<원저>

Analysis of Factors Influencing the Integrated Bolus Peak Timing in Contrast-Enhanced Brain Computed Tomographic Angiography

- Computed Tomographic Angiography (CTA)의 검사 시 조영제 집적 정점시간에 영향을 미치는 특성 인자를 분석 -

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— Abstract —

The objective of this study was to analyze the factors influencing integrated bolus peak timing in contrast-enhanced computed tomographic angiography (CTA) and to determine a method of calculating personal peak time.

The optimal time was calculated by performing multiple linear regression analysis, after finding the influence factors through correlation analysis between integrated peak time of contrast medium and personal measured value by monitoring CTA scans. The radiation exposure dose in CTA was 716.53 mGy·cm and the radiation exposure dose in monitoring scan was 15.52 mGy (2 - 34 mGy). The results were statistically significant (p < .01). Regression analysis revealed, a -0.160 times decrease with a one-step increase in heart rate in male, and -0.004, -0.174, and 0.006 times decrease with one-step in DBP, heart rate, and blood sugar, respectively, in female. In a consistency test of peak time by calculating measured peak time and peak time by using the regression equation, the consistency was determined to be very high for male and female.

This study could prevent unnecessary dose exposure by encouraging in clinic calculation of personal integrated peak time of contrast medium prior to examination.

Key Words : Test bolus method (TBM), Bolus tracking method (BTM), Monitoring scan

Ⅰ. INTRODUCTION

Early diagnosis of cerebrovascular disease through accurate examination is very important because of the serious nature of cerebrovascular disease[1]. The radiographic examination method available for cerebrovascular disease are conventional angiography (CA), computed tomographic angiography (CTA), and magnetic resonance angiography (MRA); these examinations are typical diagnostic methods[2-4]. CA is an important diagnostic method that can provide high correlation between disease level and prognosis, and is useful in determining appropriate intervention. However, there are some disadvantages such as the invasive nature of the procedure, and the associated complications and hospitalization. Recently, CA has been replaced by CTA and MRA[5]. CTA has been used generally with MRA, because CTA is a timesaving method with fast scanning of thin sections, and can easily identify cerebral infarction and cerebral hemorrhage. Recently, the accuracy of diagnosis has dramatically improved because of modernized devices and improvement in image processing. CA is superior to MRA with regards its suitability for emergency patients, because of the lesser sensitivity to hydromechanics and motion and because of the provision of high resolution ($>$ 0.5 mm^2)[6]. A study of reversible cerebral vasoconstriction syndrome (RCVS) reported that not only MRA but also CTA, which can be performed immediately, was useful; the study indicated that dual energy CTA provided high diagnosis results through creating high-resolution images, with fast examination times and using less radiation[7,8].

For high contrast imaging of blood vessels, CTA should be performed when the contrast medium is optimally integrated in the vessel; applying a universal integration time has limitations because peak time depends on the individual. Thus, the integrated peak time has been measured and applied using the test bolus method (TBM) and the bolus tracking method (BTM). The TBM is performed by injecting the contrast medium prior to the examination, and is an accurate method when applied to CTA for calculating the integrated peak time. However, the TBM has some disadvantages such as more complicated procedure due to double examination; time-delay, and increased radiation exposure. Thus, the BTM is more frequently used. This method is initiated when the contrast reaches 100 Hounsfield unit (HU) during a monitoring scan where the region of interest (ROI) is the ascending aorta. In most domestic hospitals, BTM is used in preference to TBM because of ease of use and accuracy[9]. However, for acquiring the CT number in ROI, the same region (ROI) should be scanned repeatedly, and the amount of radiation exposure increased. These exposure doses are slight compared to the whole exposure dose of CTA, but cannot be ignored compared to the exposure dose of chest posterior anterior projection (PA). A study of the usefulness of BTM, reported that the exposure dose of the monitoring scan was the greatest defect[10,11].

This study was the hypothesis if the integrated peak time for contrast medium could be calculated then the repeat monitor scan could be skipped. This study aimed to skip the monitoring scan, and thus prevent side effects associated with exposure dose, by analyzing the factors that affect the peak time of contrast medium and quantitatively calculating the optimum peak time.

