Chapter 5
Kinetic Analysis for Cardiac PET

Yuuki Tomiyama and Keiichiro Yoshinaga

Abstract *Objective:* PET has the ability to evaluate functional information as well as visualization of radiotracer uptake. Compartmental model is a basic idea to analyze dynamic PET data. C-HED has been the most frequently used PET tracer for the evaluation of cardiac sympathetic nervous system (SNS) function. The washout of norepinephrine from myocardium is associated with increasing SNS activity in heart failure (HF). However, the existence of washout of ^{11}C-HED from the myocardium is controversial. Although "retention index" (RI) is commonly calculated to quantify the uptake of HED, RI is not purely able to distinguish washout parameter and uptake parameter. Therefore, in this study, we aimed to evaluate whether HED was washed out from the myocardium using compartment model analysis.

Material and Methods: We compared HED parameters in ten normal volunteers (32.4 ± 9.6 years) and nine HF patients (age: 57.3 ± 17.3 years, LVEF: 36.1 ± 16.7 %). Each subject underwent rest ^{11}C-HED PET. We estimated RI, inflow rate K1, and washout rate k2 using single-compartment model analysis using ^{11}C-HED PET.

Result: HF patients showed lower RI and inflow rate K1 compared to normal volunteers (RI: 0.06 ± 0.02 vs. 0.15 ± 0.03 min^{-1}, $p < 0.001$, K1: 0.14 ± 0.05 vs 0.20 ± 0.03 ml/min/g, $p < 0.001$). Washout rate k2 also significantly increased in HF patients (k2: 0.036 ± 0.026 vs. 0.016 ± 0.011 min^{-1}, $p = 0.041$).

Conclusion: HF patients showed reduced RI, reduced K1, and higher washout rate k2 compared to normal. This result may imply that HED PET is able to evaluate washout parameter using compartment model.

Keywords Compartment model analysis • ^{11}C-Hydroxyephedrine • Retention index • Sympathetic nervous system function

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5.1   Introduction

Positron emission tomography (PET) is a powerful tool to evaluate functional information imaging as well as anatomical information [1, 2]. PET is the most reliable modality for assessing functional information, especially in cardiovascular imaging [3, 4]. When biomedical functions are analyzed using PET images, compartment model analysis is generally applied [5, 6]. Compartment model analysis enables to observe the pharmacokinetics of radiotracer in human body. Thus, we apply compartment model analysis to evaluating pharmacokinetics of ^{11}C-hydroxyephedrine (HED).

[11]C- HED has been the most frequently used PET tracer for the estimation of cardiac sympathetic nervous system (SNS) function [7–9]. In general, [11]C- HED data has been evaluated using the retention index (RI) [8]. RI is a parameter that can be calculated easily compared to other quantitative parameters. RI includes uptake and washout parameters. However, RI does not differentiate washout parameters from cardiac HED data. Cardiac washout parameter is widely used for evaluation of SNS function and increased cardiac washout is associated with cardiac events in heart failure (HF) [10]. Therefore, it would be important to evaluate the washout parameters using HED PET. Compartment model analysis might have a potential to evaluate precise pharmacokinetics of ^{11}C-HED and also has a potential to evaluate purely washout parameter [11].

In this study, we aimed to analyze HED uptake parameter and washout parameter using single-compartment model analysis in patients with HF.

5.2   Methods

5.2.1   Study Subjects

Ten healthy volunteers and nine HF patients participated in the current study. The healthy volunteers (ten men, 32.4 ± 9.6 years) had a low pretest likelihood of coronary artery disease (<5 %) based on risk factors [12]. HF patients were recruited from a group of patients who underwent HED PET for the assessment of sympathetic neuronal function. They were six men and three women (57.3 ± 17.3 years). The study was approved by the Hokkaido University Graduate School of Medicine Human Research Ethics Board. Written informed consent was obtained from all participants.

