



# Can expiratory or inspiratory contrast-enhanced computed tomography be more efficient for fast-track cannulation of the right adrenal vein in adrenal venous sampling?

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## PURPOSE

This study compares the usefulness of expiratory arterial phase (EAP)-contrast-enhanced computed tomography (CT) (CECT) with that of inspiratory arterial phase (IAP)-CECT in adrenal venous sampling (AVS).

## METHODS

Sixty-four patients who underwent AVS and CECT at the authors' hospital between April 2013 and June 2019 were included in this study. The patients were classified into the following two groups: EAP (32 patients) and IAP (32 patients) groups. The single arterial phase images were obtained at 40 seconds in the IAP group. The double arterial phase images were obtained at 40 seconds in the early arterial phase and 55 seconds in the late arterial phase in the EAP group. The authors then compared the right adrenal vein (RAV) visualization rate on the CECT, the difference between the CECT images and adrenal venograms in the localization of the RAV orifice, the cannulation time to the RAV, and the volume of contrast agent administered intraoperatively between the two groups.

## RESULTS

The rates of the RAV visualization in the EAP group were 84.4% in the early arterial phase, 93.8% in the late arterial phase, and 100% in the combined early and late arterial phases. The rate of the RAV visualization in the IAP group was 96.9%. There was no significant difference between the two groups in terms of the rate of the RAV visualization. However, there was a small difference in the location of the RAV orifice between the CECT images and adrenal venograms in the EAP group as compared with the IAP group ( $P < 0.001$ ). The median time to the RAV catheterization was significantly shorter in the EAP group (27.5 minutes) than in the IAP group (35.5 minutes;  $P = 0.035$ ). The rates of the RAV visualization in the EAP group were not significant between the early arterial phase, late arterial phase, and combined early and late arterial phases ( $P = 0.066$ ). However, the mean volume CT dose index in the combined early and late arterial phases was significantly higher than in the early and late arterial phases ( $P < 0.001$ ).

## CONCLUSION

The EAP-CECT is more useful for increasing the speed of the RAV cannulation due to the small difference in the localization of the RAV orifice compared to IAP-CECT. However, since EAP-CECT has double contrast arterial phases and increased radiation exposure compared to IAP-CECT, only the late arterial phase may be acceptable to reduce radiation exposure.

## KEYWORDS

Adrenal, aldosteronism, contrast, CT, venography

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The characteristic features of primary aldosteronism (PA) are hypertension and hypokalemia.<sup>1,2</sup> PA is diagnosed in between 5% and 20% of patients with refractory hypertension.<sup>2-4</sup> Compared with essential hypertension, PA significantly increases the risk of cardiovascular complications, cerebrovascular disorders, and renal damage.<sup>4,5</sup> The treatment for PA is laparoscopic adrenalectomy for patients with unilateral disease, whereas patients with bilateral disease are treated medically with mineralocorticoid receptor antagonists.<sup>6</sup> Therefore, the identification of PA lateralization is required to determine the treatment strategy. Adrenal venous sampling (AVS) is recommended for distinguishing unilateral from bilateral PA.<sup>7</sup> In a large multicenter AVS registry study conducted recently,<sup>8</sup> bilateral cannulation was successful in 80.1% of the procedures. AVS is a relatively difficult procedure, and it is especially difficult to cannulate the right adrenal vein (RAV) due to its small size, variable anatomy, and the effects of the patient's respiratory motion during cannulation. Dynamic contrast-enhanced computed tomography (CT) (CECT) before AVS is useful for increasing the success rate of AVS.<sup>9</sup> Dynamic CECT has long been used to differentiate adrenal tumors.<sup>10</sup> Matsuura et al.<sup>11</sup> reported that the RAV visualization rate was 76% using CECT. However, recent studies have reported improvements in the visualization rate of the RAV, which is challenging to cannulate, on multiple-phase dynamic CECT (>90%).<sup>12-15</sup> Many of those reports obtained CECT images with the patient in the expiratory position.<sup>9,12,15</sup> However, several reports have also focused on the inspiratory position,<sup>11,16,17</sup> and little is known about the optimal breath-holding position during dynamic CECT in AVS. Therefore, the purpose of this study is to evaluate the advantage of the expiratory arterial phase (EAP)-CECT (at 40 and 55 seconds, respectively, after contrast media injection) compared with the inspiratory arterial phase (IAP)-CECT (at 40 seconds after contrast media injection) in AVS.

