔT, is fixed and known):

$$C_{Target} = C_{Peak} \left(e^{\frac{-\hat{Q}_{CO}}{\hat{V}_B}(T_{start} + \Delta T - T_{inj})} \right) \tag{11}$$

Substituting in for C_{Peak} and simplifying yields:

$$C_{Target} = \frac{Q_{inj}}{\hat{Q}_{CO}} C_i \left(e^{\frac{-\hat{Q}_{CO}}{\hat{V}_B}(T_{start}+\Delta T-T_{inj})} - e^{\frac{-\hat{Q}_{CO}}{\hat{V}_B}(T_{start}+\Delta T)} \right) \quad (12)$$

We now have two equations (C_{Target} on the upslope and the downslope) and two unknowns (C_{Target} and T_{start}). After solving algebraically for C_{Target}, we have the following expression in terms of only Q_{inj}, T_{inj}, and known constants:

$$C_{Target} = \frac{\frac{Q_{inj}}{Q_{CO}} C_i \left(1 - e^{\frac{-Q_{CO}}{V_B} T_{inj}} \right)}{1 - e^{\frac{-Q_{CO}}{V_B} T_{inj}} + e^{\frac{-Q_{CO}}{V_B}(T_{inj}-\Delta T)}} \quad (13)$$

Note that if $T_{inj} >> \Delta T$, C_{Target} approaches the numerator (C_{Peak}), and if $\Delta T >> T_{inj}$, C_{Target} goes to zero. We now substitute equations (13) and (9) into (8) and find the parameters that minimize the cost function.

We chose to implement a brute force search strategy because the parameter range is well defined, the solution manifold is well behaved and the computational burden needed to search for the minimum is insignificant, especially realizing that a computation time of several seconds in the interval between parameter entry and protocol generation has no impact on the procedure

D. Clinical Validation

We conducted an IRB approved clinical investigation at the Medical University of South Carolina to evaluate the effectiveness of the personalized contrast protocol technique. 32 patients undergoing contrast (300mgI/ml, Iopromide, Bayer Healthcare) enhanced coronary CT (Definition DS, Siemens Medical) gave informed consent and were included in the study. A desired Left Heart target enhancement level ($CT_{Desired}$*$K_{mgItoHU}$ in (8)) was set at 250 HU for all subjects and 300 HU was set as the desired peak Left Heart enhancement in ($CP_{Desired}$*$K_{mgItoHU}$ in(8)). Quantitative measurements of contrast enhancement in the proximal, mid and distal segments of the Left Main (LM), Left Anterior Descending (LAD), Left Cirumflex (LCx), and Right Coronary arteries (RCA) were made by averaging three ROIs placed in each structure. Additionally, attenuation measurements were made in the Ascending Aorta (Ao). The overall CM volume and injection rates were compared to the clinical contrast delivery protocol at MUSC, which is based on scan duration only, at a fixed flow-rate of 6cc/sec.

III. Results

The mean (+/-SE) CM volume with use of the individualized injection protocol was 63.8±3.8ml, with a mean injection rate of 4.1±0.2ml/sec. The mean CM volume in the same patients, using the routine clinical protocol, would have been significantly ($p<0.01$) higher at 82.1±3.9ml. Thus, a mean CM savings of 18.3±4.3ml was achieved. The mean (+/-SE) attenuation in the ascending aorta and LM were 261.7±9 and 277.5±8.9HU, respectively. Mean attenuation (+/- SE) in the proximal, mid and distal segments of the LAD, LCx and RCA are given in Table I.

Table I Coronary Artery Enhancement Results

Coronary Artery Structure	Mean Contrast Enhancement [HU]	Standard Error of the Mean
LAD-proximal	278.0	9.8
LAD-mid	254.7	11.2
LAD-distal	259.0	11.5
LCx-proximal	269.7	9.1
LCx-mid	245.5	10.4
LCx-distal	233.0	8.2
RCA-proximal	273.6	8.9
RCA-mid	273.6	9.4
RCA-distal	275.0	12.0

The LM, LAD, proximal and mid LCx, and the entire RCA had significantly higher attenuation than 250HU ($p<0.05$, Wilcoxon signed-rank test).

IV. Discussion

Our proposed methodology was validated on a small cohort of subjects. Only the distal LCx did not achieve contrast enhancement greater than the specified target, and local hemodynamic effects in the narrow, distal branches of the vessel may have led to this finding. We demonstrated an ability to reduce the average contrast dose, a critically important issue in the management of patients with renal insufficiency.

Future investigations will study the ability of our technique to achieve enhancement at larger enhancement values because 250HU is the minimally accepted contrast enhancement level for CCTA. Additional research will also be taken to determine if algorithmic modifications may be made to target the right heart structures by incorporation into the cost function.

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