Ideal Bolus Geometry Predicted from *In vitro* Pulsatile Flow Phantom and Artificial Neural Networks for the Optimization of Image Acquisition Protocols for Aortic Contrast-Enhanced Computed Tomography Angiography

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Objective: This study sought to explore the novel use of artificial neural networks (ANNs) to develop a contrast-enhanced computed tomography (CT) angiographic (CECTA) protocol based on ideal bolus geometry.

Materials and Methods: An aortic phantom connected to a closed-circuit pulsatile flow system was developed to simulate the bolus geometry of the human abdominal aorta. A total of 135 CECTA datasets were obtained using a 16-row multidetector CT scanner, and time-enhancement curves (TECs) were generated using varying input conditions including heart rate (HR), iodine delivery rate (IDR) and concentration (IC), and tube potential (kVP). Time points and density values including peak enhancement (PE) and time-to-peak (TTP) were assessed as a function of injection and scan protocols. Statistical analysis was performed using correlation and linear regression analyses. By using data from phantom experiments, machine learning produced networks between four input (HR, IC, IDR, and kilovoltage) and five output [TTP–time-to-foot (TTF), PE, (PE)/(TTP–TTF), maximal-upslope-gradient (MUG), and peak-plateau-length (PPL)] conditions. The bolus geometry index was defined as $(TTP-TTF)/\Sigma(PE, (PE)/(TTP-TTF), MUG, PPL)$. The lowest bolus geometry index value was considered ideal in ANN testing.

Results: The geometric changes on TECs were observed based on changes in HR, IDR, IC, and kilovoltage value. PE was closely related to IDR ($B=17.471$) and kVp ($B=-0.208$) (corrected $R^2=0.919$; all $p<0.001$). TTF, TTP, and PPL were related to HR and IDR, respectively. HR and IDR remained contributing factors after multiple linear regression analysis (corrected $R^2=0.901$, 0.815 , and 0.363 ; all $p<0.001$). Among 39690 total datasets produced following ANN training, the combination of IC, HR, tube potential, and IDR in the 38010th dataset resulted in the lowest bolus geometry index. Tables of input variables are presented after modification to clinically acceptable ranges.

Conclusion: ANN of phantom experiments showed the potential to determine optimal CECTA parameters for ideal bolus geometry individualized for each subject.

Key words CT angiography · Neural network · CT protocol · Imaging phantom · Aorta.

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INTRODUCTION

Contrast-enhanced computed tomography (CT) angiography (CTA) (CECTA) has become an essential imaging modality that is replacing the gold-standard of digital subtraction angiography (DSA) [1,2]. Due to cross-sectional visualization and three-dimensional reconstruction, this noninvasive imaging technique has shown advantages over two-dimensional invasive DSA for lesion detection; therapeutic planning; and post-operative monitoring of aortic diseases such as dissection, aneurysm, and major branch vessels atherosclerosis. Therapeutic plans can be made and outcomes can be evaluated using CECTA findings. Other research suggests CECTA can also be used to determine the location of the Adamkiewicz artery to avoid inadvertent compromise [3], to identify aneurysm enlargement or stent-graft migration after endovascular aneurysm repair [4], and to assess the necessity of reintervention due to endoleak [5].

Current CECTA techniques encounter challenges in optimizing image contrast between an artery and the background as well as in reducing the burden of contrast medium and radiation risk. One of the significant challenges is the optimal synchronization of the scan period with that of contrast medium administration [6-9]. To generate good CECTA images, prominent arterial enhancement is necessary; image acquisition duration must therefore coincide with the arterial phase in CTA without clear venous enhancement. As compared with parenchymal CT, CECTA requires the fast acquisition of data during the arterial phase of contrast passage, especially during maximum contrast enhancement between the arterial vasculature and surrounding structures and before diffuse and microvascular enhancement and reflow of contrast material in venous structures. Furthermore, optimization of image contrast in CECTA is based on the better prediction of ideal bolus geometry [6,7, 10,11]. Bolus geometry, defined as the enhancing pattern measured in a region of interest (ROI), is plotted on a time-attenuation diagram as a function of injection protocols after intravenous injection of contrast medium [11].