#### Main points

- The right adrenal vein (RAV) was well visualized on the arterial phase contrast-enhanced computed tomography (CT) (CECT) scan.
- The RAV had a minimal difference between the expiratory CT scan images and the adrenal venograms.
- The expiratory arterial phase-CECT scan was useful for the fast-track cannulation of the RAV.

## Methods

### Patients

The Shinshu University Certified Review Board of Clinical Research approved this retrospective study, and informed consent was waived (Internal Review Board approval number: 5087).

The authors reviewed the medical records at the authors' hospital and selected 95 consecutive patients diagnosed with PA who underwent AVS between April 2013 and June 2019. Patients who did not undergo CECT at the hospital (n = 11), those who used contrast agents other than those containing 370 mgI/MI (n = 19) of Iopamiron, and those who had inferior left vena cava visualization (n = 1) were excluded from the study. Of the 19 patients who had contrast agents other than those containing 370 mgI/mL of Iopamiron, 13 were included in the IAP group and 6 in the EAP group. There are no reports comparing different iodine concentrations of contrast agents in the visualization of the RAV on CECT. However, if contrast injection conditions are constant, vascular CT values are proportional to the iodine concentration.<sup>18</sup> As the authors thought this would affect the visualization of the RAV, we only analyzed patients imaged with 370 mgI/mL of contrast agent, which was the majority of cases. Thus, 64 patients were included in the study.

### Computed tomography examinations

All abdominal dynamic CECT examinations were performed before AVS. The median interval between CECT and AVS was 28 days (range: 1–189 days). Images were obtained using any of the following CT scanners: a 64-row detector CT scanner (LightSpeed VCT; GE Healthcare, Milwaukee, WI, USA). Scan parameters were as follows: tube voltage, 120 kVp; reconstruction thickness, 1.25 mm; beam collimation, 40 mm; rotation time, 0.4 seconds; and helical pitch, 0.984. CECT was performed using 100 mL of contrast agent containing 370 mgI/mL of Iopamidol (Iopamiron 370; Bayer Healthcare, Berlin, Germany) at an injection rate of 3 mL/s. Dual-phase contrast-enhanced dynamic scans during breath-hold inspiration or three-phase contrast-enhanced dynamic scans during breath-hold expiration were performed. In the dual-phase contrast-enhanced dynamic scans, arterial phase images were obtained at 40 seconds (in the IAP group), and delayed phase images were obtained at 130 seconds after the start of the contrast agent injection. In triple-phase con-

trast-enhanced dynamic scans, the double arterial phase images were obtained at 40 and 55 seconds (in the EAP group), and the delayed phase image was obtained at 130 seconds after the start of the contrast agent injection. We defined the 40-second phase after the start of the contrast agent injection as the early arterial phase and the 55-second phase after the start of the contrast agent injection as the late arterial phase. The late arterial phase in the EAP group was added to prolong the peak contrast effect because expiration decreases cardiac output and venous circular flow.<sup>19</sup> The EAP was performed on patients with AVS, as indicated in the request details, during CECT. Alternatively, the IAP was performed as a routine abdominal CECT.

### Adrenal venous sampling procedure

During the study period, the main operator who performed AVS was among the 11 radiologists [with 5–16 years of experience in interventional radiology (IVR)] involved in this study. AVS was performed using one of the following angiography systems: Infinitix Celeve Active (Canon Medical Systems, Otawara, Japan) or Artis zee BA Twin (Siemens Healthineers, Bayern, Germany). All operators performed AVS according to the following procedure: operators inserted 5-Fr introducer sheaths via the right and left common femoral veins. A 4-Fr catheter with a two-dimensional shape (shepherd's hook catheter; Meditkit Co., Ltd., Tokyo, Japan), a 5-Fr catheter designed for the RAV (Hanaco Medical, Saitama, Japan), or a 5-Fr catheter with a three-dimensional shape designed to accommodate five RAV patterns (Adselect Series; Hanaco Medical)<sup>20</sup> were inserted into the RAV (Figure 1). A 5-Fr catheter designed for the left adrenal vein (LAV) (Hanaco Medical) was inserted into the LAV. Depending on the operator, the catheter was first inserted into the LAV and then into the RAV. After the operator performed a venography and confirmed the cannulation into the RAV and LAV (Figure 2), venous blood samples of at least 3 mL were obtained, respectively. Blood samples of the RAV were collected once or twice from each patient. Blood samples were also subsequently obtained from the inferior vena cava (IVC) above the confluence of the RAV and under the confluence of the left renal vein. The authors did not always assess the patient selectivity index (i.e., adrenal vein cortisol concentration/IVC cortisol concentration ratio) intraoperatively if the RAV was clearly observed on venography. Fifteen minutes after administration of the adreno-

