Current Contrast Media Delivery Strategies for Cardiac and Pulmonary Multidetector-row Computed Tomography Angiography

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Abstract: Recent advances in multidetector-row computed tomography (MDCT) have led to substantial improvements in coverage area, acquisition speed, and temporal/spatial resolution, which have strengthened the performance of thoracic and cardiac MDCT angiography but have also imposed new challenges for optimization of contrast medium enhancement and scan acquisition strategies. Understanding contrast media dynamics is fundamental for the design of scan acquisition and injection protocols. This article examines the fundamentals of the physiological and contrast delivery factors that determine the quality of contrast enhancement, emphasizing the modifications required in contrast delivery protocols for optimizing cardiothoracic MDCT angiography with modern-era MDCT scanners.

Key Words: coronary arteries, multidetector-row computed tomography, multidetector-row computed tomography angiography, contrast enhancement, contrast media, administration, dosage

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S ince the advent of computed tomography (CT) in the 1970s, there have been great advances in image quality and acquisition speed. Often underestimated, the use of intravenous contrast (IVC) agents has been integral in advancing multidetector-row CT (MDCT) to its current role in modern medicine. Obtaining high-quality images with consistent and homogenous vascular contrast enhancement is crucial for diagnostically accurate MDCT angiography, but is also one of the most challenging aspects to accomplish during scan acquisition. Recent advances in MDCT have dramatically increased the image acquisition speed, which has mostly rendered obsolete the traditional "fixed" contrast delivery approaches for CT angiography (CTA). These days, successful performance of CTA requires much greater flexibility for optimizing vascular opacification and improving the effectiveness of contrast

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medium delivery. A basic understanding of IVC dynamics is crucial for the rational design of injection techniques. The purpose of this study is to review the basic principles of IVC injection for cardiothoracic CTA, to propose a logical approach to protocol development for custom-tailoring IVC use to the individual patient.

INTRAVENOUS ACCESS

The ability to obtain appropriate intravenous access is essential for the successful performance of CTA. As the rate of fluid flow through a catheter is proportional to its radius to the fourth power, and inversely proportional to length, shorter- and large-diameter catheters are preferred (typically 21 to 18 gauges). Certain patient populations and risk factors can often make central venous access more appropriate than peripheral access. For cardiac CTA, it is preferable to use the right antecubital vein because dense contrast in the brachiocephalic vein has the potential to obscure the supraaortic branches, which can interfere, for example, with the appropriate interpretation of arterial coronary artery bypass grafts using the left internal mammary artery.

SCAN DELAY AND TIMING

As CT scanners become faster, scan durations become shorter, and therefore it is critical to delay scanning to capture images during peak enhancement. If volume, flow rate, and iodine concentration are kept constant, delaying the scan becomes more critical. With faster CT scanners, it becomes possible to decrease the contrast volume by using high iodine concentration (ie, 350, 370, 400 mgI/mL) contrast media and high injection flow rates ($\geq 4 \text{ mL/s}$). MDCT technology with shorter acquisition times requires further optimization and synchronization between the passage of contrast material and data acquisition to obtain consistent image quality at CTA.

For multidetector-row CT, we typically rely on 2 bolus-timing techniques: (1) test/timing bolus injection; and (2) bolus tracking/automated bolus triggering.

There are different opinions regarding whether or not bolus-timing techniques result in actual advantages over automated bolus tracking/bolus-triggering techniques in terms of optimal vascular attenuation and whether these advantages outweigh the slightly higher overall contrast volume associated with the use of the bolus-timing/test bolus technique.^{1–3}

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TEST BOLUS

This technique is based on the intravenous injection of a small (~ 10 to 20 mL) amount of contrast material during the acquisition of a series of dynamic low radiation dose (120 kV, 20 mAs) monitoring scans at the level of the vessel of interest (eg, ascending aorta). The delay between monitoring scan acquisitions is typically 1 to 2 seconds, ordinarily started at 5 to 10 seconds after the beginning of the injection of IVC material, depending on the vascular structure of interest (eg, pulmonary versus systemic arterial circulation). A region of interest (ROI) is drawn inside the target vessel lumen by the operator, to generate an enhancement curve, which shows the time needed to reach the peak of maximum enhancement for the contrast bolus (Fig. 1). The time to peak enhancement of the test bolus in the target vessel is the delay applied for angiographic scan acquisition, sometimes with the addition of several seconds (ordinarily 2 to 6s) to allow for the bolus to establish a more uniform plateau. The use of a test bolus provides the advantage that the patients undergo a test procedure, during which they have the opportunity to practice breathholding and to experience contrast infusion. Of the methods used to synchronize peak contrast enhancement with image data acquisition, the test bolus technique is the most commonly used.4