The ideal bolus geometry for aortic CECTA is immediate enhancement increase to a high maximum value or Hounsfield unit (HU) in the aorta just before the start of CT data acquisition, followed by a steady state during data acquisition [11,12]. Prediction of bolus geometry based on image acquisition protocols is of clinical importance for synchronizing scanning time with contrast medium administration, but has not yet been discussed to our knowledge because multiple factors influence bolus geometry and the attempts to follow serial changes in actual bolus geometry have been confounded by varying acquisition protocols.

Artificial neural networks (ANNs) are statistical learning algorithms inspired by biological neural networks such as systems of interconnected neurons, which can compute outputs from in-

puts. ANNs have massively parallel structures, with mechanisms of information distribution and processing similar to those of a brain, and are able to perform data processing of several related variables like complex biological systems. Previous studies applying ANNs for the prognostic prediction of several clinical disorders [13-18] hypothesized that input conditions such as image acquisition protocols can be developed by using ANNs to determine optimal bolus geometry. However, until now, no studies have investigated the usefulness of ANNs for the correlation of scanning parameters and bolus geometry.

Hence, the present study explored the novel use of ANNs to predict and optimize aortic CECTA acquisition protocols for ideal bolus geometry by applying machine learning techniques to the features of time-enhancement curves (TECs) based on CECTA acquisition protocols.

MATERIALS AND METHODS

In vitro pulsatile flow system and aortic phantom

An aortic phantom connected to an *in vitro* pulsatile flow system was developed to simulate the bolus geometry of the human abdominal aorta (Fig. 1). The closed circuit flow system contained a contrast medium injection unit, lung unit, pump unit, and imaging segment. The injection unit was used to introduce a bolus of radioopaque contrast agent, which was passed through the artificial lung unit. A self-made pulsatile flow pump unit with integrated flow measure element permitted perfusion of the closed circuit of tubing system with 50% glycerin that simulated the viscosity of human blood (36.4°C, 3.39 mPa) at a constant flow rate. Stroke volume was set at 90 cc and the cardiac output was 4.5 to 8.1 L/min. The temperature of the total 5 L of fluid volume was maintained at 36°C to 37°C.

The imaging segment of the aortic phantom was an acrylic tube with an inner diameter of 19 mm and thickness of 4 mm surrounded by an outer tube that simulated the soft tissue around the aorta. The upper half filled with air represented the lung, while the lower half filled with distilled iodine contrast medium was adjusted to 50 HU at 120 kVp to represent periaortic soft tissue. A pressure sensor was connected to the proximal portion of the imaging segment. The flow in the aortic phantom was measured using a flow meter with an in-line flow probe connected to the tubing system. Flow speed and pressure were monitored in real-time after the flowmetry settled, and the data were sent to LabVIEW reconfigurable I/O (National Instruments, Austin, TX, USA). The systole duration was modified according to the heart rate (HR) as follows: 0.31, 0.29, and 0.27 seconds for 50, 70, and 90 bpm, respectively. Three pressure-damping chambers were connected at the proximal and distal levels of the pulsatile pump and at the distal level of the contrast medium injection unit to increase the adjustability of the vascular compliance. Flow

Fig. 1. Human abdominal aorta simulation using an aortic phantom connected to a pulsatile flow system for CT angiography. (A) The closed pulsatile flow circuit is connected to the aortic phantom, with 50% glycerin simulating blood flowing counterclockwise (arrows). This circuit is composed of a contrast medium injection unit (INJECTOR), lung unit (LUNG), pump unit (PUMP), and imaging segment (TISSUE). TISSUE indicates the point at which axial CT images were obtained. (B) A damper tube is inserted proximal and distal to the pump unit, between the injection and lung units, in order to make the flow pulsatile by increasing vascular compliance. The velocity (C) and pressure (D) were monitored in real time using a flow meter. At 90 beats per minute, the systolic velocity and pressure were approximately 100 to 110 mL/sec and nearly 140 to 160 mm Hg, respectively. Sharp incisura suggested the similarity of this pulsatile flow system to human aortic flow pressure waves. (E) Axial CT image of aortic and periaortic tissue of the phantom. A round ROI measuring 10 mm in diameter was drawn from the center of the aorta. The upper and lower halves of the periaortic tissue phantom represent present lung and periaortic soft tissue, respectively. (F) TEC of intravenous boluses was measured from the ROI. HU values over time are shown as TEC. P: pressure sensor, D: damper, CT: computed tomography, ROI: region of interest, TEC: time-enhancement curves, HU: Hounsfield unit.

velocity and mean intraluminal pressure were fixed at 100 to 110 mL/s and 140 to 160 mm Hg, respectively, to simulate the velocity and pressure in the human abdominal aorta.