corticotrophic hormone (ACTH), venous blood samples were obtained again from the RAV, LAV, and IVC in the same manner. The cannulation time of the RAV, incident dose of the entire procedure, fluoroscopy time of the entire procedure, and volume of contrast agent were recorded. The cannulation time of the RAV was defined as the time from inserting the sheath to performing the RAV venography or from performing the LAV venography

to performing the RAV venography (Figure 3). The insertion time of the sheath was extracted from the intraoperative record written by the operating nurse. The venography time of each adrenal vein was recorded from the image of each adrenal vein attached to the operative report. The criterion for successful cannulation of the RAV was a selectivity index after ACTH stimulation of  $\geq 5$ .<sup>21</sup>

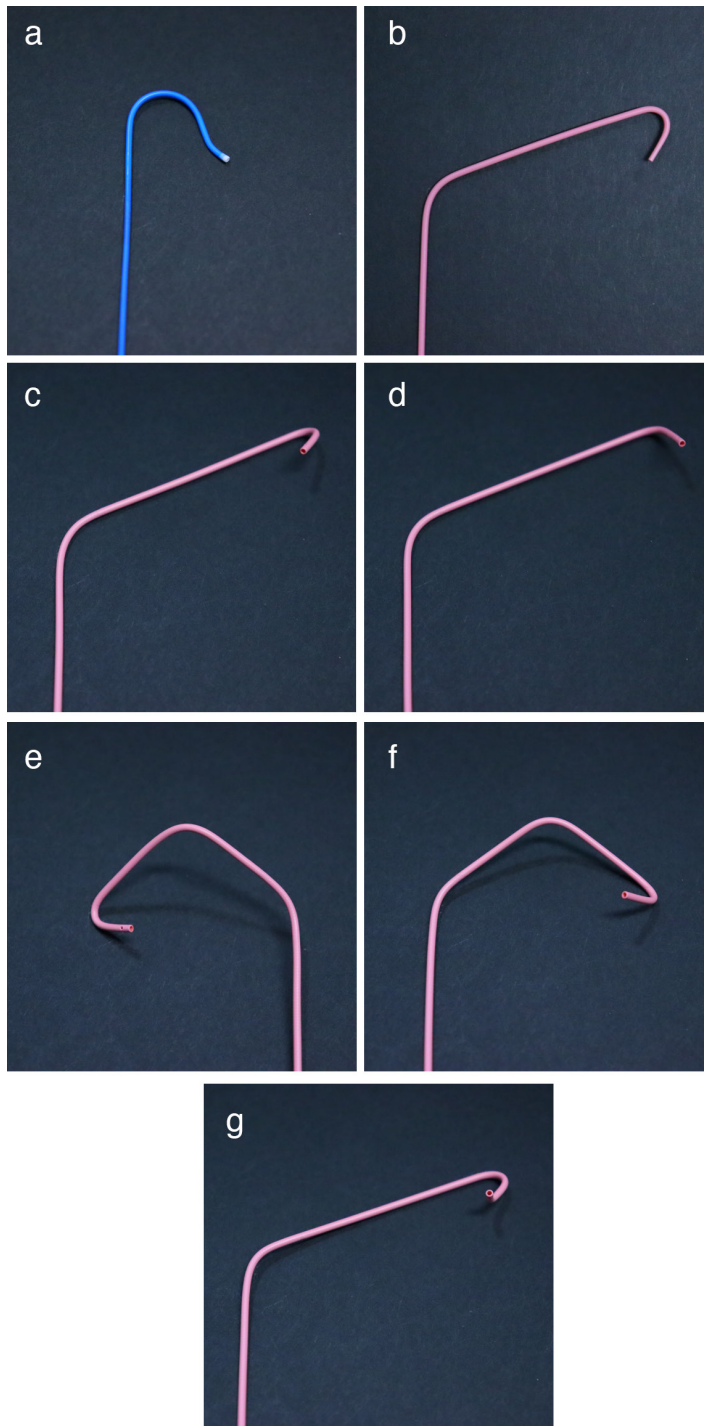
### Image analysis

Two radiologists (readers A and B, with 7 and 6 years of experience in IVR, respectively) who had not performed AVS as operators independently evaluated the CECT images using a commercial software package (EV In-site; PSP Corporation, Tokyo, Japan). The RAV was defined as an enhanced tubular or linear structure from the right adrenal gland, as observed on the CT images, which eventually entered the IVC either directly or indirectly.<sup>21</sup> The degree of visualization was recorded using a 4-point scale from a previous report:<sup>12</sup> 4, the RAV runs between the IVC and the right adrenal gland; 3, the RAV is unequivocally detectable, although the contrast of the RAV to the surrounding structures is not so strong; 2, equivocal detection of the RAV, with minimal contrast to surrounding structures; 1, the RAV is not visualized (Figure 4). A grade of 3 or 4 was regarded as RAV visualization. In cases of discrepancies between the visualization grades of 3–4 and 1–2 in readers A and B, reader C (who had 15 years of experience in IVR) evaluated the CT images to obtain a consensus. With reference to a previous report,<sup>22</sup> the localization of the RAV orifice was divided and numbered into 24 parts from the 10<sup>th</sup> thoracic vertebra to the second lumbar vertebra from the cranial side to the caudal side (Figure 5). Each vertebral body was subdivided into four equal levels from the cranial side to the caudal side and one additional section representing the vertebral disk. Reader C recorded the localization numbers of the RAV orifice on the CECT image and the adrenal venography image, respectively. The localization of the RAV on the CECT was determined by the level of the CECT-scout image corresponding to the axial CECT image visualizing the RAV. The localization of the RAV on the venogram was determined by the level of the catheter tip with the right adrenal venogram.

