A New Method with Variable Injection Parameters in Contrast-Enhanced CT: A Phantom Study for Evaluating an Aortic Peak Enhancement

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A New Method with Variable Injection Parameters in Contrast-Enhanced CT: A Phantom

Study for Evaluating an Aortic Peak Enhancement

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【背景】一般に、CT検査における造影は、Standard uniphasic injection (Single-injection method: SIM)による投与で、注入速度を示す iodine administration rate (mgI/s)と注入時間(s)の2つのパラメータにより調整する。したがって、抽出能を向上させるためには、ヨード使用量を増加させるか、または注入時間を短くすることにより注入速度を上昇させる必要がある。また、SIM は注入速度が一定なため、画一的な造影効果しか得られない問題がある。

そこで、高い造影効果を得るためには、ヨード使用量を増加させる、または注入時間を短くして 注入速度を上昇させる必要がある。そのため、SIMは注入パラメータを一定にした条件下でTimeenhancement curve(TEC)のPeak enhancementの特性を任意に調整することができない。すなわ ち、SIMのLimitationといえる。

【目 的】本研究の目的は、TECのPeak enhancementの特性を調整する新たな注入パラメータを追加することにより、ヨード負荷を変えずに描出能を向上させる新しい造影法を提案することである。 SIMと同一の条件下で操作できる注入パラメータは注入速度である。これを造影剤の注入中に可変させた場合、任意にTECのPeak enhancementの特性を調整でき、実組織の質的診断検査や3D-CTAなど検査目的に応じた最適なTECを作成できる可能性がある。造影法を理論的にアプローチする先行研究で、Baeらは注入速度を段階的に変化させるMultiphasic-injection method (MIM)を考案し、Peak enhancementの特性を調整した。また、Utsunomiyaらは段階的に造影剤と生理食塩水を混合させて注入するプロトコールにて心臓の機能解析を含めた3D-CTAに適した造影法とした。しかし、TECが段階的に大きく変化するため、タイミングによってはEnhancementが大きく変動することが懸念された。

この問題は、注入速度を連続的に変化させることで改善できる。そこで本研究では、注入速度を 可変させるパラメータをVariation factor (VF)と定義し、これを用いて注入速度を連続的に変化さ せるVariable-injection method (VIM)と称する造影法を考案した。そして、従来法であるSIMと同 一の総ヨード負荷量および注入時間で、VFを用いたVIMのPeak enhancementの特性を解析する ことにより、その有用性を評価することとした。

- 【方 法】TEC phantomによりTECを取得した。造影剤の到達時間はEnhancementが10HU以上に なった時点から2秒前とし、3回一組に3つのプロトコールの実験を行った。また、CT値(HU)はス キャン位置のホースの中心部で断面積の80%程度のRegion of interest (ROI)にて測定し、造影 剤注入前のCT値を減じた。そして、プロトコールをマスクした状態で1名の診療放射線技師 (Tsukimata T)が計測した。
- ① TEC phantomによるSIMの解析

注入速度を一定にしたSIMにおいて注入時間を変化させTECが形成される過程を検証するために、ヨード使用量を12000mgI、18000mgI および24000mgI、注入速度を720mgI/s として比

較した(造影剤用量が50mL、75mLおよび100mLで、injection flow rateはすべて3mL/s)。それ ぞれをプロトコール1(i)、プロトコール1(ii)およびプロトコール1(iii)とした。そして、TECを解 析するポイントをPeak enhancement、Time to peak enhancement、Contrast medium arrival timeとした。また、Time to peak enhancementからContrast medium arrival timeを減じた時間を Peak timeと定めて解析に加えた。

 ② TEC phantom によるPeak enhancement特性の検討 VFの違いによるVIMおよびSIMの関係を評価するために、VFを0.3, 0.5, 1.0, 1.5 と変化させ TECを取得した。すべてヨード使用量は24000mgIとし、造影剤用量は100mLとした。注入時間 は35秒で、これをプロトコール2(A)[i-iv]とした。次に、VIMにおける注入時間の変化を評価 するために、同様にVFを0.3, 0.5, 1.0, 1.5 と変化させ25秒注入のTECを取得した。これをプロ トコール2(B)[i-iv]とした。すべてヨード使用量は24000mgIとした(造影剤用量:100mL)。ま た、方法②の解析ポイントに加えPeak enhancementの80%をEnhancementが持続する時間と 定め、Enhancement timeとして比較した。

