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Research paper

Underestimation of myocardial blood flow by dynamic perfusion CT: Explanations by two-compartment model analysis and limited temporal sampling of dynamic CT

Masaki Ishida [a], Kakuya Kitagawa [a], Takashi Ichihara [b], Takahiro Natsume [b], Ryohei Nakayama [a], Naoki Nagasawa [a], Makiko Kubooka [a], Tatsuro Ito [a], Mio Uno [a], Yoshitaka Goto [a], Motonori Nagata [a], Hajime Sakuma [a, *]

[a] Department of Radiology, Mie University Hospital, Tsu, Mie, Japan
[b] Faculty of Radiological Technology, Fujita Health University School of Health Science, Toyoake, Aichi, Japan

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ABSTRACT

Purpose: Previous studies using dynamic perfusion CT and volume perfusion CT (VPCT) software consistently underestimated the stress myocardial blood flow (MBF) in normal myocardium to be 1.1–1.4 ml/min/g, whilst the O 15-water PET studies demonstrated the normal stress MBF of 3–5 ml/min/g. We hypothesized that the MBF determined by VPCT (MBF-VPCT) is actually presenting the blood-to-myocardium transfer constant, K1. In this study, we determined K1 using Patlak plot (K1-Patlak) and compared the results with MBF-VPCT.

Material and methods: 17 patients (66 ± 9 years, 7 males) with suspected coronary artery disease (CAD) underwent stress dynamic perfusion CT, followed by rest coronary CT angiography (CTA). Arterial input and myocardial output curves were analyzed with Patlak plot to quantify myocardial K1. Significant CAD was defined as >50% stenosis on CTA. A simulation study was also performed to investigate the influence of limited temporal sampling in dynamic CT acquisition on K1 using the undersampling data generated from MRI.

Results: There were 3 patients with normal CTA, 7 patients with non-significant CAD, and 7 patients with significant CAD. K1-patlak was 0.98 ± 0.35 (range 0.22–1.67) ml/min/g, whereas MBF-VPCT was 0.83 ± 0.23 (range 0.34–1.40) ml/min/g. There was a linear relationship between them: (MBF-VPCT) = 0.58 x (K1-patlak) + 0.27 (r^2 = 0.65, p < 0.001). The simulation study done on MRI data demonstrated that Patlak plot substantially underestimated true K1 by 41% when true K1 was 2.0 ml/min/g with the temporal sampling of 2RR for arterial input and 4RR for myocardial output functions.

Conclusions: The results of our study are generating hypothesis that MBF-VPCT is likely to be calculating K1-patlak equivalent, not MBF. In addition, these values may be substantially underestimated because of limited temporal sampling rate.

1. Introduction

Dynamic first-pass contrast enhanced myocardial perfusion CT provides the time-attenuation curves (TAC) of blood pool and left ventricular (LV) myocardium, which represent arterial input function (AIF) and myocardial output function, respectively. Several groups have investigated quantitative analysis of first-pass myocardial perfusion MRI with a compartmental analysis approach since the early 1990s.[1–4] As CT iodinated contrast medium and MR gadolinium contrast medium have a similar property as a perfusion tracer, i.e., extracellular distribution and similar

Abbreviations: AIF, arterial input function; CAD, coronary artery disease; CT, computed tomography; CTA, computed tomography angiography; E, extraction fraction; F, blood flow; HU, Hounsfield unit; LV, left ventricle; MBF, myocardial blood flow; MRI, magnetic resonance imaging; PET, positron emission tomography; PS, permeability-surface area product; TAC, time attenuation curve; VPCT, volume perfusion computed tomography.

* Corresponding author. Department of Radiology, Mie University Hospital, 2-174 Edobashi, Tsu, Mie 514-8507, Japan.
E-mail address: sakuma@clin.medic.mie-u.ac.jp (H. Sakuma).

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molecular weight,[5,6] AIF and myocardial output function determined by dynamic myocardial perfusion CT can also be analyzed by the same compartment model based approach as used in the myocardial perfusion MRI.[7]

The Patlak plot technique, which is based on a two-compartment model, was first introduced by Rutland.[8] In 1983, Patlak et al employed the same approach to measure the transfer constants from the blood compartment to the tissue compartment.[9] This technique is now widely known as the Patlak plot method.[8–10] The Patlak plot method permits the calculation of K_1 by linear least-square fitting, substantially simplifying the analytical procedures in a two-compartment model approach. Recently, a new technique for quantification of myocardial blood flow (MBF) by using dynamic myocardial perfusion CT datasets and its dedicated analysis software has been proposed.[11–14] The dedicated "Volume Perfusion" software (VPCT) calculates MBF according to the following equation;

$$MBF = MaxSlope(TissueTAC)/Maximum(AIF) \tag{1}$$

where tissue *MaxSlope (Tissue TAC)* is the maximum upslope of the time-attenuation curve of the myocardium and *Maximum(AIF)* is the peak signal of the arterial input function (AIF) obtained in the descending aorta.[14]