### Statistical analysis

We performed statistical analyses using Bell Curve in Excel (Social Survey Research Information Co. Ltd., Tokyo, Japan). We used the Student's t-test to compare the patient's age, body mass index (BMI), height, and body weight. The chi-squared test was used to compare the patient's sex, the visualization rate, and the catheter cannulation success rate in the RAV.

The Mann-Whitney U test was used to compare the time for cannulating the RAV, the fluoroscopy time of the entire procedure, the whole entrance dose of the entire



**Figure 1.** (a-g) The catheters used for cannulation of the right adrenal vein (RAV). The authors selected the appropriate catheter based on the shape of the RAV. (a) A 4-Fr shepherd's hook-type catheter with a two-dimensional shape. (b) A 5-Fr catheter, designed for the RAV with a two-dimensional shape. (c-g) A 5-Fr catheter with a three-dimensional shape designed to accommodate five RAV patterns.

procedure, the volume of contrast media, years of experience in IVR, and the difference between CECT images and adrenal venograms in localization of the RAV orifice. The Friedman test was used to compare the mean volume CT dose index adjusted for body size and the visualization rates of the RAV between the arterial phase, late arterial phase, and combined arterial and late arterial phases in the EAP group. If a significant difference was indicated, multiple intergroup comparisons were performed using the Scheffé post-hoc test. The inter-reader agreement was assessed using Cohen's weighted kappa analysis. A kappa value of  $\leq 0.20$  indicated poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, excellent agreement. A *P* value of  $< 0.05$  was considered statistically significant.

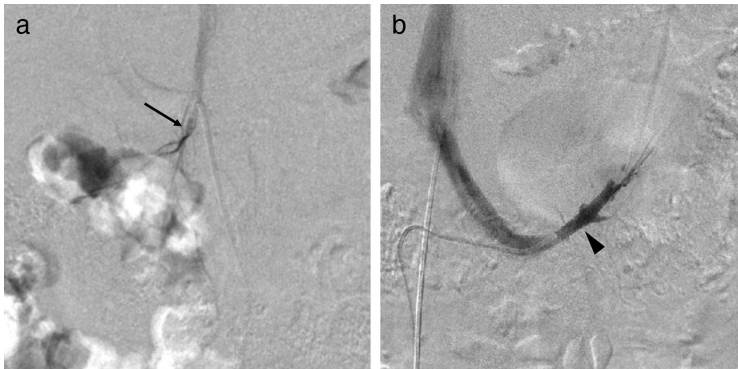
## Results

### Patient characteristics

Table 1 shows the patient characteristics, including age, sex, height, body weight, BMI, and years of IVR experience. Of 64 patients, 32 patients were classified into the EAP group and 32 in the IAP group. There were no significant differences between the two groups with regard to age, sex, height, body weight, BMI, and years of IVR experience.