AUTOMATED BOLUS TRIGGERING

This technique is based on real-time monitoring of the main bolus during injection with the acquisition of a series

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of dynamic low-dose (120-kV, 20-mAs) monitoring scans at the level of the vessel of interest. The intention is to start scanning manually or automatically once the contrast arrives or a certain trigger threshold is exceeded. An ROI as large as the vessel is drawn by the operator. Dynamic monitoring scanning typically begins 5 to 10 seconds after the start of the contrast injection. The trigger threshold inside the ROI can be variably set, for example, at +100 HU above the baseline. The delay between monitoring scan acquisitions is typically 1 to 2 seconds. As soon as the contrast bolus visually arrives or the predetermined threshold is reached, the table moves to the start position of the scan while breath-hold instructions are given to the patient. Deep inspiration seems less desirable compared with shallow inspiration, as the increased intrathoracic pressure caused by a Valsalva maneuver reduces the incoming flow of contrast material through the innominate veins and increases the influx of unopacified blood from the lower extremity through the inferior vena cava. Automated bolus tracking allows synchronization between scanning and contrast material administration in a similar manner as the test bolus technique and performs substantially better than traditional fixed delay techniques.5,6

FACTORS DETERMINING CONTRAST ENHANCEMENT

Several factors influence contrast medium enhancement and scan timing in CT imaging. Interdependent factors are those related to patient physiology and the contrast delivery



FIGURE 1. Test bolus technique allows estimating the time of contrast material arrival or bolus transit of the contrast material. This time should not be simplistically assumed to serve as the scan delay, but rather as a means of individualizing the scan delay relative to it by including an "additional delay." (Color figure available online at www.thoracicimaging.com)

protocol, while independent factors are the CT scan parameters used during image acquisition. Understanding the dynamics and interaction of these parameters is essential to achieving consistent and homogeneous vascular enhancement in cardiothoracic CTA studies.

PHYSIOLOGICAL FACTORS INVOLVED IN CONTRAST ENHANCEMENT

The degree of arterial enhancement after fixed intravenous injection of contrast media is highly variable between individuals. Several physiologic parameters have been studied relating the degree and timing of arterial enhancement. These factors include body weight, cardiac output, height, sex, age, venous access, renal function, and concomitant comorbidities. Although all of the aforementioned factors play some role in contrast medium enhancement, cardiac output and patient weight are still considered most important.^{7,8}

WEIGHT

When it is considered and analyzed as an isolated factor, patient weight acquires significant importance for designing contrast protocols. Patient weight is readily available to the clinician, and the cardiac output is generally related to weight. Patient weight and contrast enhancement are inversely related in a near one-to-one ratio (Fig. 2). There is direct correlation of patient weight to blood volume and extracellular compartments. Larger patients have a larger blood volume to dilute the contrast material and require higher iodine loads or delivery to maintain the same degree of arterial enhancement compared with smaller patients.⁹ However, this variability is usually addressed in clinical practice by altering contrast volume, contrast concentration, or injection rates.^{10,11}

As cardiac output increases proportionally to blood volume, there is no interdependent relationship between contrast media circulation time and patient weight. Designing a body weight-tailored dose of IVC media



FIGURE 2. Simulated arterial enhancement curves using 3 different body weights, based on identical injection protocols, show a near one-to-one ratio inverse relationship existing between weight and contrast enhancement and also show the absence of a relationship between contrast media circulation time and patient weight. (Color figure available online at www.thoracicimaging.com)

is rather complex, as we will address later in this review. With the exception of nonelectrocardiogram-gated cardiothoracic multidetector-row CTA in neonates and toddlers, in whom we use manual injection of $2 \text{ mL} \times \text{kg}$ of contrast media, we rarely rely only on patient weight to estimate the contrast dose in our current clinical practice.