Ⅱ. MATERIALS AND METHODS

1. Population

A total of 166 patients were, examined by BTM in CTA between November 2012 and October 2013. Of them, 133 patients were included in the study; 33 people with, a cardiac disorder or cerebrovascular disease, were excluded. The factors affecting the bolus peak time applied in this study were fundamental vital signs and personal characteristics determined in a previous study[12-16]. total of 18 factors that have a major impact on the body's metabolism were identified: [age, sex, weight, height, Systolic blood pressure (SBP), Diastolic blood pressure (DBP), heart rate,

body surface area, body mass index (BMI), fatness index, cholesterol, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), r−glutamyl transpeptidase (r−GT), blood sugar, body fat percentage, triglyceride, and creatinine].

Those factors that could be measured easily and quickly were selected for use in this study; those that had limitations with regards time and space were excluded. Thus, temperature and breath which have limitations of space, time, and large variation were excluded. Pulse was replaced with heart rate because measuring the pulse takes 30−60 seconds. r−GPT, GOP, GPT, triglyceride, and creatinine are characteristically affected by metergasis and abnormal hepato−biliary, pancreas, and kidney function. This study was approved by the institutional review board of the Asan Medical Center, Seoul, Republic of Korea (2013−5063).

2. Measurements

Data about age, sex, weight, height, body surface area, BMI, fatness index, cholesterol, GOT, GPT, r−GT, blood sugar, body fat percentage, and triglyceride were obtained from electronic medical records (EMR). Heart rate (number/min) and SBP were measured using the Vital Signs Monitor (Dash 3000, GE) before the CT scan. The contrast medium was injected the through right brachial veins using the method generally used in the clinic (flow of 4.5 − 5ml/sec, injected in the order of 60 ml of contrast medium and 40 ml of physiological saline) using an auto injector (CT Stellant, Medrad, USA)[17,18].

The integrated peak time for contrast medium was measured by bolus tracking system. The aortic arch was acquired by using the CT scan, and the ROI (ascending aorta) was set, after which the contrast medium was injected. After eight seconds of contrast medium injection, the monitoring scan was performed per second and measured artery circulation time. Integrated peak time was measured when the CT number reached 100 HU and the results of integrated peak time were presented graphically (Fig. 1). The scan was performed after four seconds by auto bolus triggering. During the scan, 60 ml of contrast medium (Ultravist 370, Iopromide) was injected with 4.5 ~ 5 mL/sec and then 40 ml of physiological saline were injected. For acquiring the image of CTA, the 64 MDCT (Somatom Definition AS, Siemens) and 128 MDCT (Somatom Definition AS+, Siemens) were employed. For scan parameter, 100 kVp, 100Eff. mAs,
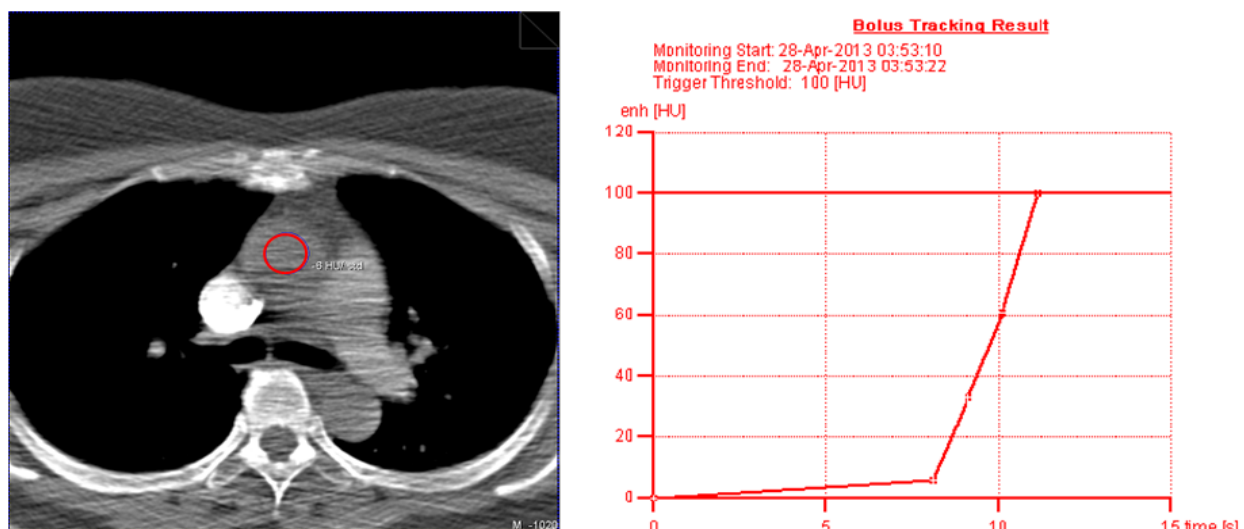