5.2.2 Positron Emission Tomography/Computed Tomography ^{11}C-HED PET/CT Imaging

[11]C-HED was produced from ^{11}C-methyl iodide and metaraminol (free base) using standard methods with high purity and high specific activity [13].

All participants were instructed to fast overnight. PET/CT imaging was performed with a 64-slice PET/CT scanner (Biograph Siemens/CTI, Knoxville, TN, USA). A low-dose CT was performed for attenuation correction. The CT co-registered to standard orthogonal PET images was then re-sliced into series of short-axis, horizontal long-axis, and vertical long-axis images.

Immediately after the administration of 5 mCi(185 MBq) of intravenous ^{11}C-HED, participants underwent 40-min 3D list-mode PET acquisition. The images were reconstructed using filtered back correction with a12-mm Hann filter and were reconstructed into 23 frames (10×10 s; 1×60 s; 5×100 s; 3×180 s; 4×300 s) [14].

5.2.3 RI Estimation

RI is obtained by normalizing late phase of tracer activity concentrations (30–40 min) of left ventricular (LV) myocardium divided by the integral of the arterial input function (AIF). The time-activity curve was derived from a small circular region of interest in the left ventricular cavity (Fig. 5.1, [10]).

5.2.4 Compartment Model Analysis

Harms HJ et al. reported the single-tissue model was more robust than two-tissue compartment model and results obtained were similar to more precise models [11]. Thus, we used single-compartment model to evaluate ^{11}C-HED washout parameter.

In single-compartment model analysis, tracer kinetics are consisted by only two parameters, which are inflow rate K1 and washout rate k2 (Fig. 5.1, [6]). In this study, K1 and k2 were estimated using the nonlinear least squares method. This approach used AIF arterial input function and tissue activity carve (TAC) of LV myocardium [15, 16]. Distribution volume was also calculated [17]. The equation of distribution volume was inflow rate K1 divided by washout rate k2.
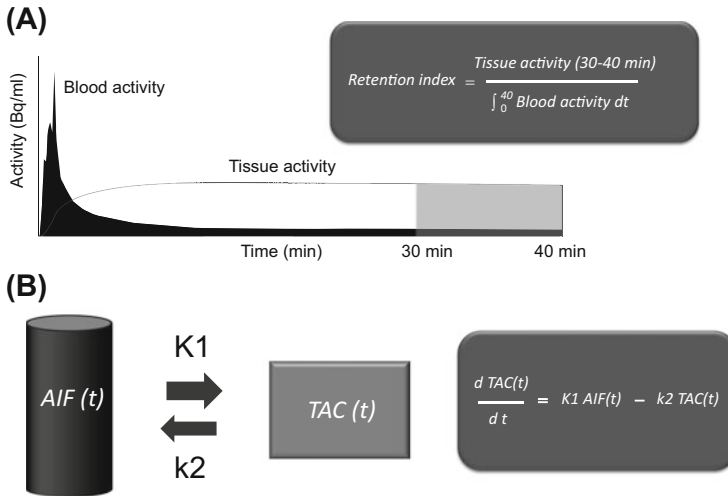
(A)

(B)

Fig. 5.1 Analysis methods of ^{11}C-hydroxyephedrine. (**a**) Calculation method of retention index: retention index was obtained by normalizing late activity concentrations of left ventricular myocardium divided by the integral of the arterial input function.(**b**) Single-tissue compartment model: single-tissue compartment model enables to monitor inflow rate K1 and washout rate k2 of radiotracer between arterial input function (AIF) and tissue activity curve (TAC). AIF and TAC were obtained from LV cavity and myocardial tissue, respectively

5.2.5   Statistical Analysis

Data are expressed as mean ± SD. The differences between the means of two volumetric results were examined using the unpaired two *t*-test. Fisher's exact tests were used for categorical variables. *P*-value of less than 0.05 was considered indicative of a statistically significant difference. Statistical calculations were carried out using JMP software version 12.0 (SAS Institute, Inc., Cary, NC).