CARDIAC OUTPUT

The volume of blood being pumped by the heart in 1 minute, that is, cardiac output, greatly influences the peak arterial enhancement timing. Cardiac output is directly proportional to the contrast bolus arrival time and inversely related to the degree of maximal arterial peak enhancement.¹² This is due to the fact that less contrast media dispersion occurs at lower cardiac output. Therefore, during cardiothoracic CTA, it is crucial to individualize the scan acquisition delay according to an individual patient's cardiac output.^{10,11} This is achieved using either the test bolus or bolus-tracking technique. Two relationships between contrast enhancement and cardiac output are essential to understand: first, in patients with low cardiac output, the peak arterial enhancement occurs later; and second, the mean contrast enhancement in patients with high cardiac output is actually lower (Fig. 3).

CONTRAST DELIVERY PROTOCOL

Uniform vascular enhancement through a selected anatomical area is the main goal for adequate processing, display, and interpretation of CTA images.^{13,14} Prolonged uniform enhancement can also contribute to more efficient use of contrast medium while providing a longer temporal window for optimal scanning. Achieving prolonged uniform vascular enhancement requires a detailed understanding of the variables involved in automatic contrast medium injection and its practical significance. These factors include injection rate, injection duration, contrast volume, and contrast media concentration. One strives to achieve consistent contrast enhancement in the cardiothoracic vessels regardless of patient habitus, scan duration, contrast concentration, and hemodynamic status. Although several approaches have been proposed to design a contrast delivery protocol that ensures uniform contrast enhancement in the vascular territory of interest, these approaches were more appropriate in the era of single- and 4-slice MDCT instruments when scan times at CTA typically ranged from 20 to 30 seconds. Today, with the advent of volume- and second-generation dual-source CT scanners, where acquisition of the entire thorax can occur in 1 second or less, there is decreased need to ensure a wide, prolonged, and uniform contrast enhancement profile. With currentera technology, the challenge is rather to design a contrast protocol that delivers a bolus that ensures high attenuation and to precisely synchronize scan acquisition with the optimal portion of the contrast enhancement (ie, peak arterial opacification).

OPTIMAL VESSEL LUMEN ATTENUATION

The minimum contrast attenuation in the cardiac structures and the pulmonary arteries for diagnostic purposes is considered to be above a 250-HU threshold. Although previous research has argued that contrast enhancement greater than 400 HU could obscure calcified or noncalcified atherosclerotic plaques,¹⁵ the trend in clinical practice has been toward preferring very high



FIGURE 3. Simulated arterial enhancement curves, based on injection of IVC medium using identical injection protocols in a single patient. The enhancement curves were generated by reducing the baseline cardiac output by 20%. Note how a reduced cardiac output leads to a delayed, prolonged, and greater pattern of enhancement. (Color figure available online at www.thoracicimaging.com)

contrast attenuation in the coronary arteries. Recently, Cademartiri et al^{16} presented convincing evidence that contrast attenuation greater than 320 HU results in better ability to assess coronary artery stenosis, when comparing 64-slice coronary CTA against conventional, catheter angiography.

INJECTION RATE

Injection rate is important for achieving homogeneous enhancement and adequate opacification of smaller vessels. If the contrast volume and concentration are kept constant, there is a direct relationship between injection rate (mL/s) and maximal enhancement magnitude and an inverse relationship with bolus arrival time and maximal enhancement duration.¹⁷ This means that a shortened but high magnitude of arterial enhancement results from an increase in the injection rate, while achieving large temporal separation between the arterial and venous phases. An increase in injection rate almost linearly increases the magnitude of peak aortic enhancement (Fig. 4). However, peripheral injection of contrast at flow rates greater than 8 mL/s does not seem to increase contrast enhancement due to the reflux of contrast into the IVC, compliance of the peripheral veins, or other unknown physiological phenomena. Synchronization of the contrast injection with image acquisition is critical, and adaptation of the scan delay may be required to ensure acquisition during peak arterial enhancement. With faster scanning technology, this timing becomes increasingly important and less forgiving compared with traditional "standard," empirical fixed scan delays.