【結 果】

- Peak enhancementおよびTime to peak enhancement(s)の関係を求めると、プロトコール1(i) は165.7±6.5(HU)、25.3±1.2秒、1(ii)は207.7±6.5(HU)、34.7±1.2秒、1(iii)は229.7± 5.5(HU)、42.7±1.2秒であった。それぞれのPeak timeを求めると、プロトコール1(i)は15.3、 1(ii)は24.7、1(iii)は 32.7秒であった。Peak timeを比較すると、プロトコール1(i、iii)は注入 時間とほぼ等しくなったが、プロトコール1(i)は1.4秒短くなった。
- ② VFを変化させたVIMの関係を比較すると、プロトコール2(A)[i-iv]および2(B)[i-iv]ともに VFが1.0より低い場合、Time to peak enhancementがSIMより早くなった。一方、VFが1.0より高 い場合はTime to peak enhancementがSIMより遅延した。TECはVFが0.3および1.5のときPeak enhancementの前後で急激な変化を示し、Peak enhancementはSIMより上昇した(P<0.05)。 一方、VFが0.5のときはSIMより高いEnhancementは得られなかったが、Peak enhancementを中 心にTECに急激な変化がなく、Enhancementを持続するような安定した形状になった。
- 【考 察】VFが0.3および0.5のではVIMはSIMに比べ注入初期に注入速度が上昇することから、動 脈系と静脈系および動脈系と実組織Enhancementとのコントラストを向上できると考えられた。ま た、SIMよりContrast medium arrival time が早期になることから、実質臓器および静脈系との時 間的分離を向上させると考えられた。
- 【結論】注入時間を変化させることや、ヨード負荷を増加させることなくTECのカスタマイズを行うことで質的診断検査における動脈系と実組織の時間的分離による描出能向上および形状解析による形態診断の精度向上を可能にした。その特性の解析により①、②が臨床応用法として有用と示唆された。
- ① VF=0.3によるVIMは肝質的診断検査等のコントラストの改善が期待できる。
- ② VF=0.5によるVIMはSIMに比べ3D-CTAにおけるより正確な形状解析が可能である。

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# TITLE

A New Method with Variable Injection Parameters in Contrast-Enhanced CT: A Phantom Study for Evaluating an Aortic Peak Enhancement

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# ABSTRACT

Contrast-enhanced CT employs a standard uniphasic single-injection method (SIM), wherein administration is based on two parameters: the iodine administration rate (mgI/s) and the injection duration (s). However, as the SIM uses a fixed iodine administration rate, only a uniform contrast enhancement can be achieved with this method. The iodine administration rate can be increased only by increasing the iodine dose or shortening the injection duration, and no arbitrary adjustments can be made to the peak enhancement characteristics of the time-enhancement curves (TECs) at the fixed injection parameters used in the SIM. To address this problem, we developed a variable-injection method (VIM) with a new parameter, the variation factor (VF), to adjust the TECs. A phantom study with the VIM indicated that arbitrary adjustments to the iodine load. In our study, VFs of 0.3 and 0.5, which showed earlier achievement of peak enhancements, showed better temporal separation between arterial vasculature and parenchyma or the venous vasculature than that obtained with the SIM. The higher peak enhancement provided by the VF of 0.3 was also considered to improve the contrast in qualitative diagnostic examinations. A VF of 0.5 increased

the duration of the enhancement and was considered to produce stable enhancement of contrast in vascular investigations. The VF is now an essential parameter, and the VIM is useful as a reasonable contrast method that may contribute to both improved visualization and improvement in the accuracy of morphologic diagnosis.

#### **KEYWORDS**

Time enhancement curve (TEC); Variable injection method (VIM); Variation factor (VF); Contrast enhancement; Contrast material

# **1 INTRODUCTION**

Contrast-enhanced computed tomography (CT) has been used for two main purposes, for observing differences in contrast between the arterial vasculature and parenchyma in qualitative diagnostic examinations of organs [1,2], and for generating a constant, high degree of arterial enhancement as in three-dimensional CT angiography (3D-CTA), a form of vascular investigation [3,4]. Prior to the introduction of helical CT in clinical practice, contrast methods involved the administration of a fixed dose of contrast material (mL) at a fixed injection rate (mL/s). The protocol employed in such methods was uniform across all examinations. However, the development of helical CT and the improved image quality and faster scanning afforded by this technique have facilitated studies on the optimization of contrast methods. These studies were aimed of making adjustments to contrast methodology in an effort to maximize its diagnostic performance, and investigators have begun to explore patient-related factors, such as the circulating blood volume, that govern iodine dosage. More specifically, adjustments based on each examinee's physique have been investigated in such studies.