CT protocols and image reconstruction

CECTA imaging was performed on a 16-row multidetector CT scanner (LightSpeed 16 Xstream; GE Healthcare, Marlborough, MA, USA). Data were acquired from a slice orientation perpendicular to the direction of flow in the aortic phantom while the iodinated contrast agent was introduced through the injection unit. The acquisition parameters were as follows: the tube potentials were 80, 100, or 120 kVp and the conditions included a tube current of 100 mA, 10-second delay time, 80-second scan duration, 20-cm field of view, and 5-mm slice thickness and increment.

Three kinds of nonionic iodine monomers were used as contrast medium; their concentrations, osmolarities, and viscosities were as follows: ioversol (Optiray, Mallinckrodt, St. Louis, MO, USA) at either 240 mg/mL, 502 mOsm/kg/H₂O, and 3.0 cps at 37°C or 320 mg/mL, 702 mOsm/kg/H₂O, and 5.8 cps at 37°C; iopamidol (Isovue, Bracco, Milano, Italy) at 300 mg/mL, 616 mOsm/kg/H₂O, and 4.7 cps at 37°C or 370 mg/mL, 796 mOsm/kg/H₂O, and 9.4 cps at 37°C; and iohexol (Omnipaque, GE Healthcare) at 350 mg/mL, 780 mOsm/kg/H₂O, and 10.4 to 11.2 cps at 37°C.

A total of 135 CECTA image datasets were obtained with varying HRs (50, 70, or 90 bpm), iodine concentrations (ICs) (270, 300, 320, 350, or 370 mg/mL), injection speeds (1, 3, or 5 mL/sec), iodine delivery rates (IDRs) (0.24–1.85 g/sec), and tube potentials (80, 100, or 120 kVp). The injection duration was fixed at two seconds in all cases.

Assessment of time-enhancement curves

From measurements taken at the imaging segment, TECs of intravenous bolus iodine injections were produced using a Syngo workstation (Siemens, Erlangen, Germany). The measurements of CT numbers of circular ROIs with a 10-mm diameter were carried out with slice orientation perpendicular to the tubes. Measurements were repeated 10 times in order to reduce measurement bias, and the mean attenuation value in HUs and standard deviation were recorded. Enhancement was calculated by subtracting the attenuation value of an unenhanced baseline scan from the attenuation values in the enhanced scans.

Multiple TECs were obtained from varying HR, contrast medium injection speed, IC, and tube potential values and assessed by a single reader (KJY) blinded to the CECTA protocol. Multiple time points, intervals, and density values were defined to describe TEC features (Fig. 2). Time point and density features included foot, maximal upslope and downslope, peak, and tail of curve. Secondary parameters calculated from primary measure-

Fig. 2. Time-enhancement curve produced after a bolus of contrast medium injection, showing several time points (sec) and density values (HU). Baseline: baseline density, Foot: beginning of first-pass bolus, MUG: point of maximal upslope gradient, Peak: peak density, PPL: peak plateau length, MDG: maximal down-slope gradient, Tail: density at end of a bolus, PE: peak enhancement (=peak density-baseline density), AUC: area under the curve, BL: bolus length (=TTT-TTF, suggesting total length of first-pass bolus), RE: recirculation enhancement (=tail density-baseline density), TTF: time to foot, TTU: time to maximal upslope gradient, TTP: time to peak, TTD: time to maximal down-slope gradient, TTT: time to tail, HU: Hounsfield unit.

ments included bolus length (BL), peak-plateau-length (PPL), peak enhancement (PE), and recirculation enhancement (RE). The signal-to-noise (SNR) and contrast-to noise ratio (CNR) were also calculated.