Pharmacological stress agents such as adenosine can induce maximal microvascular vasodilation resulting in hyperemic myocardial blood flow (MBF).[15] At present, the most robust technique to quantify MBF noninvasively in the human heart is the positron emission tomography (PET).[16–18] Myocardial perfusion tracers such as O 15-water, ^{13}N-ammonia and ^{82}Rb provide absolute information of MBF over a wide range of blood flows. Stress MBF in normal healthy subjects measured by using PET and those myocardial perfusion tracers is known to be 3–5 ml/min/g.[16–19]

However, previous studies using dynamic perfusion CT and VPCT provided the stress MBF of 1.1–1.4 ml/min/g in normal myocardium.[11–14] Thus, the range of stress MBF up to 1.5 ml/min/g in normal myocardium observed in the previous CT studies is substantially underestimated as compared with stress MBF obtained in PET studies.[16–19] Previous investigators speculated that the observed inaccuracies of "MBF" calculated with VPCT can be due to the limited temporal sampling.[12] Recently Ichihara et al proposed that "MBF" determined by Eq. (1) mathematically equals to the blood-to-myocardium transfer constant, K1, determined by the Patlak plot analysis.[20]

The purposes of this study, therefore, were (1) to determine K1 using Patlak plot analysis and compare the K1 value with "MBF" determined by VPCT and (2) to evaluate the influence of temporal sampling rate of the perfusion CT acquisition scheme on the accuracy of K1 calculation.

2. Theory

2.1. Patlak plot method

The Patlak plot method is based on a two-compartment model and describes the K_1, the one-way transfer constant of contrast material from the blood to the myocardium. The mass balance of extracellular contrast medium across the capillary membrane is described by the following first-order differential equation[2,4,21]:

$$\frac{dC_{myo}(t)}{dt} = V_b\frac{dC_a(t)}{dt} + K_1C_a(t) - k_2C_{myo}(t) \tag{2}$$

$$\therefore C_{myo}(t) = V_bC_a(t) + K_1\int_0^t C_a(t)dt - k_2\int_0^t C_{myo}(t)dt \tag{3}$$

$$\therefore \frac{C_{myo}(t)}{C_a(t)} = V_b + K_1\frac{\int_0^t C_a(t)dt}{C_a(t)} - k_2\frac{\int_0^t C_{myo}(t)dt}{C_a(t)} \tag{4}$$

where Cmyo(t) and Ca(t) are the relative concentrations of extracellular contrast medium, such as iodinated contrast medium for CT or gadolinium based contrast medium for MR perfusion imaging, in the myocardium and in the blood. K1 and k2 represent the one-way transfer constants from the LV blood pool to the myocardium and from the myocardium to the vascular system, respectively. Vb represent the blood volume.

In the early phase after the arrival of contrast agent in the myocardium, it is assumed that $C_{myo}(t)$ is negligibly small compared with $C_a(t)$. Then, Eqs. (2), (3) and (4) is described as follows, respectiely:

$$\frac{dC_{myo}(t)}{dt} \cong V_b\frac{dC_a(t)}{dt} + K_1C_a(t) \tag{5}$$

$$C_{myo}(t) \cong V_bC_a(t) + K_1\int_0^t C_a(t)dt \tag{6}$$

$$\frac{C_{myo}(t)}{C_a(t)} \cong V_b + K_1\frac{\int_0^t C_a(t)dt}{C_a(t)} \tag{7}$$

The plot of $Y(t)\frac{C_{myo}(t)}{C_a(t)}$ against $X(t) = \frac{\int_0^t C_a(t)dt}{C_a(t)}$ yields a straight line with a slope of K_1 (Patlak plot) and Y intercept of V_b.

$$Y(t) = V_b + K_1X(t) \tag{8}$$

This linear relationship is no longer maintained after the amount of iodinated contrast medium transferred from myocardial tissue back to the blood pool increases.

In the two-compartment model, K_1 is related to the extraction fraction (E, dimensionless) across the capillary membrane and the blood flow (F, ml/min/g) as:

$$K_1 = E\cdot F \tag{9}$$

$$E = 1 - \exp(-PS/MBF)\ (\text{Renkin/Crone equation}) \tag{10}$$

where PS denotes the permeability-surface-area product (ml/min/g).[22,23] This equation suggests that K1 and extraction fraction depend on both permeability and blood flow and that the extraction fraction decreases in the hyperemic states

2.2. Patlak plot-derived K1 and upslope index from the same model

C_a (t_{peak}) is the local maximum concentration of contrast agent in the arterial blood at time $t = t_{peak}$[20] (see "p" in Fig. 1). Then,

$$\frac{dC_a\left(t_{peak}\right)}{dt} = 0 \tag{11}$$

In this time point in the early phase after the arrival of contrast agent in the myocardium, it is assumed that $C_{myo}(t_{peak})$ is negligibly small compared with $C_a(t)$. Therefore, from Eq. (5), we can obtain