### Evaluation of right adrenal vein visualization and radiation exposure on contrast-enhanced computed tomography

Table 2 shows the degree of the RAV visualization. On the early arterial phase image, although the IAP group had a better visualization rate than the EAP group, the visualization rates were not significantly different between the two groups. In the EAP group,



**Figure 2.** (a, b) A case of adrenal venous sampling in a 52-year-old man with primary aldosteronism. (a) A 5-Fr catheter with a three-dimensional shape designed for the right adrenal vein (RAV) is successfully cannulated in the RAV (arrow). (b) A 5-Fr catheter designed for the left adrenal vein (LAV) is successfully cannulated in the common trunk of the LAV (arrowhead).

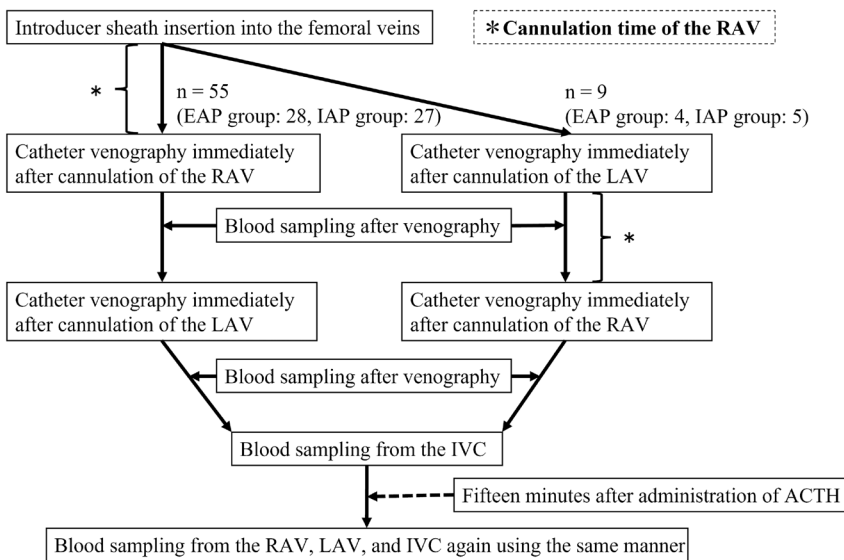
visualization rates for the late arterial phase were improved compared with the early arterial phase. In the combined early and late arterial phase images of the EAP groups, the visualization rates were 100%, which were not significantly different from those of the IAP group. Furthermore, the EAP group showed no significant difference in the RAV visualization rate between the early arterial phase, late arterial phase, and combined early and late arterial phases (*P* = 0.066).

In the EAP group, the weighted kappa values for the RAV visualization score on the early and late arterial phase images were 0.71 and 0.54, respectively, which indicated good inter-reader agreements. Furthermore, in the IAP group, the weighted kappa value for the RAV visualization score on the early phase image was 0.35, which indicated a fair inter-reader agreement.

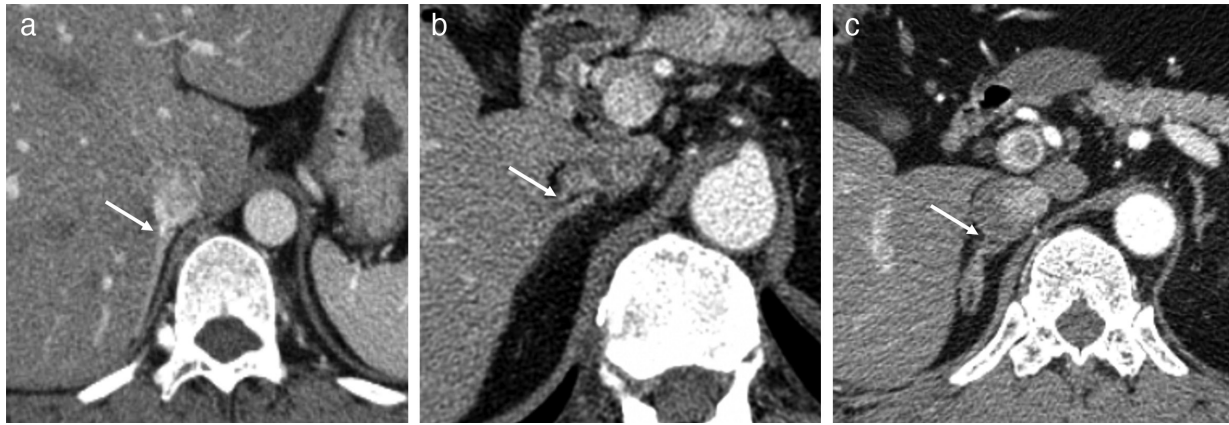
The mean volume CT dose indexes of the EAP group were  $18.74 \pm 3.16$  mGy in the early arterial phase,  $18.54 \pm 3.06$  mGy in the late arterial phase, and  $37.27 \pm 6.21$  mGy in the combined early and late arterial phases. No significant differences were noted in the mean volume CT dose indexes between the early and late arterial phases (*P* = 0.75). However, the mean volume CT dose indexes in the combined early and late arterial phases were significantly higher than those in the early and late arterial phases (*P* < 0.001). The mean volume CT dose index of the IAP group was  $19.06 \pm 3.35$  mGy in the early arterial phase.