Statistical analysis

Statistical analyses were performed with using the Statistical Package for the Social Sciences version 17.0 for Windows software program (SPSS Inc., Chicago, IL, USA). To identify the relationship between CECTA protocols and TEC features, correlation and regression analyses were performed on 135 datasets. The input variables included HR, IC, IDR, and tube potential, while the output variables included time-to-peak (TTP), time-to-foot (TTF), PE, maximal-upslope-gradient (MUG), PPL, SNR, CNR, and area under the curve (AUC). Pearson correlation coefficients were calculated to measure linear associations between input and output conditions. B and adjusted R^2 values were calculated in multiple linear regression models to overcome multicollinearity. Variables identified as insignificant were not included in multivariate logistic regression analysis, and data were expressed as means $\pm$ standard errors of the mean. P-values of less than 0.05 were considered to be statistically significant.

Artificial neural network creation and training

ANNs were constructed using multilayer perceptron (MLP) architecture and trained using a back-propagation algorithm in MATLAB 8.0 and Statistics Toolbox 8.1 (MathWorks Inc., Natick, MA, USA) on a Pentium III personal computer (Intel, Santa Clara, CA, USA) using 2 GB of RAM and a 32-bit Windows 7 operat-

ing system (Microsoft Corp., Redmond, WA, USA). For training, the nodes were organized into three layers: an input layer with four neurons, a hidden layer with 32 neurons, and an output layer with five neurons (Fig. 3). The four input variables included HR, IC, IDR, and kVp, while the five output variables included in the ANNs were TTP-TTF, PE, (PE)/(TTP-TTF), MUG, and PPL. A total of 135 CECTA image datasets were generated, each containing both input and output variables corresponding to the bolus geometry; these images underwent extraction and preprocessing, including dimension reduction and parameter modification.

Prediction of input variables resulting in ideal bolus geometry

New datasets were generated for the prediction of input variables that would result in ideal bolus geometry. HR was increased from 50 to 90 bpm in 5-bpm intervals. Similarly, IC was increased from 200 to 400 mg/mL in 10-mg/mL intervals. The speed of contrast medium injection was increased in 0.2-mL/sec intervals from 0.2 to 6.0 mL/sec. Tube potentials were increased from 80 to 140 kVp at 10-kVp intervals.

Based on the classical concept of bolus geometry, which was defined as the enhancing pattern measured in a ROI and plotted on a time-attenuation diagram after contrast medium injection [11], bolus geometry index was further proposed as follows: bolus geometry index=(TTP-TTF)/ Σ (PE, (PE)/(TTP-TTF), MUG, PPL). This was to show the degree of immediate enhancement followed by a steady state during data acquisition [11,12]. As the steeper enhancement peak and longer steady

Fig. 3. Architecture of artificial neural network between input and output variables. A total of 135 datasets were extracted, and machine learning was applied to four input parameters (HR, IC, IDR, and kVp) and five output conditions (TTP-TTF, PE, (PE)/(TTP-TTF), MUG, and PPL) through 32 hidden layer nodes. HR: heart rate, IC: iodine concentration, IDR: iodine delivery rate, kVp: kilovoltage, TTP: time-to-peak, TTF: time-to-foot, PE: peak enhancement, MUG: maximal-upslope-gradient, PPL: peak-plateau-length.

state bolus, the index value is reduced and the lowest index value would be the most ideal bolus geometry in our study. Therefore, the datasets with the lowest index values were searched for among all datasets during ANN test sessions to produce the ideal bolus geometry. Subsequently, the input variables identified during this testing were proposed as the optimized CECTA acquisition protocols to produce ideal bolus geometry.

RESULTS

Changes in TEC features in response to changes in HR, kVp, and injection speed

Serial changes in TECs depended on the combination of altered HR, speed of contrast media injection, tube potential, and IC (Fig. 4). As HR increased, TTF and TTP decreased. With increased injection speed, PE was taller, with a steeper slope. As kVp increased, PE decreased. However, IC changes did not result in consistent TEC trends.

Correlation and regression analysis between CECTA protocols and TEC features

PE was closely related to IC ($r=0.270$; $p<0.01$), IDR ($r=0.903$; $p<0.001$), and kVp ($r=-0.322$; $p<0.001$). IDR ($B=17.471$) and kVp ($B=-0.208$) remained significant contributing factors for PE (corrected $R^2=0.919$; all $p<0.001$) (Table 1).

