Relationships between patient characteristics and contrast agent dose for successful computed tomography venography with a body-weight-tailored contrast protocol

Yuji Iyama, MDa,b,∗, Takeshi Nakaura, MDa, Masafumi Kidoh, MDb, Kazuhiro Katahira, MDa, Seitaro Oda, MDb, Daisuke Utsunomiya, MDb, Yasuyuki Yamashita, MDa

Abstract
The aim of this study was to evaluate the effect of patient characteristics on the contrast agent dosage that is required to reach effective enhancement of the inferior vena cava (IVC) on computed tomography venographs (CTV).

This retrospective study included 50 patients who underwent CTV at 80kVp. The contrast injection protocol (iodine 600 mg/kg) was tailored to their body weight. We calculated the required contrast agent volume (CAVmean-IVC) to reach the mean enhancement of IVC. We performed univariate and multivariate linear regression analyses between the sex, age, body weight (BW), lean body weight (LBW), body surface area (BSA), height (HT), estimated glomerular filtration rate (eGFR), and CAVmean-IVC.

The univariate linear regression analysis show that HT, BW, LBW, and BSA were significantly correlated with CAVmean-IVC (P < .01 for all). The CAVmean-IVC was significantly higher for males than females (P < .01). Multivariate regression analysis showed that BW, LBW, and BSA had a statistically significant effect on CAVmean-IVC. There was no significant correlation of age, HT, or eGFR with CAVmean-IVC.

BW, LBW, and BSA each had an independent significant effect on CAVmean-IVC. The conventional BW-tailored contrast injection protocol might be insufficient for CTV.

Abbreviations: BSA = body surface area, BW = body weight, CAVmean-IVC = required contrast agent volume, CTPA = pulmonary CT angiography, CTV = computed tomography venography, DVT = deep vein thrombosis, eGFR = estimated glomerular filtration rate, FOV = field-of-view, GLM = generalized linear model, IVC = inferior vena cava, LBW = lean body weight, PE = pulmonary embolism.

Keywords: computed tomography, contrast agent dose, venography

1. Introduction
Deep vein thrombosis (DVT) is the most important predisposing factor for developing pulmonary embolism (PE).[1,12] To avoid PE, it is important to make a prompt diagnosis of DVT.[3] Although ultrasound (US) remains the workhorse for detection of DVT,[4] this technique is highly operator-dependent. However, previous reports have suggested the usefulness of computed tomography angiography (CTA) for the evaluation of vascular stenosis and vascular dissection.[5,6] Generally, venous enhancement is significantly lower than arterial enhancement on enhanced CT, and the degree of venous enhancement on CT venography (CTV) is important for a DVT diagnosis. Earlier reports suggested that higher venous attenuation on CTV images can be achieved with a high concentration of iodine contrast medium, a larger volume of contrast medium, or with low tube-voltage- or optimal scan-delay techniques.[7–10] However, it can be difficult to obtain diagnostic venous enhancement in some patients with suspected DVT.[11,12]

Yamashita et al.[11] reported that a body weight (BW)-tailored protocol yields high-quality hepatic dynamic CT images. In addition, various body size indices, such as lean body weight (LBW) and body surface area (BSA), have been proposed to determine the contrast agent dose for dynamic CT.[12,13] Using multiple stepwise regression analyses with a fixed contrast agent protocol, a previous report[14] suggested that patient ‘BW played a significant role in CT pulmonary angiography (CTPA) and venography. However, they did not evaluate the height and the estimated glomerular filtration rate (eGFR). Additionally, there have been no previous reports about the influence of the LBW and BSA on CTV and the CTPA protocol. There have been no previous reports about the validity of the contrast agent volume field-of-view determined by a BW-tailored protocol in CTV and CTPA. Additionally, there have been no previous reports about the influence of the LBW and BSA on the validity of the contrast agent volume on CTV and CTPA protocols.
We hypothesised that the BW-tailored protocol would be suitable to keep the contrast agent volume to yield varied venous enhancement on CTV images. The purpose of this study was to evaluate the relationship between the required contrast agent dose to acquire diagnostic-quality CTV with a BW-tailored contrast dose protocol, and patient characteristics including the age, height, BW, LBW, BSA, sex, and the eGFR using univariate and multivariate linear regression analysis.

2. Material and methods

Our institutional review board approved this retrospective study and waived the requirement for informed patient consent.

2.1. Patients

We enrolled 50 patients with suspected DVT or PE owing to elevated D-dimer levels (>5 μg/mL) or clinical symptoms (swelling of the calf, or thigh, or dyspnea). They underwent CTV and CTPA between November 2015 and May 2016. They were 26 men and 24 women ranging in age from 19 to 89 years (mean 69.4 years); their BW ranged from 38 to 82 kg (mean 59.2 kg).