Fig. 1 Setting region of interest (ROI) in computed tomographic angiography image and the time Hounsfield unit (HU) curve. The aortic arch was acquired by computed tomography scan, the ROI (ascending aorta) was set and then contrast medium was injected. Eight seconds after contrast medium injection, the monitoring scan was performed per second and integrated peak time was measured when the CT number reached 100 HU

0.8 pitch, 0.5 rotation time were set before injecting the contrast medium. 120 kVp, 200 quality ref. mAs, 0.6 mm collimation, 0.8 pitch, 0.5 rotation time were set and care dose 4D was used after injecting the contrast medium. The image area was set from skull base to vertex of overall head.

The measurement of CTA dose was performed by dose length product (DLP), dividing into monitoring scan and total scan. The effective dose was calculated in accordance with the conversion factor, considering the stochastic effects.

3. Statistics

The results of general characteristics and measurements were divided into two groups: male and female. Descriptive statistics such as frequency and standard deviation were used. A correlation test was conducted to investigate the correlation between integrated peak time and individual characteristics. The regression equation of integrated peak time was formularized by using multiple linear regression analysis for the measurement values that were classed as influencing factors. After calculating the integrated peak time using regression equation, the coincidence test was conducted to evaluate the coincidence between the calculated integrated peak time and measured time. The measured values were processed by encoding and inquiring error and statistical analysis were conducted using the SPSS for Windows Program (version 18.0 : IBM : USA). The coincidence test was conducted using Bland-Altman plot (MedCalc version 12 : MedCalc[TM] : Belgium).

III. RESULTS

1. Individual Characteristics

The subjects were 51 male and 86 female. The average age, height and weight were 57.28 years ± 11.49 years, 161.35 cm ± 9.51 cm, and 62.50 kg ±

11.34 kg, respectively. Compared to female, the male had higher SBP, body surface area, GOT, r-GT, body fat percentage, triglyceride, and creatinine. The female had the higher DBP, heart rate, BMI, fatness index, cholesterol, GPT and blood sugar than male (Table 1).

2. Integrated Peak Time

The average integrated peak time was 13.73 ± 2.65 seconds. Male showed longer integrated peak time compared to women (14.72 ± 2.61 and 13.61 ± 2.51, respectively); the difference was statistically significant (Table 2).

3. Radiation Dose

The average number of monitoring scans was 6.34 ± 2.58 times (range: 1 − 14 times). The average radiation dose for the whole scan was 716.53 mGy·cm (range: 540.0 − 1078.0 mGy·cm). The average radiation dose by monitoring scan dose was 15.52 mGy (range: 2 − 34 mGy). In measuring radiation dose by converting the DLP to the conversion factor[19] which is generally applied to CT for calculating the effective dose, the average dose of the monitoring scan and CTA was 0.23 and 1.5 mSv, respectively. In DLP results, the percentage of monitoring scan for CTA was 2.2%. In effective dose by applying the conversion factor, the percentage of monitoring scan for CTA was 15.33% (Table 3).

4. Correlation Analysis between Integrated Peak Time and Individual Characteristics

There was a negative correlation between integrated peak time and heart rate in male; the results were statistically significant ($r = -.630$, $p < .01$). Statistical significance of other characteristics, except for heart rate, was insignificant. There was a negative correlation between integrated peak time and heart rate in female; the results was statistically significant ($r = -.675$, $p < .01$). A less significant negative correlation was observed for DBP and blood sugar in female,