INJECTION DURATION

Injection duration is determined by the total contrast volume divided by the injection rate and has implications for both peak time of contrast enhancement and the magnitude of contrast enhancement.⁹ The appropriate injection duration is determined by the scanning conditions and clinical objectives. Injection duration at fixed injection rates determines total iodine mass delivered to the patient and the maximal magnitude of arterial enhancement.



FIGURE 4. Simulated enhancement curves of 3 patients with different injection rates using the same contrast media amount and concentration to illustrate the inverse relationship existing between injection rate (mL/s) and time to peak enhancement and maximal enhancement duration. There is also a direct relationship with the maximal enhancement magnitude. (Color figure available online at www.thoracicimaging.com)

Injection duration should be a function of the actual scan time to maintain adequate enhancement during the image acquisition and avoid unnecessarily high volumes of contrast media.¹² One strategy is to set the injection duration equal to the scan duration. This has a disadvantage for fast scans, however, because the bolus may not be long enough to accommodate dispersion through the cardiothoracic vasculature. It is common, therefore, to calculate the injection duration of a contrast bolus as the scan duration plus an additional few seconds. This additional duration also helps to account for delays introduced by the scanning system (eg, secondary to automated bolus triggering) and the delay between the start of contrast injection and scan acquisition. For cardiothoracic CTA, a rapid contrast delivery rate and short injection duration are desirable for optimal arterial enhancement.18

CONTRAST VOLUME

If iodine concentration and flow rate are kept constant, a larger contrast volume leads to greater and prolonged enhancement, which may be beneficial for extended coverage (Fig. 5). Again, the same fixed dose of contrast material provides different effects in patients with different body weights. Therefore, it has been a recent trend in MDCT for the contrast material volume to be customized according to body weight. This body weight–tailored dose of contrast material can help minimize variation in the degree of contrast enhancement obtained in the aortic, pulmonary, and coronary arteries among patients with different body types.¹⁹ Nevertheless, the optimal body weight–tailored dose of contrast material needs to be adjusted according to the iodine concentration of the contrast media.

CONTRAST MEDIA CONCENTRATION

As the degree of vascular enhancement over time is proportional to the amount of iodine molecules administered,



FIGURE 5. Simulated enhancement curves of 3 patients using different contrast volumes keeping constant iodine concentration and flow rate show how the use of larger contrast volumes leads to greater and prolonged enhancement. Adjusting contrast volume may be useful when extended coverage is required. (Color figure available online at www.thoracicimaging.com)

the concentration of contrast media is another essential variable in achieving optimal enhancement. When contrast volume, injection rate, and scan parameters (kV, mAs) are kept constant, a significantly higher attenuation of the vessels can be reached by using high iodine concentration contrast agents (Fig. 6). Clinically, the iodine delivery rate can be customized by either changing the iodine



FIGURE 6. Simulated contrast enhancement curves with a fixed amount of iodine mass but 3 different contrast medium concentrations injected at a constant rate show that the use of high-concentration contrast material is associated with narrow but earlier and greater peak arterial enhancement. The use of high-concentration contrast media allows decreasing the injection rate, which may help to minimize the risk of contrast extravasation. (Color figure available online at www.thoracic imaging.com)

concentration of the contrast medium or modifying the injection rate. The same degree of vascular enhancement can be obtained with low iodine concentrations by increasing the injection flow rate. As high iodine administration rates (1.6 to 2 g/s) are optimal for arterial enhancement (250 to 400 HU), the routine use of high iodine concentration (ie, 350, 370, or 400 mgI/mL) agents allows for decreasing the injection rate, which may minimize the risk of contrast extravasation. However, high iodine concentration agents are not recommended if monophasic (ie, without saline flush) injection is used, due to marked perivenous streak artifacts at the level of the brachiocephalic veins.²⁰

MONOPHASIC INJECTION PROTOCOL

Before the introduction of double-head, dual-syringe power injectors, the routine administration of contrast media consisted of a single bolus of contrast material only. Because scan times at CTA for single-, dual-, and 4-slice CT could be 20 to 30 seconds, it was quite common that scan acquisition occurred during the injection of contrast and ended while the brachiocephalic veins were still full of contrast material. This undiluted contrast medium in the peripheral veins would frequently lead to streak and beamhardening artifacts (Fig. 7). One could wait additional seconds until the injection of the contrast was completed, but this would often come at the expense of missing the peak contrast enhancement. Furthermore, the administration flow rate of contrast at CTA is typically greater than the endogenous flow rate of blood draining through the peripheral veins. On termination of the contrast injection, the column of contrast in the peripheral veins slows to the endogenous flow rate in the vessels. This can lead to an excessive broadening of the contrast bolus.