Predictions of the timing of contrast material arrival based on the circulatory dynamics have been used for making adjustments according to the examinee's physique, and these adjustments may maximize the diagnostic performance while using the lowest iodine dose necessary for diagnosis. The typical methods employed for predicting the disposition of contrast material include a compartmental model analysis described by *Bae et al.* [1,2] and computer simulations based on linear models described by *Fleischmann et al.* [3,4]. Simulations with use of a mechanical contrast material flow phantom can also be used for prediction [5]. Studies with use of these methods have led to the establishment of contrast-enhanced CT, which combines contrast methods or scanning methods to individualize the iodine dose (mgI) for each examinee with a fixed injection duration (s) [6-10].

Contrast enhancement for CT generally involves the standard uniphasic injection (singleinjection method: SIM) protocol, in which adjustments are made with use of two parameters: the iodine administration rate (mgI/s), which represents the rate of injection, and the injection duration (s). Therefore, to improve contrast enhancement, it is necessary to increase the iodine administration rate by either increasing the iodine dose or by shortening the injection duration.

In a study by use of simulations, Bae et al. reported that a higher administration rate could

provide better temporal separation between the arterial and venous phases and the arterial and parenchymal phases of enhancement [2]. The resultant increase in the difference between the time to arterial peak enhancement and the time to parenchymal peak enhancement would yield better contrast. Similarly, a higher administration rate can also produce stable degrees of enhancement and improve the temporal separation between the arterial and venous phases in 3D-CTA.

In contrast, *Murakami et al.* compared the scans obtained at 20, 30, and 40 s following the start of an injection by hepatic dynamic-CT with those obtained at an injection duration of 25 s, and they found that the scans obtained at 30 s were the best for detecting hypervascular tumors [11]. However, it was unclear whether the time to aortic peak enhancement obtained by the SIM was reflective of the greatest parenchymal contrast achieved in qualitative diagnostic examinations. The findings indicated that the peak enhancement in the time-enhancement curves (TECs) [1-5] generated by the SIM might be suitable for examinations. However, because it is difficult to change the characteristics of the peak enhancement flexibly while maintaining constant injection parameters in the SIM, an optimized contrast method for diagnostic examinations is required.

In response to this need, a new contrast method that could improve visualization without changing the iodine load was developed and coupled a new injection parameter to allow adjustment of the characteristics of the peak enhancement in TECs.

The iodine administration rate is the injection parameter that can be operated under the same conditions as the SIM. If this parameter can be varied during the injection of contrast material, the characteristics of the peak enhancement in TECs can be appropriately adjusted and optimized, and TECs specific to the purposes of the examination, such as those for qualitative diagnostic examinations of parenchyma or 3D-CTA, can be generated and assessed. In a previous study that approached contrast methods logically, *Bae et al.* developed a multiphasic-injection method (MIM), which varied the iodine administration rate in a stepwise manner and adjusted the characteristics of the peak enhancement [12]. In addition, *Utsunomiya et al.* developed a protocol involving stepwise injection of a mixture of contrast material and normal saline and employed it for 3D-CTA with cardiac functional analysis [13]. However, because of the prominent stepwise changes in the TECs, there was concern about the large time-dependent variability observed in the enhancement.

For solving this problem, the iodine administration rate must be varied in a non-stepwise manner. To facilitate this process, we defined the variation factor (VF), a parameter for variable iodine administration rates, and we developed a contrast method called the variable-injection method (VIM), in which the injection rate was varied in a non-stepwise manner. The usefulness of the VIM was then assessed by analyzing the characteristics of the peak enhancement obtained by use of the VIM with VFs under the same injection parameters as in the conventional SIM.

#### 2 MATERIALS AND METHODS

#### 2.1 Overview of the VIM with VFs

The VF can be determined by dividing the iodine administration rate at the completion of injection (aX) by that at the start of injection (X). Figure 1 shows the relationship between the iodine administration rate and time in the VIM. When the VF is 1.0, the VIM shows an injection profile

equivalent to that of the SIM [Figure 2(b)]. When the VF is lower than 1.0 [Figure 2(a)], the iodine administration rate decreases with time. When the VF is higher than 1.0 [Figure 2(c)], an injection profile in which the iodine administration rate increases is obtained. As the VIM allows the iodine administration rate, i.e., the injection rate, to be varied in a non-stepwise manner, the injection duration and the iodine dose are not dependent on the VF.



Fig.2 Schematic diagrams of variable injection (a) Represents a VF of <1, (b) a VF of 1.0 (same as the SIM), and (c) a VF greater than 1.0

#### 2.2 CT scanner and Phantom

The CT system used in this study consists of a 64 multidetector-row CT unit (Aquilion Multi 64, Toshiba Medical Systems Co., Tochigi, Japan) and a double-head power injector (Dual Shot GX, Nemoto Kyorindo Co., Tokyo, Japan), which was used as the automatic contrast medium injector. This automatic injector can store parameters, including the iodine dose per body weight, the injection duration, and the formula for the VIM, on a memory card to formulate injection protocols. The contrast material flow phantom (TEC phantom, Nemoto Kyorindo Co., Tokyo, Japan) that was used to generate TECs was a modification of the original circulation phantom, as shown in Figure 3(a) and (b) [5]. The TEC phantom also provides a dynamic description of the equipment settings

and circulatory dynamics, allowing the verification of the contrast enhancement according to the actual levels of enhancement. The TECs obtained simulated the abdominal aorta.