2.2. Body size parameter

We adopted BW, LBW, and BSA as the body size indexes. We calculated the LBW using a similar equation in women: LBW \( = \frac{(1.07\, \text{BW} - 2.2)}{2.2} \). We also calculated the BSA using the following equation: BSA = \( 0.007184 \times \text{HT}^{0.425} \times \text{BW}^{0.725} \). In addition, we calculated the LBW using a similar equation in women: LBW = \( (1.07 \times \text{BW}) - 148 \times (\text{BW}^2/100 \times \text{HT})^2 \). In addition, we also calculated the BSA using the following equation: BSA = \( \text{BW}^{0.425} \times \text{HT}^{0.725} \times 0.007184 \).

2.3. CT scanning and contrast infusion protocols

Of the 50 patients, 29 underwent precontrast CT-, CTV-, and CTPA studies on a 64-detector CT scanner (Brilliance-64; Philips Medical Systems, Cleveland, OH); the other 21 were scanned on a 128-detector CT scanner (Brilliance-iCT; Philips Medical Systems). Precontrast CT- and CTPA scans were acquired in the caudocranial direction during a single inspiratory breath-hold. The parameters for 64-detector CT scanning were 80 kVp, detector collimation 64 × 0.625 mm, 750-ms tube rotation time, and 0.49 helical pitch (beam pitch). For 128-detector CTV studies, they were 80 kVp, detector collimation 128 × 0.625 mm, 750-ms tube rotation time, and 0.61 helical pitch (beam pitch). The CT dose index of CTV for 64- and 128-detector CT scanning was 14.2 and 11.7 mGy, respectively. The range of precontrast CT was from the diaphragm to the pelvis. CT scanning was from just above the diaphragm to the end of the feet in a caudocranial direction.

For all studies, the contrast medium (BW 600 mgI/kg; iopamidol, 370 mgI/mL [Iopamiron-370]; Bayer Yakuhin Ltd., Osaka, Japan); iomeron, 350 mgI/mL [Iomeron-350]; Bracco-Eisai Co Ltd., Tokyo, Japan); or omnipaque, 300 mgI/mL [omnipaque 300; GE Healthcare Inc., Princeton, NJ]) was injected with a power injector (DUAL SHOT GX; Nemoto-Kyorindo, Tokyo, Japan) in the course of 30 seconds via a 20-gauge catheter inserted into the antecubital vein.

CTPA was at 80 kVp; the scan start time was determined with a computer-assisted bolus tracking program (Bolus Pro Ultra; Philips Medical Systems) with a trigger threshold of 175 Hounsfield units (HU) in the pulmonary trunk. Real-time serial monitoring studies began 5 sec after the start of contrast injection.

Scanning started 10 seconds after triggering; 80-kVp CTV scans were acquired 270 seconds after contrast injection.

2.4. CT image reconstruction

The field of view (FOV) ranged from 30 to 45 cm depending on the patient physique. All CTV images were reconstructed with a slice thickness of 2.5 mm and slice interval of 2.5 mm. All CTV images were reconstructed with hybrid iterative reconstruction (HIR) (iDose4, Philips Healthcare). The iDose level was a parameter to adjust the image noise; the higher its level, the greater the noise reduction. Based on the results of preliminary studies, we selected an HIR level of 50% (iDose level 4) for image reconstruction.

2.5. Data analysis (CTV)

We acquired the patients' age and sex from their electronic health records. Their BW and HT were measured just before CT scanning. For all patients, we recorded the eGFR obtained within 3 days before CT.

A radiologist with 6 years of experience with CTV on BW-tailored contrast injection protocol performed quantitative image analysis using reconstructed 2.5-mm-thick axial CTV images. For each patient, images above the level of the inferior vena cava (IVC) bifurcation were selected. The average venous attenuation of two circular regions of interest (ROI) on 2 slices above the level of the IVC bifurcation on precontrast and CTV images (ROIplain-IVC and ROI(CTV-IVC)) was measured. Attempts were made to select an ROI in the IVC that was as large as possible and was unaffected by pixel variability and small enough to exclude the vessel wall or perivascular fat. We assessed the effects on venous contrast enhancement; its degree was expressed as the change in the venous CT number (ΔHU(IVC)), calculated by subtracting ROIplain-IVC from ROI(CTV-IVC). We also calculated the mean ΔHU of the 'study' patients (ΔHU(IVC-mean)).

The contrast agent dose (gram of iodine) to elevate mean enhancement of IVC (ΔHUplain-IVC/ΔHU(IVC-mean)) was calculated to evaluate the effect of these factors on venous contrast enhancement (CA(IVC-mean)). We calculated that contrast agent volume for 300 mgI/mL, as follows: CA(IVC-mean)/0.3 (CA(IVC-mean)).