### Difference between the contrast-enhanced computed tomography images and adrenal venograms in the localization of the right adrenal vein orifice

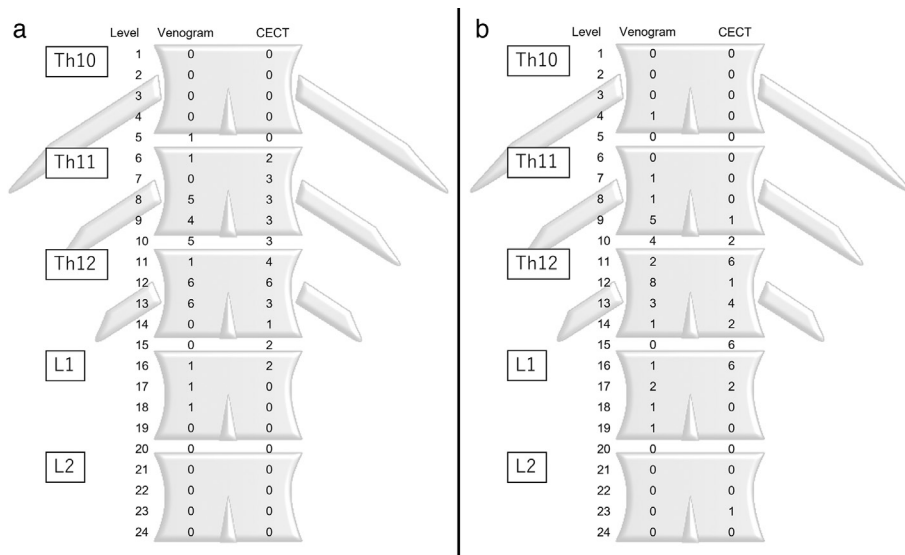
In the EAP group, the CECT image showed that the RAV orifice was located between level 6 and level 16 (median: 11), whereas on the adrenal venogram, the RAV orifice was located between level 5 and level 18 (median: 10.5; Figure 5a). On the other hand, the RAV orifice on the CECT image in the IAP group was located between level 9 and level 23 (median: 14), whereas on the adrenal venogram, it was located between level 4 and level 19 (median: 12; Figure 5b). The EAP group had a smaller location difference in the RAV orifice between the CECT images and adrenal venograms than the IAP group (*P* < 0.001; Figure 6).



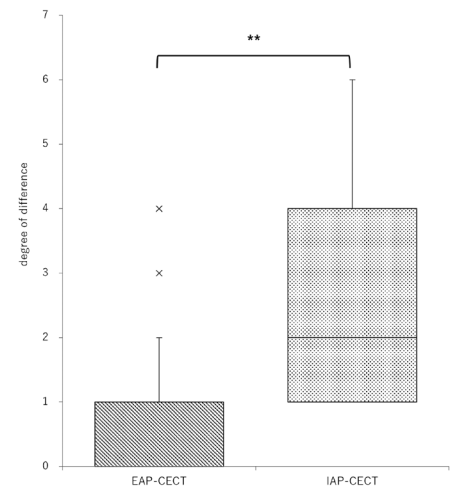
**Figure 3.** A flowchart of the adrenal venous sampling procedure. The cannulation time of the right adrenal vein is marked with asterisks. RAV, right adrenal vein; EAP, expiratory arterial phase; IAP, inspiratory arterial phase; LAV, left adrenal vein; IVC, inferior vena cava; ACTH, adrenocorticotropic hormone.