**Fig.3** a, b The components of the contrast material flow phantom (TEC phantom). (1) Plastic water tank, (2) flow pump, (3) flow meter, (4) water-filled acrylic cylinder, (5) closed metallic tank, and (6) connecting tube. Contrast material is injected into (1)

#### 2.3 Settings and Methods of Measurement of the TEC Phantom

As illustrated in Figure 3(b), the TEC phantom consisted of a plastic water tank, a pulsatile flow pump, a flow meter, a water-filled acrylic cylinder, a closed metallic tank, and tubes for connection and circulation. The top of the plastic water tank was open, and contrast material was injected into (1) of Figure 3(a) through a tube with the Dual Shot GX. Then, the contrast material was circulated with the pulsatile flow pump at a rate of 60 pulses per minute.

The following settings were used for the TEC phantom: a circulating water volume of 5600 mL and a circulation rate of 5400 mL/min. This represents an examinee weighing 70 kg, with a blood volume of approximately 7% to 8% of the body weight [14,15]. Iohexol 240 (Omnipaque 240, Daiichi Sankyo Co., Tokyo, Japan) with an iodine concentration of 240 mgI/mL was used as the contrast material to generate the TECs for both the SIM and VIM.

The scanning conditions were 120 kV, 150 mA, 1.0 s/rot., and a  $64 \times 0.5$  mm detector configuration. The CT images were reconstructed by filtered back projection (FBP) with a 180-mm display field of view (DFOV), a 2.0-mm slice thickness, and a reconstruction kernel of FC13. The contrast medium arrival time [16] was 2 s prior to achievement of an enhancement greater than 10 HU [6].

This study involved experiments with three protocols over a set of three runs. The CT values (HU) were measured in regions of interest accounting for approximately 80% of the sectional area at the center of the hose in the scanning position, and the CT values before the injection of contrast material were subtracted. The measurements from the TECs were taken by a single radiological technologist (T.T.), who was blinded to the protocols. For comparison of SIM and VIM peak enhancement, we used the two-tailed Student's t test. Statistical analysis was performed with a statistical software package (IBM SPSS Statistics 20).

# 2.4 Methods of Assessments

# 2.4.1 Analysis of the SIM

First, a process in which TECs were generated with varying injection durations in SIM by use of a fixed iodine administration rate was verified. This provided a reference for assessing the *in vivo* circulatory dynamics and the VIM profile. With reference to an iodine administration rate of 720 mgI/s, the findings obtained at 3 iodine doses (12000 mgI, 18000 mgI, and 24000 mgI) were compared. These iodine doses represented contrast medium doses of 50 mL, 75 mL, and 100 mL, respectively, all injected at a flow rate of 3 mL/s. These conditions were designated as Protocol 1(i), Protocol 1(ii), and Protocol 1(iii) and have been described in detail in Table 1. The TECs were analyzed at the following points: the peak enhancement, the time to peak enhancement, and the contrast medium arrival time. The peak-time, calculated by subtraction of the contrast medium arrival time from the time to peak enhancement, was also included in the analysis.

Protocol 1	Dose of contrast	Iodine	Iodine
	material (mgI)	administration rate	volume
		(mgI/s)	(mL)
i	12000	720	50
II	18000	720	75
iii	24000	720	100

Table 1 The Phantom study with the SIM: The injection parameters in Protocol 1

# 2.4.2 Evaluation of the Peak Enhancement

For evaluation of the time-enhancement relationship for the VIM and SIM at different VFs, TECs were generated while the VF was varied from 0.3 to 0.5, 1.0, and 1.5 in a stepwise manner. For all of the VFs, an iodine dose of 24000 mgI and a contrast medium dose of 100 mL were used with an injection duration of 35 s. These conditions were designated as Protocol 2(A) [i-iv].

For evaluation of the changes in injection duration for the VIM, TECs were generated over an injection duration of 25 s while the VF was varied from 0.3 to 0.5, 1.0, and 1.5 in a stepwise manner, as described above. These conditions were designated as Protocol 2(B) [i-iv]. For all of the VFs, an iodine dose of 24000 mgI and a contrast medium dose of 100 mL were used. Further details are shown in Table 2. In addition to the analysis points described in Section 1.4.1, the enhancement-time, defined as the duration over which 80% of peak enhancement was achieved, was also compared.