BIPHASIC INJECTION PROTOCOL

A biphasic injection protocol consists of contrast material followed by saline, typically injected at the same



FIGURE 7. Beam-hardening artifact. Coronal CT reconstruction shows a marked beam-hardening artifact from dense contrast in the superior vena cava that obscures the right margin of the ascending aorta.

rate as the contrast material. The introduction of a saline "chaser" or "flush" immediately after the contrast media alleviates the problems encountered when delivering a monophasic injection at multidetector-row CTA. A 30- or 40-mL saline bolus (the volume should approximate the so-called "dead space" in the peripheral arm veins)²¹ injected at the same flow rate as the contrast bolus ensures a tight bolus of contrast material into the central circulation and allows for—assuming that scan timing is properly adjusted—the reduction of streak and beam-hardening artifacts due to contrast in the peripheral veins and the right side of the heart. An additional benefit of the saline flush of a biphasic protocol is the more economized use of contrast by recruiting contrast material for vascular enhancement that would otherwise be left in the injection tubing.^{1,22}

TRIPHASIC INJECTION PROTOCOL

The judicious use of a saline chaser in a biphasic protocol results in contrast enhancement devoid of streak artifact. A limitation of the technique at cardiac CTA is that the right ventricle may be completely devoid of contrast material, thus making the visualization of thrombo-emboli, congenital defects, or tumors difficult or impossible. A triphasic contrast protocol can overcome the challenge of reduced right heart opacification (Fig. 8). Triphasic protocols consist of 3 distinct contrast phases: a contrast-only phase, followed by a contrast or saline mixture injected at the same rate of the first phase, with a saline flush phase as the third component. To achieve the mixed middle phase, a power injector capable of simultaneous contrast and saline injection is required. The middle phase can also consist of a small volume of contrast injected at a lower rate than the first phase. A theoretical disadvantage of reducing the flow rate between phases is that the contrast column loses momentum, which may result in timing deficiencies or a very broad enhancement profile. Kerl et al²³ showed improved visualization of right heart structures while maintaining left heart (coronary arteries included) image quality using a triphasic protocol consisting of a 50-mL, 70%/30% saline/contrast medium mixture and 30 mL of saline, all injected at 6 mL/s. They computed the contrast medium volume for the initial iodine phase of injection individually as the product of the scan duration and the flow rate.

MULTIPHASIC INJECTION PROTOCOL

Some effort has been invested in creating injection schemes making use of multiple contrast phases. Bae et al²⁴ developed a protocol based on the inverse solution of a mathematical model of contrast propagation. Their contrast protocol consists of phases with flow rates decreasing exponentially, with the intent to provide a uniform contrast enhancement profile at CTA. This scheme was more appropriate in the era of 4-slice MDCT, however, when scan times typically lasted 20 to 30 seconds. Fleischmann and Hittmair²⁵ developed a novel approach for designing multiphase injection protocols based on numerical analysis of data from a test bolus scan. They showed, at aorto-iliac CTA, an ability to reduce enhancement variability within individual patients. Their approach, however, necessitates analysis of and operation on the test bolus data.