Figure 1 shows the lesions of each ROI for CTV images.

2.6. Statistical analysis

All statistical analyses were performed with the free statistical software “R” (R, version 3.2.2; The R Project for Statistical Computing; http://www.r-project.org/). Univariate linear regression analysis was used and Pearson correlation coefficients (r) were determined to compare the patient characteristics (age, sex, one body size parameter [BW, LBW, or BSA], height, and eGFR) and the required contrast agent volume (CA(IVC-mean)). The absolute of r was determined as follows: a correlation of 0 to 0.19 was rated very weak, 0.2 to 0.39 was rated weak, 0.40 to 0.59 was rated moderate, 0.6 to 0.79 was rated strong, and 0.8 to 1 was rated very strong. We also compared ΔHU/gI and ROI(IVC) between males and females using Student t test.

We also performed multivariate linear regression analysis to determine which of the patient characteristics (age, sex, one body size parameter [BW, LBW, or BSA], height, and eGFR) affected...
the CAVIVC-mean. P values < .05 were considered to indicate a significant difference. If there was a significant difference between a patient characteristic and the CAVIVC-mean, we created an optimized linear regression model of that characteristic for the CAVIVC-mean. To assess the magnitude of association, we calculated the squared coefficients of determination (R² and adjusted R²) between the patient characteristic(s) and the CAVIVC-mean.

3. Results
The patient characteristics are presented in Table 1. The age of the 26 males and 24 females ranged from 19 to 89 years, their BW from 37.5 to 81.7kg, their LBW from 40.7 to 60.9kg, their BSA from 1.33 to 1.88m², their HT from 141.2 to 179.3cm, and their eGFR from 37.0 to 123.4mL/min/1.73m². ROIIVC ranged from 93.7 to 202.8 HU, DHUIVC from 195 to 601 HU, CAIVC-mean from 22.0 to 49.8gI and CAVIVC-mean from 73.3 to 166.0mL. DHUIVC-mean is 104.1 HU.

3.1. Effect of patient characteristics on CAVIVC-mean
On univariate linear regression analysis, significant inverse correlations were seen between CAVIVC-mean and BW (r = 0.59), height (r = 0.55), BSA (r = 0.63), and LBW (r = 0.64) (P < .01 for all). There are significantly different in the CAIVC-mean between male and female (P < .01). Multivariate linear regression analysis showed that only BW maintained their independent predictive value (ß = 0.27, P = .03). The regression formula (CAV IVC-mean[mL] = 57.5+BW [kg]) suggests that for each 1-kg increase in BW, contrast agent volume is increased by about 1.0mL.

We also create the regression formula of the BSA and LBW as follows: (CAV IVC-mean[mL] = 17.7+53.4/C²BSA [m²]) and (CAVIVC-mean[mL] = 47.3+1.7/C²LBW [kg]).

Tables 2 to 4 showed the relationship between patient characters including each 3 body size parameters and CAVIVC-mean.

4. Discussion
Our result suggested that BW, LBW, and BSA were independent predictive values at multivariate linear regression analysis for affecting the CAVIVC-mean. Our most important finding is that our BW-tailored contrast injection protocol (2mL/kg [300mg/mL]) is unsuitable for CTV. The regression formula CAVIVC-mean was as follows, CAV IVC-mean mL = 57.5+BW [kg] for 300mg/ml. Therefore, our BW-tailed protocol showed that excessive contrast agent might be given in heavy patients to keep the mean

Table 1
Patient characteristics and venous enhancement.

| Number of patients | 50 |
|--------------------|----|
| Males: females     | 24:26 |
| Age, y             | 69.4±15.8 |
| Body weight, kg    | 59.2±11.8 |
| Lean body weight, kg | 55.3±6.4 |
| Body surface area, m² | 1.59±0.14 |
| Height, cm         | 158.6±9.9 |
| eGFR, mL/min/1.73m² | 66.1±16.5 |
| Mean venous enhance (ΔHU_IVC-mean) (HU) | 104.1±18.1 |
| Venous enhancement per gram of iodine, HU/g | 3.0±0.7 |
| Required contrast agent volume to success the mean enhancement of NC (CAIVC-mean), mL | 120.9±24.8 |
| Mean pulmonary arterial enhancement (ΔHU_PA-mean), HU | 369.6±126.3 |
| Pulmonary arterial enhancement per gram of iodine, HU/g | 0.11±0.05 |
| Required contrast agent volume to success the mean enhancement of PA (CAPA-mean), mL | 133.9±56.0 |

Values are the mean±standard deviation. eGFR = estimated glomerular filtration rate, NC = inferior vena cava, PA = pulmonary artery.