Protocol 2	Dose of contrast	Injection	Variation
	material (mgI)	duration (s)	factor (VF)
A			
i	24000	35	0.3
ii	24000	35	0, 5
iii	24000	35	1
iv	24000	35	1.5
В			
i	24000	25	0.3
ii	24000	25	0.5
iii	24000	25	1
iv	24000	25	1.5

Table 2 Phantom study with varying VFs: The injection parameters in Protocol 2 (A) and Protocol 2 (B)

A contrast material dose of 100 mL was used in all protocols; Protocol 2 (A) involved 35 s of injection and Protocol 2 (B) involved 25 s of injection

# **3 RESULTS**

#### 3.1 TECs with the SIM among Different Injection Durations

Figure 4 shows the TECs obtained with Protocol 1(i-iii). Comparisons of the TECs obtained with varying injection durations revealed that all protocols produced a sharp increase in the TECs up to 22–23 s following the start of injection. In contrast, Protocol 1(ii) and Protocol 1(iii) produced a slow increase, starting at 22–23 s after the start of injection, which was identified as the change point of increments in enhancement in the TECs. When the injection duration was longer than that in Protocol 1(i), the TECs exhibited a bi-phasic slope up to the peak enhancement. However, the TEC obtained with Protocol 1(i) exhibited a uniphasic shape. The contrast medium arrival time in Protocol 1(i) was 10 s less than that in any other protocol.

Protocol 1	Injection duration (s)	Peak time (s)
i	16. 7	15.3
ii	25	24. 7
iii	33. 3	32. 7

Table 3 The relationship between injection duration and peak-time in Protocol 1

Peak-time is defined as the duration of time elapsed between the arrival of the contrast medium and the peak enhancement The peak enhancement occurred following the completion of the injection of contrast material with any of these protocols. The peak enhancement and the time to peak enhancement (s) were  $165.7 \pm 6.5$  (HU) and  $25.3 \pm 1.2$  s,  $207.7 \pm 6.5$  (HU) and  $34.7 \pm 1.2$  s, and  $229.7 \pm 5.5$  (HU) and  $42.7 \pm 1.2$  s with Protocol 1(i), Protocol 1(ii), and Protocol 1(iii), respectively. The peak-times were calculated to be 15.3 s, 24.7 s, and 32.7 s with Protocol 1(i), Protocol 1(ii), and Protocol 1(ii), and Protocol 1(iii), respectively (Table 3). Analyses showed that the peak-time was approximately the same as the injection duration in Protocol 1(ii) and (iii), whereas Protocol 1(i) produced a peak-time that was 1.4 s shorter than the injection duration.



#### 3.2 TECs with Varying VFs and Injection Durations

Figures 5(a) and (b) show TECs with injection durations exceeding 35 and 25 s with varying VFs of 0.3, 0.5, 1.0, and 1.5. The peak enhancement, time to peak enhancement, and contrast medium arrival times obtained with each of these protocols are shown in Table 4. The contrast medium arrival time was 10 s for each of these protocols.

Comparisons of the time-enhancement relationship for the VIM with varying VFs showed that Protocol 2(A) [i-iv] and Protocol 2(B) [i-iv] both had a shorter time to peak enhancement as compared to the SIM when a VF less than 1.0 was used. When a VF higher than 1.0 was used, the time to peak enhancement was delayed in comparison with the SIM. When VFs of 0.3 and 1.5 were used, the TECs obtained showed sharp changes before and after peak enhancement, the magnitude of which was higher than that in the SIM. In contrast, although a VF of 0.5 did not provide a higher level of enhancement than did the SIM, no sharp changes in the TECs were observed before and after peak enhancement, and a stable shape, consistent with persistent enhancement, was formed.

Protocol 2	Peak	Time to peak	Contrast
	enhancement (HU)	enhancement (s)	enhancement
			arrival time (s)
A			
i	240±5.6*	26.7±1.2	10
ii	221.7±5.1	28.7±1.2	10
iii	227.7±4.5	44.7±1.2	10
iv	245.7±7*	46.7±1.2	10
В			
i	324.7±4.7*	24.7±1.2	10
ii	304±4.6	26.7±1.2	10
iii	313.8±4.3	34.7±1.2	10
iv	332.7±7.5*	36.7±1.2	10

Table 4 Data on the analysis points in Protocol 2 (A) and Protocol 2 (B)

The relationship between the time to peak enhancement, peak enhancement, and the contrast enhancement arrival time

\*P<0.05 vs VF 1 (iii)

Table 5 The relationship between the enhancement-time and VF in Protocol 2 (A) and Protocol