5.3   Results

5.3.1   Subjects' Background

Table 5.1 summarizes the baseline characteristics of the volunteers and HF patients. HF patients also had laboratory data and echocardiography data. The HF patients were older than normal.

Table 5.1 The baseline characteristics

	Normal volunteers ($n = 10$)	Heart failure patients ($n = 9$)	P-value
Age (year)	32.4 ± 9.6	57.3 ± 17.3	<0.001
Sex (M/F)	10/0	6/3	0.09
Height (cm)	172.7 ± 8.8	162.2 ± 8.4	<0.001
Wight (kg)	68.2 ± 13.5	56.8 ± 17.4	<0.001
Laboratory data			
BNP (pg/ml)	–	633.7 ± 876.8	–
Plasma noradrenalin (pg/ml)	–	469.4 ± 317.7	–
Urinary noradrenaline (μg/day)	–	127.9 ± 54.5	–
Echocardiography			
LVEF (%)	–	36.1 ± 16.7	–
LVEDV (ml)	–	180.2 ± 95.2	–

Data expressed as mean $\pm$ SD. *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *M* male, *F* female

Fig. 5.2 Difference of retention index between the heart failure and normal. Heart failure patients showed significantly decreased RI compared to normal volunteers
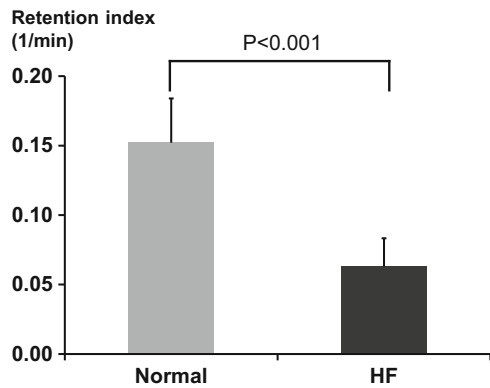
5.3.2   HED PET Data Normal Volunteers and HF Patients