Table 1 Individual characteristics of the subjects

Specific characteristic	Measurement (mean ± SD)		
	Total	Male	Female
Age	57.28 ± 11.49	56.59 ± 11.41	57.69 ± 11.59
Height	161.35 ± 9.51	170.39 ± 5.81	155.98 ± 6.84
Weight	62.50 ± 11.34	69.32 ± 10.69	58.46 ± 9.70
Systolic blood pressure	109.35 ± 53.00	112.67 ± 54.28	107.45 ± 52.49
Diastolic blood pressure	80.92 ± 18.15	79.33 ± 19.17	81.84 ± 17.60
Heart rate	74.26 ± 9.66	71.12 ± 10.27	76.08 ± 8.84
Body surface area	1.68 ± 0.19	1.82 ± 0.16	1.60 ± 0.16
Body mass index	24.37 ± 3.36	24.05 ± 2.90	24.54 ± 3.60
Fatness index	0.21 ± 0.17	0.11 ± 0.08	0.25 ± 0.18
Cholesterol	161.87 ± 42.08	158.04 ± 29.95	164.27 ± 48.24
Glutamic oxaloacetic transaminase	24.17 ± 8.78	24.60 ± 9.67	23.91 ± 8.25
Glutamic pyruvic transaminase	21.47 ± 15.11	20.33 ± 10.60	22.15 ± 17.29
r-glutamyl transpeptidase	33.79 ± 36.30	50.16 ± 49.65	22.68 ± 16.91
Blood sugar	119.22 ± 28.07	114.62 ± 28.84	121.97 ± 27.42
Body fat percentage	28.36 ± 6.38	23.46 ± 4.34	31.47 ± 5.51
Triglyceride	128.14 ± 60.01	131.18 ± 63.24	125.56 ± 57.84
Creatinine	0.72 ± 0.23	0.89 ± 0.17	0.62 ± 0.20

Table 2 Measured peak time of the subjects

Specific character	Measurement (mean±SD)			Sig.
	Total	Male	Female	
Measured peak time (sec)	13.73±2.65	14.72±2.61	13.61±2.51	0.002

Table 3 Number of monitoring scans and computed tomographic angiography radiation dose of subjects

Classification		Mean	Minimum	Maximum
Monitoring No.		6.34	1.00	14.00
DLP (mGy·cm)	Monitoring dose	15.52 (2.17%)	2.00	34.00
	CTA total dose	716.53	540.00	1078.00
DLP Conversion factor (mSv)	Monitoring dose	0.23 (15.33%)	0.03	0.51
	CTA total dose	1.5	1.13	2.26

DLP, dose length product; CTA, computed tomographic angiography
Conversion factor: CTA total dose (head) 0.0024, monitoring dose (abdomen) 0.015

indicated ($r = -.253$, $r = -.227$, $p < .05$). Statistical significance of other characteristics was insignificant.

5. Regression Analysis between Integrated Peak Time and Influence Factor

In male, multiple linear regression analysis between integrated peak time and heart rate indicated the significant value, R^2 was 0.630 and regression was 63%. In results of variance analysis, the F−test was 30.958 ($p = 0.000$), which was significant and the gradient value was not zero (Table 4).

The regression equation was formularized by using the regression intercepts and gradient value of 26.084 and −0.160 ($y = 26.084 - (0.16\chi1) + \varepsilon(1)$: y = calculated the optimal time; $\chi1$= inspection of HR; ε = error).

Table 4 Model summary and ANOVA (male computed tomographic angiography subjects)

Adjusted R square	F	Significance
0.630	30.958	.000

Table 5 Coefficients of factors affecting contrast media optimal time (male computed tomographic angiography subjects)

	Unstandardized coefficients		t	Significance
	B	Standard error		
(Constant)	26.084	2.064	12.639	.000
Heart rate	-.160	.029	-5.564	.000

Table 6 Model summary and ANOVA (female computed tomographic angiography subjects)

Adjusted R square	F	Significance
0.619	11.614	.000

Table 7 Coefficients of factors affecting contrast media optimal time (female computed tomographic angiography subjects)

	Unstandardized coefficients		t	Significance
	B	Standard error		
(Constant)	27.648	2.503	11.045	.000
DBP(mmHg)	-.004	.015	-.268	.790
Heartrate(L/min)	-.174	.033	-5.204	.000
Blood sugar(mg/dl)	-.006	.010	-.600	.551

DBP, diastolic blood pressure

This equation indicated that the integrated peak time was decreased by −0.160 times with a one-step increase of heart rate (Table 5).

In female multiple linear regression analysis among the integrated peak time, heart rate, DBP, and blood sugar indicated the significant value, R^2 was 0.619 and regression was 61.9%. In results of variance analysis, the F-test was 11.614 (p = 0.000), which was significant and the gradient value was not zero (Table 6).