2 (B)		
Variation	Protocol 2 [A]	Protocol 2 [B]
factor (VF)	Enhancement	Enhancement
	time (s)	time (s)
0. 3	18.2±0.3	14±0.3
0. 5	26±0.4	16.4±0.3
1	22.3±0.4	14.8±0.3
1. 5	13.3±0.3	10.8±0.3

Enhancement-time is defined as the duration of time in which 80% of peak enhancement is achieved

Table 5 shows the enhancement-time obtained with each protocol. Comparisons of the enhancement-time obtained with VFs of 0.5 and 1.0 showed that the enhancement-time was 26 s with Protocol 2(A) and a VF of 0.5 and 22.3 s when the SIM was used. The enhancement-time was

16.4 s with Protocol 2(B) and a VF of 0.5 and 14.8 s when the SIM was used. When compared to the SIM, the use of a VF of 0.5 extended the duration of the enhancement.

Comparisons of the time-enhancement relationship for the VIM with varying injection durations revealed that the VIM with use of either Protocol 2(A) [i-iv] or Protocol 2(B) [i-iv] showed changes depending on the VF, regardless of the injection duration [Figs. 5(a) and (b)]. However, the peak-to-peak time was different between the two conditions: 20 s for Protocol 2(A) [i] and 12 s for Protocol 2(B) [i]. In addition, the VIM showed less change in the time leading up to the peak enhancement with shorter injection durations, and tended to produce more uniformly shaped TECs. As shown in Fig. 6, assessments of the relationship between the peak-to-peak time and the injection duration was found of a strong correlation (r = 0.99).



**Fig.5 a, b** Time enhancement curves simulating the abdominal aorta with use of the TEC phantom. These TECs represent the mean and standard deviation following the administration of 240 mgI/mL contrast material at a dose of 100 mL with use of varying VFs (3 measurements per protocol). Protocol 2(A) involved 35 s of injection, and Protocol 2(B) involved 25 s of injection. VF was 0.3 ( $\blacksquare$ ), 0.5 ( $\blacktriangle$ ), 1.0 ( $\blacklozenge$ ), and 1.5 ( $\bigcirc$ )

Fig.6 Relationship between the peak-to-peak time and the injection duration ( in the case of an injection duration of 15 s and peak-to-peak time of 0 ). Peak-to-peak time is defined as the time obtained by subtraction of the minimum peak enhancement-time from the maximum in each protocol, shown in Figs. 5(a) and (b)



#### 4 DISCUSSION

In the time-enhancement relationship for the SIM, which involves a fixed iodine administration rate and varying injection durations, a longer injection duration led to a greater enhancement and a longer time to peak enhancement. The peak enhancement occurred after completion of the injection, regardless of the injection duration. However, the TECs exhibited two different patterns of increase before and after the 22–23–s period following the start of injection. Because this time point was the change point, it can be considered that an increase in the enhancement is simply additive, with the iodine dose increasing up to this time point, as shown in Fig. 4(i). However, Figure 4 (ii, iii) shows a slow increase in the enhancement at 22–23 s following the start of injection. This was considered to be due to the presence of limitations on the input side (right atrial/ventricle), whereas the slow increase was attributed to increases in the enhancement associated with recirculation of the injected contrast material [17.18].

Based on these findings, the TECs beyond the change point are formed by addition of the enhancement associated with recirculation to the persistent enhancement according to the injection duration. Based on the time-enhancement relationship of the TECs having two slopes, the evaluation of peak-time versus the injection duration in Protocol 1 showed that the peak-time was approximately equal to the injection duration with Protocol 1(ii, iii). This is unlike that the findings observed with Protocol 1(i), which produced a peak-time that was 1.4 s shorter than the injection duration, as shown in Table 3. Given that either of the TECs obtained with Protocol 1(ii) and Protocol 1(iii) demonstrated a change point, it is possible to predict the time to peak enhancement from the injection duration that exceeds the change point is used.

Yamaguchi et al. reported that there was a strong correlation between the time to peak enhancement and the injection duration [18], and that the correlation became weaker when an injection duration of less than 10 s was used. In short, an injection duration of at least 10 s provides a stable TEC. However, it appeared difficult to obtain a stable TEC with an injection duration that was shorter than that used in Protocol 1(i), because the actual measurement with use of the TEC phantom showed a difference of 1.4 s from Protocol 1(i). As the injection duration in Protocol 1(i) was 16.7 s, use of an injection duration of even 10 s or more for predicting the time to peak enhancement is not rational. Therefore, we thought that an injection duration of at least 15 s would be necessary. Although, for this correlation, there was a concern about individual differences, such as those in cardiac output (L/min), *Bae et al.* indicated that the cardiac output affected the contrast medium arrival time [19]. It appeared that an injection duration of at least 15 s beyond the change point could produce stable TECs in the presence of any changes in the contrast medium arrival time.