**Figure 4.** (a-c) The scores of the right adrenal vein (RAV) visualization on computed tomography images. Examples of score 4 (a), score 3 (b), and score 2 (c). The RAV is marked with arrows.



**Figure 5.** (a, b) Localization of the right adrenal vein (RAV) orifice. The location of the RAV orifice was determined and numbered from cranial to caudal in 24 anatomical levels from the top of the 10<sup>th</sup> thoracic vertebra to the bottom of the second lumbar vertebra. (a) The number of the RAV orifice on contrast-enhanced computed tomography (CECT) images and venograms in the expiratory arterial phase-CECT group. (b) The number of the RAV orifice on CECT images and venograms in the inspiratory arterial phase-CECT group.



**Figure 6.** The positional difference between contrast-enhanced computed tomography and venography at the localization of the right adrenal vein orifice. **\*\*** $P < 0.001$ ; CECT, contrast-enhanced computed tomography; EAP, expiratory arterial phase; IAP, inspiratory arterial phase.

Table 1. Characteristics of the patients			
	EAP group (n = 32)	IAP group (n = 32)	P value
Age (years)			
Mean $\pm$ SD	48.34 $\pm$ 11.82	50.91 $\pm$ 11.03	$P = 0.70$
Sex (M/F)	19/13	14/18	$P = 0.32$
Height (m)			
Mean $\pm$ SD	1.66 $\pm$ 0.088	1.63 $\pm$ 0.079	$P = 0.52$
Weight (kg)			
Mean $\pm$ SD	71.08 $\pm$ 13.82	69.97 $\pm$ 15.03	$P = 0.64$
BMI (kg/m <sup>2</sup> )			
Mean $\pm$ SD	25.65 $\pm$ 4.35	26.40 $\pm$ 5.20	$P = 0.32$
Experience in IVR (years)			
Median (range)	7 (5–16)	8 (6–16)	$P = 0.051$

EAP, expiratory arterial phase; IAP, inspiratory arterial phase; SD, standard deviation; BMI, body mass index; IVR, interventional radiology; M, male; F, female.

### Comparison of adrenal venous sampling between the expiratory arterial phase-contrast-enhanced computed tomography group and the inspiratory arterial phase-contrast-enhanced computed tomography group

Table 3 shows the comparison of AVS between the EAP-CECT group and the IAP-CECT group. The median time to RAV cannulation was significantly shorter in the EAP-CECT group (27.5 minutes) than in the IAP-CECT group (35.5 minutes;  $P = 0.035$ ). No significant intergroup differences were noted in terms of exposure dose, fluoroscopy time during the entire procedure, and volume of contrast agent.

**Table 2.** Visualization rates of the right adrenal vein

	EAP group (n = 32)	IAP group (n = 32)	P value
Early arterial phase	27/32 (84.4%)	31/32 (96.9%)	$P = 0.20$
Late arterial phase	30/32 (93.8%)		<sup>†</sup> $P = 1.00$
Early and late arterial phase	32/32 (100%)		<sup>††</sup> $P = 1.00$

<sup>†</sup>Comparison between the late arterial phase (EAP group) and the early arterial phase (IAP group); <sup>††</sup>Comparison between the arterial and late arterial phases (EAP group) and the arterial phase (IAP group). EAP, expiratory arterial phase; IAP, inspiratory arterial phase.

**Table 3.** Adrenal venous sampling between the expiratory arterial phase and inspiratory arterial phase groups

	EAP group (n = 32)	IAP group (n = 32)	P value
Success rate of RAV cannulation	100% (32 of 32)	97% (31 of 32)	$P = 1.00$
Time to RAV cannulation (min) Median (range)	27.5 (5–154)	35.5 (7–174)	$P = 0.035^*$
Exposure dose (mGy) Median (range)	429.20 (94–1548.16)	497.84 (93.2–1824)	$P = 0.40$
Fluoroscopy time (min) Median (range)	45.25 (13.8–92.6)	45.95 (17.2–130.1)	$P = 0.51$
Volume of contrast agent (mL) Median (range)	76.5 (25–260)	100 (20–280)	$P = 0.11$

\*Statistically significant. EAP, expiratory arterial phase; IAP, inspiratory arterial phase; RAV, right adrenal vein.