RE was related to IC ($r=0.278$; $p<0.01$), IDR ($r=0.895$; $p<0.001$) and kVp ($r=-0.324$; $p<0.001$). HR ($B=0.053$; $p<0.001$), IDR ($B=11.424$; $p<0.001$), and kVp ($B=-0.139$; $p<0.001$) remained significant contributing factors of RE (corrected $R^2=0.922$; $p<0.001$).

TTF, TTP, PPL, and BL were related to HR and IDR. HR and IDR remained significant contributing factors for TTF, TTP, PPL, and BL in multiple linear regression analysis (corrected $R^2=0.901, 0.815, 0.363$, and 0.831 , respectively; all $p<0.001$).

MUG was related to HR ($r=0.262$; $p<0.01$), IC (0.201 ; $p<0.05$), IDR ($r=0.855$; $p<0.001$) and kVp ($r=-0.293$; $p<0.001$). HR ($B=0.022$; $p<0.001$), IDR ($B=2.144$; $p<0.001$), and kVp ($B=-0.024$; $p<0.001$) remained significant contributing factors of MUG (corrected $R^2=0.882$; $p<0.001$).

AUC was related to IC (0.262 ; $p<0.001$), IDR ($r=0.898$; $p<0.001$), and kVp ($r=-0.319$; $p<0.001$). HR ($B=8.706$; $p<0.001$), IDR ($B=1932.037$; $p<0.001$), and kVp ($B=-22.859$; $p<0.001$) remained significant contributing factors of AUC (corrected $R^2=0.922$; $p<0.001$). SNR was related to IDR ($r=0.363$; $p<0.001$) and IC ($r=-0.370$; $p<0.01$). IDR ($r=48.575$; $p<0.001$) and kVp ($r=0.728$; $p<0.05$) were contributing factors of SNR in multiple linear regression (corrected $R^2=0.222$; $p<0.001$). CNR was related to HR, IDR and kVp were contributing factors to CNR in multiple linear regression (corrected $R^2=0.660$; $p<0.001$).

ANN to determine ideal bolus geometry

In training, the ANN optimized parameters of the four input and five output conditions until the mean error of the network decreased below a uniform predetermined level. Separately, the error rate decreased with increased rounds of learning (Fig. 5). A total of 39690 datasets were newly produced, and an estimator found that the 38010th dataset had the lowest bolus geometry index value (Fig. 6). The values included in this dataset were: IC: 400 mg/mL, HR: 50 bpm, tube potential: 140 kVp, and IDR: 7.4 mg/sec (Table 2A). However, the IC and tube potential values of 400 mg/mL and 140 kVp, respectively, were not in the clinically accepted ranges. Therefore, these input variables were further narrowed into appropriate clinical ranges (Table 2B).

DISCUSSION

This study described a systematic approach to establish aortic CECTA acquisition protocols that optimize image quality while reducing contrast medium burden and radiation risk. In addition to modifiable contrast medium factors and radiation dosage, human factors such as HR, which cannot be controlled and therefore requires protocol adjustment, were also considered when developing personalized imaging protocols.

The optimization of image quality requires a clear understanding of bolus geometry in order to synchronize image acquisition timing and duration with the first pass of the contrast medium [6-12]. Although actual bolus geometry steadily increases in the arterial enhancement until peak maximal enhancement, followed by a steady decline, ideal bolus geometry in this study was presumed to have a broad rectangular TEC in order to produce

Fig. 4. Serial changes in TECs with varying input conditions. TECs changed according to alterations in HR (A; horizontal direction, change of tube potential; vertical direction, change of injection speed), contrast media injection speed (B; horizontal direction, change of HR; vertical direction, change of tube potential), tube potential (C; horizontal direction, change of HR; vertical direction, change of injection speed), and iodine concentration (D; horizontal direction, change of tube potential; vertical direction, change of injection speed). X axis: time (seconds), Y axis: density (HU), TEC: time-enhancement curve, HR: heart rate, HU: Hounsfield unit.