The regression equation was formularized by using the regression intercepts of 27.648 and gradient values for heart rate, DBP, and blood sugar of −0.174, −0.004, and −0.006 (y = 27.648 − (0.004χ1 + 0.174χ2 + 0.006χ3) +ε(2): y = calculated the optimal time; χ1 = inspection of DBP; χ2 = inspection of HR; χ3 = inspection of BS; ε = error). This equation indicated that the integrated peak time decreased by −0.004, −0.174, and 0.006 times with increasing the one-step of DBP, heart rate, and blood sugar, respectively. However, DBP and blood sugar did not affect the integrated peak time because the partial regression coefficient of DBP and blood sugar was insignificant (Table 7).

6. Coincidence result of Bland−Altman plot

The integrated peak time by actual measure and regression equation are listed in Table 8. The average of integrated peak time by actual measure and regression equation was 13.73 ± 2.65 seconds and 13.76 ± 1.66 seconds, respectively. The difference between the values was 0.03 seconds (0.22%). The coincidence result of Bland−Altman was very high although the average integrated peak time by actual measure and regression equation had differences. Results indicated that the difference in integrated peak time between actual measure and regression equation was not associated with the number or characteristics of subjects because there were not any relation and the population was distributed randomly (Fig. 2).

Table 8 Descriptive statistics of measured optimal time and calculated optimal time from the regression equation

Unit: second

Classification		Measured time (A)	Calculated time (B)	A-B
Computed tomographic angiography	Entirety	13.73 ± 2.65	13.76 ± 1.66	-0.03(0.22%)
	Male	14.72 ± 2.61	14.70 ± 1.64	0.02(0.14%)
	Female	13.16 ± 2.51	13.44 ± 1.54	-0.28(2.13%)

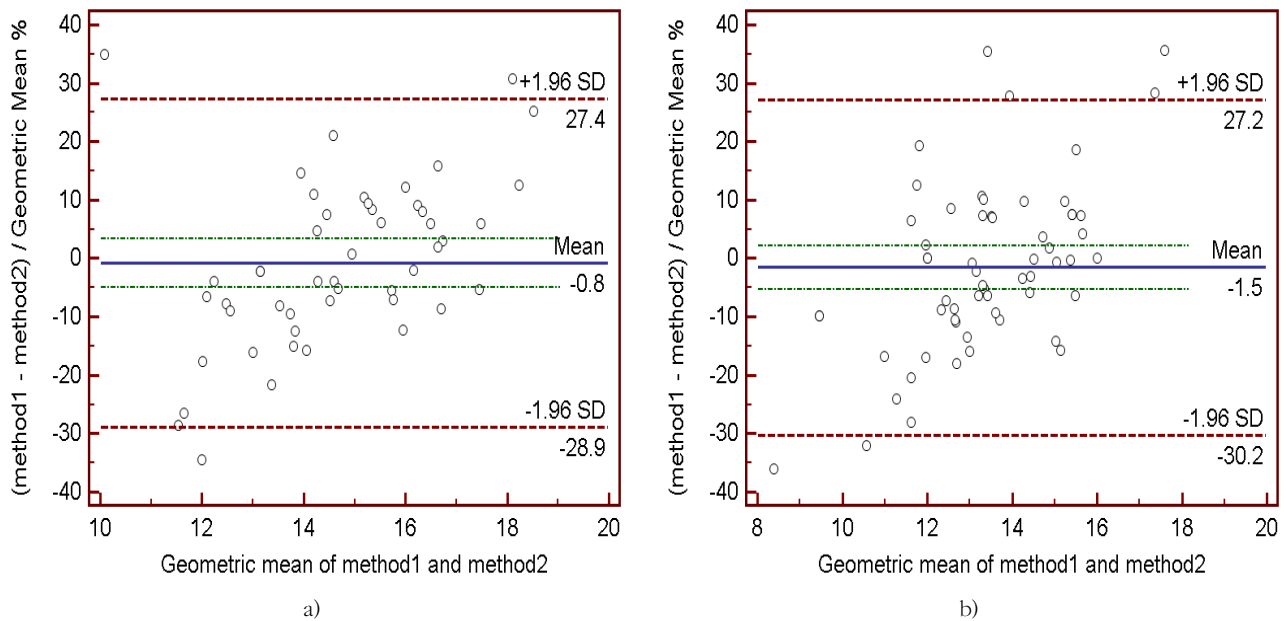a)   b)