## Discussion

To the authors' knowledge, there are no reports mentioning the cannulation time of the RAV and the amount of contrast media in AVS as a result of different CECT imaging methods used before AVS. This study's results showed no significant between-group differences in the RAV visualization and the cannulation success rate. However, the cannulation time of the RAV was significantly shorter in the EAP group than in the IAP group.

The RAV visualization rate of the IAP group was 96.9% in the early arterial phase. The RAV visualization rates of the EAP group were 84.4% in the early arterial phase and 93.8% in the late arterial phase. The RAV visualization rate of the EAP group in the combined early and late arterial phases was 100%. Hence, there was no significant difference in the RAV visualization rates between the IAP and EAP groups. In the EAP group, there was an improvement in the RAV visualization rate in the late arterial phase compared with that in the early arterial phase. This finding may be attributed to changes in venous circular flow caused by respiration. In the expiratory position, intrathoracic pressure decreases, causing a decrease in venous circular flow, and cardiac output is correspondingly decreased. Therefore, the peak of the contrast-enhanced effect on the RAV was considered to be prolonged.<sup>19</sup> Some reports have evaluated the RAV visualization rates of

CECT in the expiratory position.<sup>9,12,15,22</sup> Morita et al.<sup>15</sup> reported the usefulness of the dual adrenal venous phase images obtained at 45 and 55 seconds using the constant injection time technique of contrast media (iodine of 600 mgI/kg body weight) in the expiratory position. They found combined rates of the RAV visualization of the first and the second adrenal venous phase of 98%. In this study, the contrast media injection technique was constant regarding both injection time and injection rate. However, the rate of the RAV visualization in the combined early and late arterial phases was satisfactory at 100% in the EAP group. Nevertheless, there was no significant difference in the RAV visualization rate between the combined early and late arterial phases and early and late arterial phases. In contrast, the mean volume CT dose index in the combined early and late arterial phases was significantly higher than in the early and late arterial phases. From the viewpoint of exposure dose reduction, only the late arterial phase in the EAP group may be acceptable.

The authors found a smaller location difference in the RAV orifice between the CECT images and the adrenal venograms in the EAP group than in the IAP group. This result suggests that the CECT images in the expiratory position were closer to the location of the RAV orifice than those in the inspiratory position. In addition, because the adrenal venogram was usually obtained during nat-

ural breath holding to keep the catheter stable, the RAV orifice on AVS was closer to that on the CECT images in the expiratory position. The authors, therefore, believe that preoperative simulation using the CECT images in the expiratory position has the advantage of reducing the procedure time required for the RAV catheterization. Some studies have compared the CECT images in the expiratory position and the images on AVS for the location of the RAV orifice. Onozawa et al.<sup>9</sup> compared the cannulated position of the RAV orifice with the RAV orifice on dynamic CECT in the expiratory position and interventional CT (a system that combines angiographic and CT equipment with a single fluoroscopy table). According to their report, the median difference of the RAV between the dynamic CECT and the interventional CT was only half a vertebra. Degenhart et al.<sup>22</sup> compared the location of the RAV orifice between a CECT image obtained in the expiratory position and a venogram. The location of the RAV orifice on the CECT image and the venogram was highly consistent between the two readers (70% and 88%, respectively). Their results support those in this study.

As mentioned above, the authors speculated that the RAV cannulation time was shorter in the EAP group due to the smaller difference of the RAV orifice on the CECT. This preoperative simulation reduces the stress on the patient and the operator. Furthermore, this could lead to a reduction of radiation exposure on AVS. Based on the authors' findings, the authors believe that the EAP is a useful imaging method for selecting the RAV on AVS. Although the EAP group had a lower dose of radiation exposure and shorter fluoroscopy time throughout the entire procedure as compared with the IAP–CECT group in this study, there was no significant difference.

The authors must also mention the limitations of this study. First, this was a retrospective study, and the sample size was small because the authors excluded many samples due to the different types of contrast media used in the CECT procedure. Moreover, the AVS procedure was performed by several operators. Second, because interventional CT of the RAV was not performed at AVS, the authors could not confirm whether the RAV on the abdominal dynamic CECT was the same as the blood vessel visualized by the adrenal venography.

In conclusion, EAP–CECT is useful for increasing the speed of the RAV cannulation due to the small difference in the localization

of the RAV orifice compared to IAP–CECT. However, since EAP–CECT has double contrast arterial phases and increases radiation exposure compared to IAP–CECT, only the late arterial phase may be acceptable to reduce radiation exposure.

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