Fig. 4. Serial changes in TECs with varying input conditions (continued). TECs changed according to alterations in HR (A; horizontal direction, change of tube potential; vertical direction, change of injection speed), contrast media injection speed (B; horizontal direction, change of HR; vertical direction, change of tube potential), tube potential (C; horizontal direction, change of HR; vertical direction, change of injection speed), and iodine concentration (D; horizontal direction, change of tube potential; vertical direction, change of injection speed). X axis: time (seconds), Y axis: density (HU), TEC: time-enhancement curve, HR: heart rate, HU: Hounsfield unit.

Table 1. Association between image acquisition conditions (input variables; horizontal axis) and enhancement curve features (output variables; vertical axis). Input variables underwent (A) correlation and (B) multiple linear regression analyses versus output variables

A								
	HR		IC		IDR		kVp	
	r	p	r	p	r	p	r	p
PE	-0.821		0.270	†	0.903	‡	-0.322	‡
TTF	-0.927	‡	-0.003		-0.204	*	0.004	
TTP	-0.875	‡	-0.064		-0.229	†	0.038	
MUG	0.262	†	0.211	*	0.855	‡	-0.293	‡
RE	0.125		0.278	†	0.895	‡	-0.324	‡
PPL	-0.344	‡	-0.185	*	-0.492	‡	0.129	
BL	-0.899	‡	0.127		-0.492	‡	-0.015	
AUC	0.121		0.262	*	0.898	‡	-0.319	‡
SNR	-0.057		-0.167		0.363	‡	0.197	*
CNR	-0.025		0.112		0.808	‡	-0.092	

B									
	Constant		HR		IC		IDR		Adj.R ^{2§}
	B	p	B	p	B	p	B	p	
PE	21.084	‡	-0.013		0.011		17.471	‡	0.920
TTF	58.447	‡	-0.433	‡	0.009		-3.072	‡	0.901
TTP	26.239	‡	-0.241	‡	-0.001		-1.897	‡	0.815
MUG	1.150	†	0.022	‡	0		2.144	‡	0.882
RE	9.438	‡	0.053	‡	0.009	*	11.424	‡	0.922
PPL	14.766	‡	-0.085	‡	-0.006		-3.555	‡	0.363
BL	71.276	‡	-0.490	‡	0.020	†	1.744	†	0.831
AUC	1638.098	‡	8.706	‡	1.032		1932.037	‡	0.922
SNR	185.422	‡	-0.210		-0.370	†	48.575	‡	0.222
CNR	43.260	†	-0.044		-0.060		43.384	‡	0.660

Pearson correlation; r, HR, IC, IDR, and kVp. *p<0.05, †p<0.01, ‡p<0.001, §all multiple linear regression models, p<0.001. HR: heart rate, IC: iodine concentration, IDR: iodine delivery rate, kVp: kilovoltage, PE: peak enhancement, TTF: time-to-foot, TTP: time-to-peak, MUG: maximal-upslope-gradient, RE: recirculation enhancement, PPL: peak-plateau-length, BL: bolus length, AUC: area under the curve, SNR: signal-to-noise, CNR: contrast-to noise ratio

the maximal contrast between artery and background tissues. A rectangular shape was considered to be ideal for CECTA if the enhancement did not change substantially during data acquisition and was intense enough to produce the largest contrast between the imaged aorta and the background tissue [7,10-12]. Among TEC features, steeper slope and longer steady state on bolus geometry were associated with higher PE, MUG, and PPL and short TTP–TTF. This study proposed the concept of ideal bolus geometry index as an objective parameter to characterize the optimal geometry of bolus enhancement. The ideal bolus geometry index emphasized the importance of the time of appearance and disappearance and degree of PE.

This phantom study investigated the effects of several input conditions in determining bolus geometry. This study furthermore showed that IDR was one of the most significant factors affecting nearly all TEC features among input conditions. In particular, PE and TTP were the main TEC features characterizing bolus geometry. Correlation and regression analysis re-

vealed that IDR was a significant contributor to PE. Previous studies have found that increased injection rates result in higher PE and faster TTP, while increased injection volumes shift TEC rightward, with higher PE and slower TTP [7,11]. In this study, the injection volumes were proportional to injection speed because the injection duration was fixed at two seconds.