Fig. 2 a) Coincidence result of Bland-Altman plot for males (computed tomographic angiography): (method 1: measured peak time), (method 2: calculated peak time). Results indicated that the difference in integrated peak time between actual measure and regression equation was not associated with the number of subjects because there were not any relation and the population was distributed randomly

b) Coincidence result of Bland-Altman plot for females (computed tomographic angiography): (method 1: measured peak time), (method 2: calculated peak time). Results indicated that the difference in integrated peak time between actual measure and regression equation was not associated with the number of subjects because there were not any relation and the population was distributed randomly

IV. DISCUSSION

Cerebrovascular disease most commonly affects elderly people and is associated with considerable expense due to medical costs. This disease is gradually becoming more prevalent in younger people[19]. The average age of subjects in this study was, 57.28 years. For acquisition of the high quality images, CTA should be performed when the contrast medium is highly integrated into the cerebral vessels. Previous studies have identified factors that affect peak integration time: Hany et al. identified age,

weight, breath, and injection of normal saline (NS)[12]; Strouse et al. identified the flow rate of injection[13]; Seo et al. identified weight, age, heart rate, total blood flow, and flow rate of injection[14]; and Bae et al. identified flow rate of injection, scan duration, and organ[15]. Thus, this study referred to previous studies to set the vital signs and individual characteristics that affect peak integrated time directly or indirectly. Because CTA examination requires speed, the factors needed to be easily measured and be found easily in EMR prior to the examination. In this study, we divided the subjects into male and female because

previous studies by Kirchner et al. and Dinkel et al., reported that sex affected the peak integration time[10,20]; we determined that heart rate affected peak integration time in male and that DBP, blood sugar, and heart rate affected the integrated time in female.

For individual characteristics, Seo et al. reported that the peak integration time was affected by weight, age, heart late, total blood flow, and flow rate of injection[14]. However, in this study, the results for heart rate only were consistent with the previous study. In this study, the flow late of injection was applied uniformly and total blood flow did not compare because this factor was not set as an individual characteristic. Hany et al. did not set the age, weight, and breath as factors and reported that injection of NS was a significant factor, which differed from the findings in this study[12]. Because the injection of NS, breath, and injection flow of contrast medium reported by Bae et al. were applied to this study uniformly, these factors was not required to consider the relation[21]. This study indicated that sugar flow was an effective factor despite less weighted value. The peak integration time decreased with decreasing the blood sugar. This result was not reported in the previous study. Although there were differences in characteristics between the sexes, in terms of weighted value, heart rate was a significant factor for male and female. Thus, for calculating the peak integration time accurately, effective factors (DBP, blood sugar, and heart rate) by regression equation should be included. Heart rate was determined to be a significant factor for male and female in this study. Thus, the peak integration time could be calculated by applying the heart rate; the results were significant within the error range.

Kim et al., reported that the average time after intravenous injection for contrast medium to reach the carotid artery was 15.7 seconds, the optimum time was 7.78 seconds, and the integrated peak time was 23.48 seconds in MRA performed in nine patients[22]. Bae et al., reported that the integrated peak time, in BTM by applying to pigs, was about 30 seconds different from our study of 13.73 seconds[21]. However,

these studies included a limited number of human subjects (nine patients) and pigs. Cai et al., studied the 30 patients for characteristics of bolus injection, stay time, spread, and flow in aorta[23]. The maximum speed of flow was 5 − 13 cm/sec and stay time was 7 − 13 seconds. However, this study was about CT control device for moving and scan duration in BTM, and had less similarity with our study, which was an analysis of scan time by calculating the integrated peak time.

The recent studies were about usefulness of BTM and calculation of integrated peak time. CT scans using BTM have been performed based on these studies commonly for several decades. This study was not calculated integrated peak time and analyzed the influence factors and applied weighting of influence factors by regression equation to individuals. Based on this study, good quality cerebrovascular images could be acquired without monitoring scan. Thus, this study has academic significance and differentiation. The main problem associated with BTM is radiation exposure because of repeated monitoring scan. Brenner et al. reported that 1.52% of cancer occurrence in America was attributed to radiation exposure by CT exam[11]. It is an inaccurate assumption that radiation dose of the monitoring scan during the BTM is minimal compared to the whole CT scan.