HF patients significantly decreased RI compared to normal volunteers (0.060 ± 0.020 vs. 0.150 ± 0.032 1/min, $P < 0.001$, Fig. 5.2). In compartment model analysis, HF patients showed decreased inflow rate K1 (0.14 ± 0.03 vs. 0.20 ± 0.05 ml/min/g, $P = 0.004$, Fig. 5.3a) and reduced distribution volume (5.17 ± 2.93 vs. 22.4 ± 23.1 mL/g, $P = 0.04$, Fig. 5.3c). In addition, HF patients significantly increased washout rate k2 compared to normal volunteers (0.036 ± 0.026 vs. 0.016 ± 0.011 1/min, $P = 0.044$, Figs. 5.3b and 5.4.).
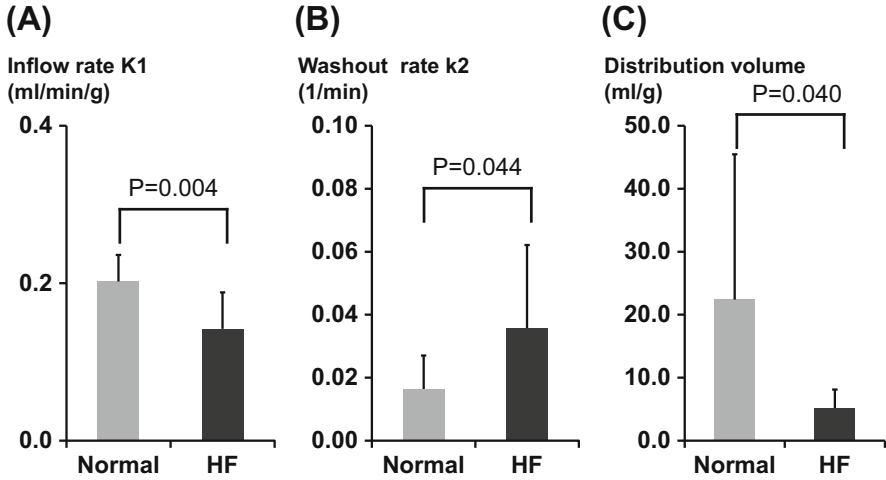
Fig. 5.3 Difference of parameters calculated using compartment model analysis. Heart failure patients showed significantly decreased inflow rate K1 and distribution volume (**a**, **c**). Heart failure patients also showed significantly decreased washout rate k1 (**b**)
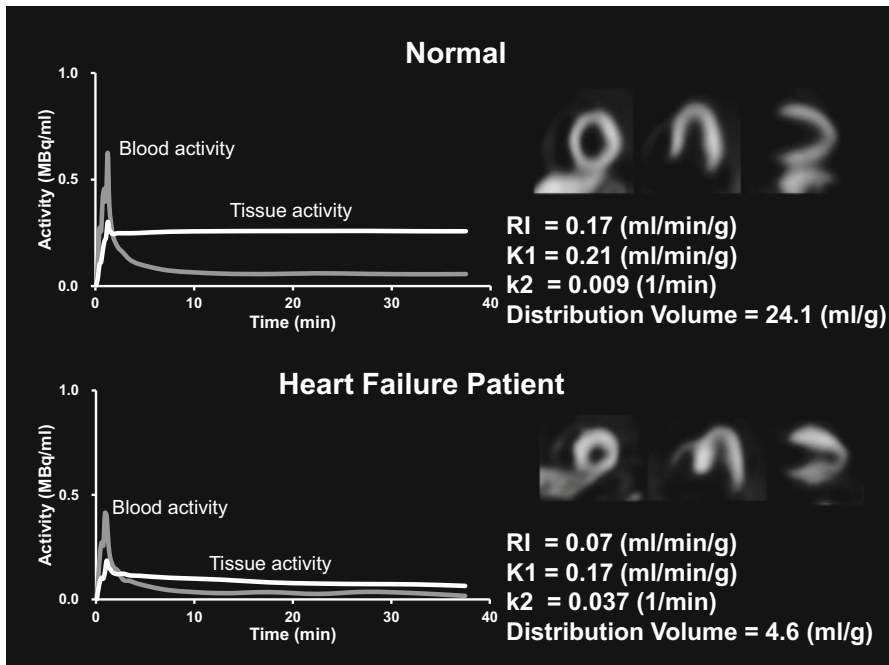

Fig. 5.4 Example of myocardial time activity curveswith[11]C-hydroxyephedrine. Heart failure patient's time-activity curve showed enhanced washout compared to normal volunteer's one

5.4   Discussion

HF patients showed decreased RI, inflow rate K1, and distribution volume compared to normal volunteers. In contrast, the HF patients increased washout parameter k2.

Many previous studies reported patients with imparted SNS function showed lower ^{11}C-HED uptake [8, 17]. Thus, the present data agree with previous reports.

In this study, HF patients showed significantly increased washout rate k2 compared to normal volunteers. Previous studies using ^{123}I-MIBG reported HF patient showed increased washout rate [10, 18]. Previous study also reported that washout parameter of ^{11}C-HED was well correlated with plasma and cardiac norepinephrine in experiments with rats [7]. Therefore, current data that HF patient showed increased washout rate may be considered to be appropriate.

5.4.1   Study Limitation

Our study had a small population and HF patients were significantly older than normal volunteers. Therefore, further investigations with larger and age-matched populations are required.

In addition, washout parameters were not compared to other clinical indexes. Comparison washout of ^{11}C-HED and other clinical parameter such as ejection fraction, laboratory parameter, and washout of ^{123}I-MIBG should be the next step.

5.5   Conclusion

In this study, we applied compartment model analysis to evaluating washout of ^{11}C-hydroxyephedrine (HED).

As a result, HF patients showed reduced RI, K1, and distribution volume and higher washout rate k2 compared to normal. This result may imply that HED PET is able to evaluate washout parameter using compartment model.

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