IC did not result in consistent changes and did not contribute to TEC factors including PE, MUG, TTF, TTP, and PPL. This result was discordant with those of several previous studies [10,19, 20]. Intravenous administration of iomeprol at a concentration of 400 mg/mL provides higher attenuation of the coronary and the greater arteries of the thorax versus 370 mg/mL of iopromide using the same injection parameters [19]. In other studies, low viscous iopromide (300 mg/mL) results in a better-defined bolus with significantly higher PE, steeper up-slope, and smaller full-width-at-half-maximum in comparison with the administration of 400 mg/mL of iomeprol [19,20]. These different results might be because of differences in bolus viscosities, which may influ-

Fig. 5. Error rate and ANN training rounds. (A) Error rate or RMSE is reduced by increasing the number of epochs during learning. (B) Match degree of the estimator for the original data. The estimator showed fairly similar output variables with TTP-TTF (green) as compared with the original TTP-TTF (blue), with uniformly low RMSE. RMSE: root mean square error, TTP: time-to-peak, TTF: time-to-foot, PE: peak enhancement, MUG: maximal-upslope-gradient, PPL: peak-plateau-length.

ence their travel properties.

Correlation and regression analysis in this study revealed that the time points around PE are closely related to HR and IDR. HR affected mainly time points including TTF, TTP, PPL, and BL. In particular, as HR increases, TTF and TTP occur more quickly. This finding appears to corroborate with the following algorithm proposed by Puskás and Schuierer: “ $TTP = (\text{duration of 12 heart actions}) \times 60 / (\text{HR})$ ” [21]. TTP was unaffected by patient characteristics such as age, weight, height, body surface, blood

pressure, and gender in clinical measurements, and Puskás and Schuierer suggested the usefulness of the venoarterial circulation time measurement using a test bolus of contrast medium. A recent study supported the idea that aortic TTP and PE are closely related to cardiac function [22]. The possible pitfalls of higher HR and HR variability should be considered in selecting the appropriate scan protocol to obtain diagnostic image quality with an as-low-as-reasonably-achievable radiation dose [23].

To our knowledge, this is the first study to use an ANN to de-

Fig. 6. An estimator to optimize lowest bolus geometry index. Among 39690 generated datasets, the estimator determined that the 38010th dataset (asterisk) had the lowest bolus geometry index.

termine input conditions of aortic CECTA to produce ideal bolus geometry. ANNs have been previously used for complex pattern recognition and classification tasks, to identify relationships among data, and to support the development of decision-making algorithms based on previous training. ANNs have also been applied clinically for the diagnosis of individual cases. Several authors have reported using ANNs to predict clinical outcomes, including ischemic tissue fate in acute stroke imaging [13-15], malignant risk stratification of mass lesions [16,17], and differentiation between innocent and pathological physical signs [18]. The ANN used in this study consisted of three layers of processing units—i.e., input, hidden, and output—connected in sequence. The MLP algorithm is a well-established network architecture, and MLP with hidden layers was trained with the back propagation algorithm. The four input conditions included HR, IC, IDR, and kVp, while the five output conditions included TTP, TTF, PE, MUG, and PPL. Machine learning techniques identified the optimal association between input and output variables; increased learning rounds decreased the mean error of the network to a minimum predetermined value. In this study, ANN was used to identify a specific dataset with the lowest index value among all tested datasets. This dataset having the lowest index value or ideal bolus geometry revealed the value of IC, HR, kVp, and IDR. Finally, these conditions were further modified to clinically acceptable HR and kVp ranges; tables of specific input variables within acceptable clinical ranges were proposed for determining optimized CECTA protocols. This strategy resulted in protocols for ideal bolus geometry that could be customized for individual subjects with more specific or medically defined conditions by modifying input variables.