In this study, average DLP of CTA was 716.53 mGy-cm and of the monitoring scan was 15.52 mGy-cm (2.2%). However, when the DLP converted the effective dose by applying the conversion factor, the radiation dose of the monitoring scan was 0.23 mSv (15.33) in comparison with 1.5 mSv of the whole CTA scan (Table 3). CTA was performed by using 0.0024 as the head conversion factor, and the monitoring scan was obtained by using 0.015 as the abdomen conversion factor. Generally, CTA scans the head over 600 times with 0.6 slice sickness. DLP is calculated by adding up the whole dose. However, monitoring scan is a repeated scan to one section of the ascending aorta. Thus, 5.52 mGy (0.23mSv) of the monitoring scan could be more harmful than 716.53 mGy-cm (1.5 mSv) of the whole CTA scan. In 2009, the FDA reported that

patients who underwent brain perfusion CT examinations had hair loss of band shape. Brain perfusion CT performs repeated scans to several sections over 30 − 40 times. Thus, the monitoring scan of CTA could be harmful. In this study, the average times of the monitoring scan was 6.34 times and the maximum was 14 times. In a previous study by Kirchner et al., the average times of the monitoring scan was 13 times. Thus, the radiation dose of the monitoring scan cannot and should not be ignored[10]. According to a previous study by Brenner, CT examination is commonly applied to patients and performed repeatedly for follow-up[24]. Thus, the region of monitoring scan is repeatedly exposed to radiation. Pierce et al., proved an increase in breast cancer, colorectal cancer, thyroid cancer, and pulmonary cancer with radiation exposure below 50 mSv, based on long-term follow-up test for survivors of atom bombing in Japan[25]. According to a previous study, breast cancer and pulmonary cancer could be associated with the monitoring scan. Therefore, these factors, with regard to body's metabolism, have a significant effect on the peak time of contrast medium and improved or revised CTA exam is required for "as low as reasonably achievable (ALARA)" radiation exposure as recommended by International Commission on Radiological Protection.

V. CONCLUSION

The objective of this study was to prevent unnecessary radiation exposure by skipping the monitoring scan. A limitation of this study was that it was not performed in a wide range of subjects who had cardiac disorder or vessel disease. However, few studies, regionally or internationally, have investigated the factors that, affect the integrated peak time and therefore, this study could be a base study for clinical application.

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Computed Tomographic Angiography (CTA)의 검사 시 조영제 집적 정점시간에 영향을 미치는 특성 인자를 분석

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Computed tomographic angiography (CTA)의 (조영제 집적 정점시간에 영향을 미치는 특성 인자를 분석하여: analyzing factors influencing on the integrated bolus peak timing in contrast-enhanced) 개인별 정점시간을 계량적(Systems analysis)으로 산정해 검사에 직접 적용함으로써 예비검사(monitoring scan)에 의한 불필요한 방사선 피폭을 예방하는데 목적이 있다.

CTA의 예비검사(monitoring scan)을 통해 얻은 조영제 집적 정점시간과 개인별 측정치들 간의 상관관계분석을 통해 영향인자를 파악한 다음, 다중선형회귀분석에 의한 회귀식으로 적정시간을 산출하였다.

결과로는 CTA의 평균 방사선 노출량은 716.53 mGy·cm였고, 예비검사(monitoring scan) 15.52 mGy (2 ~ 34 mGy)로 나타났다. 장기별 변환요소(conversion factor)를 적용한 결과, 전체 선량은 평균 1.5 mSv였고, 예비검사 선량은 0.23 mSv로 나타났다. 특성인자의 측정치와 조영제 정점시간의 상관관계분석 결과, 남성은 심박동수에서, 여성은 심박동수와 최저혈압, 혈당에서 음의 상관관계를 보였으며, 통계적으로 매우 유의하였다 (p<.01). 회귀분석결과, 남성은 심박동수가 한 단계 증가할 때마다 -0.160배로, 여성은 최저혈압과 심박동수, 혈당에 따라 각각 -0.004, -0.174, -0.006배로 유의하게 감소하였다. 실측한 조영제 정점시간과 회귀식에 의해 산출된 정점시간의 일치도 검사에서 남녀 대상자 모두에서 일치도가 매우 높았다.

본 연구에서는 검사 전에 환자 개인별 조영제 집적 정점시간을 산정하여 적용하면 예비검사를 생략함으로써 불필요한 방사선피폭을 예방할 수 있을 것으로 사료된다.

중심 단어: 덩어리예비촬영법, 덩어리추적법, 예비검사