In a clinical study of parenchymal tissues, Awai et al. reported the evidence for a strong correlation between aortic peak enhancement and the enhancement of hypervascular tumors in hepatic dynamic-CT based on an assessment of tumor-to-liver contrast (TLC) [20]. This finding is consistent with the temporal separation between the arterial and parenchymal phases of the enhancement in the simulation by Bae et al [2]. This suggests that a peak enhancement higher than that obtained with the SIM leads to improvement in the TLC. In addition, as the parenchymal

enhancement also increases with time, a longer time to peak enhancement may result in a lower contrast for hypervascular tumors. Circulatory dynamics with the SIM shown in Fig. 4 (i-iii) indicated that the time to the peak enhancement occurred following the completion of injection, regardless of the injection duration, and that no peak enhancement could be achieved with an incomplete injection when the SIM was used. Thus, The TLC may be improved if the peak enhancement occurs more quickly than in the SIM condition, and if the peak enhancement is of a greater magnitude that can be achieved with the SIM condition.

Therefore, a contrast method that satisfies these requirements for temporal separation between the arterial and parenchymal phases of enhancement should show better accuracy in qualitative diagnostic examinations. In contrast, highly stable TECs are necessary for accurate morphologic analysis in 3D-CTA. *Fleischmann et al.* reported that it was reasonable to obtain optimal enhancement on the basis of the relationship between the injection duration and the duration of enhancement [21]. Thus, the enhancement-time must be adapted to the scan time and must be stable. In other words, a high and stable magnitude of enhancement is required. Additionally, to ensure improvement in the temporal separation between the arterial and venous phases, the accuracy of 3D-CTA could be improved if the time to peak enhancement occurs earlier than in the SIM, and if more persistent enhancement could be achieved than in the SIM.

Figures 5(a) and (b) show TECs obtained with the VIM. Even though the same fixed iodine dose and injection duration were used in both conditions, the VIM yielded peak characteristics different from these of the TECs. This difference is likely to be due to differences in the iodine administration rates associated with the specified VFs. *Kim et al.* reported that higher enhancement levels required an increase in the iodine administration rate based on the relationship between the iodine administration rate and the TEC [22]. Thus, it appears that a peak enhancement higher than that observed in the SIM condition could be achieved by use of VFs that provide higher iodine administration rates during the initial and final phases of the injection. Examples of such VFs were 0.3 and 1.5.

With regard to temporal separation, the time to peak enhancement must occur earlier than that obtained with the SIM. Comparisons of the VIM protocols showed that the highest peak enhancement was achieved prior to the completion of the injection with a VF of 0.3. These findings indicate that the conditions for improvement in TLC were met, as a larger interval separated the aortic and parenchymal peak enhancements and a higher peak enhancement was achieved, when compared to the SIM condition. For example, the time to peak enhancement with Protocol 2(A) was 26.7 s with a VF of 0.3 and 44.7 s with a VF of 1.0 for SIM, representing a difference of 18 s. Given that parenchymal enhancement increases with time, it is evident that a longer time to peak enhancement leads to poorer temporal separation, which significantly affects the TLC.

Therefore, a VF of 0.3 is suitable for improving the contrast in examinations of hypervascular lesions. In other words, the VIM with a VF of 0.3 can be regarded as a reasonable contrast method for qualitative diagnostic examinations of parenchyma, such as hepatic dynamic-CT based on aortic peak enhancement. However, it is also important to determine the iodine administration rate because of its implications for the safety of examinees in clinical practice [23]. In that regard,

attention should be paid to the higher iodine administration rate during the early phase of injection with a VF of 0.3 in comparison with that in the SIM [24].

When we used a VF less than 1.0, the time to peak enhancement was earlier than that in the SIM. However, a VF of 0.5 produced long stable characteristics in the TEC, whereas a VF of 0.3 generated a TEC that was consistent with persistent enhancement. Nevertheless, the enhancement levels obtained were still lower than those in the SIM. The time to peak enhancement was shorter with the VF of 0.3 than in the SIM, due to an increased iodine administration rate during the early phase of injection. This can be explained by the presence of a change point for the SIM. The SIM showed an evident relationship in which the TECs reach a plateau due to limitations in the right heart following the change point, and it showed a slow increase resulting from the enhancement associated with recirculation, reaching peak enhancement, which was followed by a rapid decline [18].