INDIVIDUALIZED CONTRAST PROTOCOLS

The topic of weight- and patient-based contrast protocol design has been discussed for many years. The work of Bae and Fleischmann, in particular, shows the feasibility and utility of customizing a contrast protocol based on additional properties beyond merely weight.^{6,12,24–26} Recently, commercial software tools have been introduced that enable the computation of patient- and procedure-specific protocols at the point of care in the CT suite.²⁷ This technology holds promise for delivering consistent contrast protocols regardless of technologist skill, patient habitus, and procedural variations. Such software customizes the injection protocol using patient weight, scan duration, contrast



FIGURE 8. A, Contrast-enhanced, retrospectively electrocardiogram-gated CT coronary angiogram using a dual-syringe injector with biphasic bolus (saline chaser technique), displayed as multiplanar reformat in a 4-chamber view. There is high and homogenous contrast attenuation in the left atrium and the left ventricle (LV), which allows assessment of the mitral valve apparatus. The coronary arteries show high attenuation of the left and right coronary systems (left circumflex and right coronary artery). However, the low attenuation in the right atrium and right ventricle (RV) limits the visualization of the moderator band in the RV. B, Contrast-enhanced, retrospectively electrocardiogram-gated CT coronary angiogram using a dual-syringe injector with the "dual-flow" split bolus technique (triphasic injection protocol), displayed as multiplanar reformats in a 4-chamber view. There is high and homogenous contrast attenuation in the left atrium and the LV, which allows assessment of the mitral valve apparatus. The coronary and the left atrium and the LV, which allows assessment of the mitral valve apparatus. The coronary arteries show high attenuation of the left atrium and the LV, which allows assessment of the mitral valve apparatus. The coronary arteries show high attenuation of the left atrium and the LV, which allows assessment of the mitral valve apparatus. The coronary and the triph attenuation of the left antirum and right coronary arteries. The level of attenuation in the right atrium and RV is not high enough to cause streak artifacts, but allows visualization of right heart structures, such as the moderator band and the tricuspid valve apparatus.

concentration, and attributes of a bolus-timing scan. These algorithms adapt the iodine delivery rate (gI/s) based on a nonlinear relationship between patient weight, scan duration, and concentration of the contrast material. Numerical simulations based on the pharmacokinetic model of Bae-Brink-Heiken¹² were used to refine the relationship between iodine administration rate and patient weight. In addition, by considering procedure information, patient characteristics, and data from a test bolus injection, individualization of the scan delay computation is possible. With knowledge of scan delay and scan duration, further refinements and customizations of the contrast protocol are made. For example, because the scan's end-time is known, point-ofcare algorithms can ensure that contrast injection is completed several seconds before the completion of scan acquisition, ensuring the maximum use of the contrast material.

More advanced individualized contrast protocols that use test bolus data derived from multiple ROI in the cardiopulmonary anatomy are in development.²⁸ This class of algorithm allows a clinician to prospectively choose a contrast enhancement target in the vascular territory of interest while attempting to deliver a minimally sufficient dose of contrast material for that patient and procedure. With enhanced communication and interoperability between the power injector and the imaging system, these advanced algorithms become more robust and practical in clinical practice. In addition, this interoperability will allow for the implementation of contrast protocol design and delivery strategies as envisioned by Fleischmann, Bae, and others,^{12,25,29} while also enhancing technologist workflow and enabling contrast delivery data collection.

Although the principles of contrast protocol design are well described in the literature, a practical challenge for practicing clinicians is how to translate these findings and include them in everyday patient care. The individualization of contrast protocols could be time- and attentionconsuming for radiology technologists at the point of care. It is for these reasons, therefore, that software integrated unobtrusively into the clinical workflow holds promise for reducing the variation in contrast delivery across patients, indications, and clinicians while ensuring adequate opacification and thus leading to enhanced patient care. Jones and Wittram,³⁰ for example, discovered that 40% of indeterminate CT pulmonary angiograms at their institution were attributable to poor contrast bolus enhancement. With individualized contrast protocol technology at the point of care, the potential exists to minimize the frequency of subdiagnostic scans due to poor contrast delivery and scan synchronization.31

CONCLUSIONS

Currently, no single injection protocol strategy can be applied universally for cardiothoracic CTA, as marked variations exist depending on the MDCT technology used; nevertheless, understanding the pharmacokinetic and physiological principles of arterial enhancement is crucial for customizing the optimal injection protocol independently of MDCT technology to address a specific clinical scenario. Current trends favor high injection rates and higher iodine concentration contrast media to maximize the degree of vascular enhancement. Synchronization between peak contrast enhancement and data acquisition can be accomplished using either the test bolus or bolus-triggering technique, using a biphasic or triphasic injection protocol depending on the need for assessment of intracardiac anatomy.

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