The main strength of this study was its use of an *in vitro* aortic phantom connected to a closed-circuit-flow system that simulated human aortic velocity and pressure [24-29]. Phantom

Table 2. Optimization of ideal bolus geometry. (A) A total of 39690 datasets were produced after artificial neural networks training; an estimator revealed the lowest bolus geometry index in the 38010th dataset, with an IC of 400 mg/mL, HR of 50 bpm, peak tube potential of 140 kVp, and IDR of 7.4 mg/sec. However, the IC of 400 mg/mL and tube potential of 140 kVp were not within clinically acceptable ranges. (B) Proposed computed tomography angiographic protocols based on neural network results included injection speeds based on IC, HR, and peak tube potential (kVp), after limiting these values to clinically acceptable ranges

A				
	IC	HR	kVp	IDR
1	200	50	80	0.04
↑↓				
2132	210	55	90	0.08
↑↓				
19845	300	70	110	0.9
↑↓				
37559	390	85	130	2.26
↑↓				
38010	400	50	140	7.4
↑↓				
39690	400	90	140	2.4
B				
HR	kVp	80	100	120
50	IC	400	400	400
	IDR	6	6	6
60	IC	290	400	400
	IDR	6	6	6
70	IC	270	290	280
	IDR	6	6	5.8
80	IC	260	300	310
	IDR	6	6	5.8

IC: iodine concentration, HR: heart rate, kVp: kilovoltage, IDR: iodine delivery rate

studies that simulate human circulation enable repeated CT scans without the risk of radiation damage and iodine exposure in human subjects and can provide thousands of datasets by manipulating multiple variables. In clinical circumstances, multiple contrast media injections and radiation exposure are harmful to the human body, and prospective trials are limited due to ethical concerns over radiation safety. Therefore, it is probably not possible to generate multiple datasets with varying imaging conditions by performing multiple CT scanning sessions with repeated contrast injections in the same subject. Previous human studies typically assessed the influence of various parameters by comparing two or more groups of patients who may have different baseline parameters. In this background, most clinical studies compared images between different subjects, which are influenced by differences in patient characteristics such as body weight or cardiac function [22]. However, phantom experiments allow for intraindividual comparisons. *In vitro* studies also en-

able complete bolus time course measurements from baseline to RE by measuring TEC with high temporal resolution in response to the manipulation of various input variables.

However, this study has innate drawbacks to consider before clinical application as well: first, we acknowledge potential pitfalls of pulsatile flow phantom. The conditions of pump and phantom devices were carefully manipulated while monitoring velocity and pressure to simulate human circulation, since the reliability of this feasibility study depends on the degree of agreement between the *in vitro* phantom simulation and actual human circulation. Although fine adjustments in the pump and phantom devices were made to produce bolus geometry mimicking human circulation [24-29], the differences might have affected the experimental results. Despite the precisions revealed from the repeated scanning or the trends found in this phantom study, particular cautions need to be taken in the context of clinical interpretation, and this study's results need to be confirmed in a successive clinical study. Also, further assessment of the accuracy of the phantom simulation of human circulation is warranted in future research efforts. Second, the training and testing performance of the ANN was not evaluated. In future work, predicting performance using ANNs will be compared with that of test boluses [30-32] or bolus tracking techniques [6,32] in the synchronization of scan and contrast medium administration, since the calculators of CECTA protocols using the above techniques are clinically available with real-time decision support. This study was supported by the fact that increased rounds of learning reduced the minimal error rate to below the uniform level, and multiple clinical event prediction studies using ANNs have shown the diagnostic accuracy of MLP models to be similar to standard methods [13-18]. Third, the ideal bolus geometry index was designed to assess image quality, instead of using SNR and CNR to measure image contrast [33]. There is no standard method, and the differences between these methods might have affected the results of this study. Fourth, among possible patient factors, only HR was considered in this study. Additional patient characteristics such as body weight and thickness and cardiac output should be taken into account in future studies. Finally, this study did not assess the impact of several issues discussed recently in the literature. Promising future work would cover the recording and analysis of radiation dose of each dataset to reduce risk and evaluate the effects of dual-energy-source CT [33,34] or electrocardiogram-triggered high-pitch CTA protocols [23,35,36] upon bolus geometry.

In conclusion, use of an ANN in *in vitro* phantom experiments showed potential as a simulation technique for determining CECTA acquisition parameters for ideal bolus geometry. The ideal bolus geometry can be determined for individual subjects from the ANN analysis of datasets by modulating contrast medium injection and CT scanning protocols based on HR. Aortic

CECTA protocols based on ideal bolus geometry might offer reduced iodine and radiation doses and improve image quality by determining optimal individual input conditions to produce appropriate bolus geometry, although further clinical application studies are necessary. A similar procedure could potentially be effective in clinical applications.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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