Table 2
Multivariate GLM analysis of the effect of patient characteristics including body weight on CAIVC-mean (mL).

| Optimized model | β coefficients | P |
|-----------------|----------------|---|
| Intercept       | 57.49          | <.01 |
| Age             |                |     |
| Body weight, kg | 1.00           | <.01 |
| eGFR            |                |     |
| Height          |                |     |
| Sex             |                |     |
| Adjusted R²     | 0.31           |     |

eGFR = estimated glomerular filtration rate, GLM = generalized linear model.
adjusted sex, height, and eGFR. In conclusion, BW, LBW, and BSA each had an independent significant effect on CAV̄mean-IVC. The conventional BW-tailed contrast injection protocol might be insufficient for CTV.

**Author contributions**

**Conceptualization:** K. Katakara, T. Nakaura, Y. Iyama.

**Data curation:** K. Katakara, T. Nakaura, Y. Iyama.

**Formal analysis:** T. Nakaura, Y. Iyama.

**Investigation:** Y. Iyama.

**Methodology:** T. Nakaura, Y. Iyama.

**Project administration:** T. Nakaura, Y. Iyama.

**Software:** Y. Iyama.

**Supervision:** T. Nakaura, Y. Yamashita.

**Validation:** D. Utsunomiya, M. Kidoh, S. Oda, T. Nakaura, Y. Yamashita, Y. Iyama.

**Writing – original draft:** T. Nakaura, Y. Iyama.

**Writing – review & editing:** T. Nakaura, Y. Iyama.

**References**

1. Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost 2005;3:1611–7.
2. Wells PS, Anderson DR, Rodger MA, et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Arch Intern Med 2005;165:733–8.
3. Duru S, Ergun R, Dilli A, et al. Clinical, laboratory and computed tomography pulmonary angiography results in pulmonary embolism: retrospective evaluation of 205 patients. Anadolu Kardiyol Derg 2012;12:142–9.

---

**Table 3**

Multivariate GLM analysis of the effect of patient characteristics including lean body weight on CAV̄mean (mL).

| Optimized model | β coefficients | P  |
|-----------------|----------------|----|
| Intercept       | 47.25          | <.01|
| Age             | —              | —  |
| Lean body weight| 1.67           | <.01|
| eGFR            | —              | —  |
| Height          | —              | —  |
| Sex             | —              | —  |
| Adjusted $R^2$  | 0.38           |    |

*eGFR = estimated glomerular filtration rate, GLM = generalized linear model.*

---

**Table 4**

Multivariate GLM analysis of the effect of patient characteristics including BSA on CAV̄mean (mL).

| Optimized model | β coefficients | P  |
|-----------------|----------------|----|
| Intercept       | 17.74          | .36 |
| Age             | —              | —  |
| Body surface area| 53.44         | <.01|
| eGFR            | —              | —  |
| Height          | —              | —  |
| Sex             | —              | —  |
| Adjusted $R^2$  | 0.37           |    |

*eGFR = estimated glomerular filtration rate, GLM = generalized linear model.*

---

Correlation with aortic and hepatic enhancement and Yanaga et al(21) reported that an LBW-tailed dose yielded more consistent aortic enhancement with reduced interpatient variability than the CTA protocol that delivered a BW-tailed dose. According to Bae et al,25 a contrast dose based on the BSA was useful for obtaining consistent contrast enhancement on cardiac CT angiograms. However, the intercept of our optimized linear model using the BSA and LBW was also not zero. Therefore, the simple BSA- and LBW-tailed protocol cannot offer the stable enhancement of IVC. The intermediate protocol between the fixed- and body-size-tailored contrast injection protocol might be well suited for the CTV.

Our study has some limitations. First, it was a single-center study and the small sample size may limit the statistical significance of our findings. Second, we did not evaluate the relationship between CO, which may affect the blood volume and blood pooling, and venous attenuation. According to Bae et al,26 the CO directly affects vessel enhancement by contrast media. Third, because our precontrast CT scan range covered mainly the chest to the pelvis, we only evaluated CT attenuation of the IVC; we did not study attenuation of veins in the lower and upper thigh. We will address these issues in future studies. Last, we did not use the optimized protocol in clinical practice. Theoretically, the optimized protocol yields the contrast agent volume to success the valid enhancement of IVC on CTV for all patients. However, it might affect the CTPA protocol. Previous report suggested that 1.2 mL/kg for 350 mg/mL (about 1.5 mL/kg for 300 mg/mL) can yield varied contrast enhancement of PA on CTPA.50 Therefore, we can use the loose slope to determine the contrast agent volume to success the valid enhancement of IVC and PA on CTV and CTPA.

**5. Conclusion**

In conclusion, BW, LBW, and BSA each had an independent significant effect on CAV̄mean-IVC. The conventional BW-tailed contrast injection protocol might be insufficient for CTV.