In contrast, the TECs associated with a VF of 0.5 exhibited a relationship in which a slow decline was observed after peak enhancement. As the change point for the SIM almost coincided with peak enhancement with a VF of 0.5, a VF of 0.5 produced iodine administration rates that might maintain a plateau after the change point. In other words, as recirculation contributes to the maintenance of, but not the increase in, the magnitude of enhancement after a certain level of peak enhancement is achieved, a flat TEC might be formed. A comparison of the enhancement-times in Table 5 shows that a VF of 0.5 was associated with an increase in the duration of enhancement of 3.7 s with Protocol 2(A) and 1.6 s with Protocol 2(B). This represents an increase in the injection duration for the SIM. Therefore, the VIM with a VF of 0.5 can be considered as the contrast method that provides a more stable enhancement-time than dose the SIM.

In addition, 3D-CTA provides a high degree of enhancement by taking scans around the peak enhancement. Thus, it is possible that the SIM, which is associated with a sharp decline in TECs after the peak enhancement, will provide no stable contrast enhancement when the scan timing is poor. In contrast, the shape of the TEC from the VF of 0.5 suggests a degree of contrast enhancement that is stable and less variable among cases. In other words, the VIM with a VF of 0.5 effectively maintains the highest possible stable degree of enhancement for the purpose of examinations. Quicker achievement of the peak enhancement also results in a shorter scan time as compared to the SIM. This method has the potential to improve the temporal separation between the arterial and venous phases. Therefore, the VIM with a VF of 0.5 can be considered as a reasonable contrast method for 3D-CTA, a form of vascular investigation [25,26].

As shown in Figs. 5(a) and (b), assessments of the relationships of the injection duration in the VIM showed that, as the injection duration decreased, the peak enhancement characteristics were likely to be more similar to those in the SIM, despite being dependent on the VF. Given that the TECs ended at the change point for the SIM, the differences in the peak-to-peak time of the TECs should disappear when an injection duration of approximately 15 s is used. As shown in Fig. 6, assessments of the relationship between the peak-to-peak time and the injection duration showed evidence of a strong correlation. Based on this result, the effect of the VIM with VFs should be considered limited to 15 s of injection. More specifically, it can be seen that stable TECs can be

generated in a manner similar to the SIM. Therefore, the effect of the VIM with extremely short injection duration is small.

However, with the recent advent of area detector CT (ADCT) and the availability of other new scanning methods that shorten the injection duration in the heart or head, high levels of enhancement in vascular investigations, including 3D–CTA, are now possible. Nevertheless, the VIM may not be applicable to these scanning methods, because they assess localized sites with specialized scanning methods. In contrast, if scanning of extensive areas, including the aorta and the lower extremities, is required, the injection duration should be determined in consideration of the circulation time. In addition, in a study of visualization for qualitative diagnostic examinations, *Yanaga et al.* described that an injection duration of approximately 30 s was reasonable for a hepatic dynamic–CT [27]. Thus, it appeared that the contrast enhancement obtained with the VIM could be used widely and that the simulations of TECs with varying VFs may serve as an indicator of practical clinical use.

In this study, We determined the usefulness of the VIM by assessing TECs obtained with VFs less than 1.0, but failed to clarify the usefulness of VIM with VFs greater than 1.0, with support from clinical assessments. This was due to a delay in the onset of peak enhancement and a shorter enhancement-time in comparison with that of the SIM. Thus, the study failed to discuss suitable examination regions in consideration of temporal separation or the contrast between the arterial vasculature and parenchyma or venous vasculature. However, the greatest magnitude of enhancement was achieved among the simulations performed. It appeared that this result could serve as the foundation for discussions of future constructive contrast methods.

#### 5 CONCLUSION

This phantom study has overcome the limitation of uniform contrast enhancement posed by the SIM through the development of the VIM with a new parameter, VF. The study indicated that varying levels of contrast enhancement could be achieved under the same conditions for injection parameters as employed in the SIM. This finding suggests that the generation of varying TECs suitable for the purposes of examinations is possible. The VIM is characterized by two great advantages over the traditional SIM. First, the VIM can contribute to improvements in visualization due to temporal separation between the arterial vasculature and parenchyma or the venous vasculature in qualitative diagnostic examinations. Secondly, the VIM demonstrates improvements in the accuracy of the morphologic diagnosis in morphologic analyses by customizing TECs without varying the injection duration or increasing the iodine load. Thus, the VF is now an essential parameter for considering contrast methods with a focus on peak enhancement in TECs. These findings indicate that the VIM with VF is a reasonable contrast–enhanced CT method that considers the iodine load and is useful for flexibility in varying the contrast enhancement.

#### Conflict of Interest

Our study is basic research involving a new method of contrast-enhanced CT examination and, therefore, does not require ethical approval. All authors have approved the content and the submission of the manuscript. The authors declare no particular conflicts of interest relevant to this manuscript. The manuscript has not been submitted to other publications. We have received no research grant funding for this study.

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# 研究業績リスト

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