Iodine Concentration and Optimization in Computed Tomography Angiography

Current Issues

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Abstract: Computed tomography (CT) technology has seen a dramatic evolution in the recent past that has deeply changed the face of this diagnostic modality. Since the early days of helical single-slice and then multislice CT, CT angiography (CTA) has been one of the most technically demanding applications, both in terms of scanning technique and contrast medium (CM) injection protocol, due to the need to acquire a large amount of high-resolution data over a limited period corresponding to the peak contrast enhancement of the arterial system. Iodine concentration is one of the main determinants of arterial enhancement in CTA, and current low-osmolar and iso-osmolar nonionic CM for intravascular administration still come in a handful of molecules, but a relatively wide range of different iodine concentrations. This gives the opportunity to optimize CTA protocols as a function of several factors such as patient characteristics, CT technology, and CM features in an attempt to maximize the diagnostic yield of CTA examinations while considering patient safety and avoiding unnecessary extra costs. Our aim is to provide an up-to-date overview of the existing evidence on how changing iodine concentration can have an impact on CTA performance, especially with the use of state-of-the-art CT and power injector technology, in the perspective of improving patient care while minimizing overall exposure to ionized CM and ionizing radiation.

Key Words: iodinated contrast medium, iodine concentration, CT angiography, iodine delivery rate, viscosity, signal-to-noise ratio, contrast-to-noise ratio, protocol optimization

Over the last decade, computed tomography (CT) has been revolutionized by a number of huge technological advancements, leading to the current possibility to acquire thousands of thin-slice images with voxel isotropy in a few seconds. Among modern CT applications, CT angiography (CTA) is one that has gained the most benefit from such evolution in terms of improved diagnostic performance and broadened clinical indications. In fact, while in nonvascular CT, intravenously administered iodinated contrast medium (CM) tends to accumulate into the microcirculation and then in the interstitial space relatively slowly after the beginning of intravenous injection, the following conditions must be fulfilled for optimal depiction of the arterial system:

• narrow slice width (usually ≤1 mm for peripheral CTA, or even narrower down to approximately 0.5 mm for coronary CTA) for proper evaluation of the smallest arterial vessels and high quality of 2-dimensional and 3-dimensional postprocessing;
• fast imaging time (usually in the order of seconds), so as to acquire CTA data at the peak of arterial contrast enhancement before venous enhancement occurs;
• high selective contrast enhancement of the arteries throughout the whole acquisition volume.

In order for those requirements to be met, accurate coupling between CM injection and CTA image acquisition is of paramount importance to fully exploit the contrast bolus over the entire scan duration. In other terms, both the bolus geometry and the scan parameters should be tailored to achieve optimal, homogeneous enhancement of the arterial lumen as well as an accurate assessment of vessel walls, taking into account several factors related to patient (eg, size, cardiac output [CO], circulating blood volume [BV]), CT scanner (eg, scan speed, tube voltage, radiation dose), CM properties (eg, iodine concentration, viscosity, safety issues), and CM injection protocol (eg, flow rate and volume, administration of a saline flush or multiple CM/saline boluses). Among them, iodine concentration (defined as the mass of iodine per unit volume of CM in terms of grams per milliliter) is a key element because it is directly related to contrast enhancement in CTA, as outlined in the following sections.

While CT technology has been evolving quickly and offers several ways to optimize scan acquisition for CTA examinations, iodinated CM technology has remained substantially unchanged since the introduction of low-osmolar and iso-osmolar nonionic CM for intravascular administration. Therefore, on the CM side, optimization of CTA protocols can currently rely on the most appropriate choice of a limited number of iodinated CM, each of which is commercially available at different iodine concentrations (Table 1).

This short review will focus on how iodine concentration can have an impact on the optimization of CTA studies depending on the available CT scanner technology and diagnostic scenario, based on evidence from the existing literature.

Iodine Concentration and Iodine Delivery Rate

As pointed out previously, CTA is technically more demanding than CT venography or CT imaging of parenchymal tissues (especially those with predominantly venous perfusion, where contrast enhancement depends on the gradual accumulation of iodine over time into a capacitive system), as image acquisition occurs during the arterial first-pass of CM for maximum arterial enhancement with no or minimized venous overlap. As blood opacified by iodinated CM is continuously flushed away from the vascular segment under examination as an effect of systolic pressure and tends to be quickly replaced by unenhanced blood coming from the heart, CM with an adequate amount of iodine per injected unit of volume (hence, iodine concentration) must be supplied at high enough a rate to keep luminal enhancement above a given target level. Therefore, for arterial contrast enhancement to be increased for CTA in a given patient, one can increase iodine concentration, the flow rate at which CM is injected, or both.

The aforementioned considerations can be synthesized by the concept of iodine delivery rate (IDR), which is defined as:

\[ \text{IDR} = [I] \times f \]  

(Equation 1)

where \([I]\) is the iodine concentration of CM and \(f\) is the flow rate at which it is injected into the vessel (eg, via intravenous injection, as in the case of CTA). In other terms, IDR represents the rate at which iodine...
is delivered into the arterial system and is the main determinant of arterial enhancement in CTA.\textsuperscript{3–7} As a matter of principle, for a fixed IDR value, a given CM at a higher iodine concentration may thus be administered at a slower flow rate or lower concentration CM can be used with the same dye/saline ratio. A target IDR of approximately 1.2 to 1.6 gI/s and up to 2.0 gI/s is usually recommended for noncoronary and coronary CTA applications, respectively.\textsuperscript{3–7} On this basis, a wide range of combinations of iodine concentration and flow rate for a given CM can be selected to achieve the desired IDR value (Fig. 1).

Of course, different combinations of iodine concentration and flow rate affect the magnitude of peak enhancement and contrast bolus geometry, as well as the injection pressure due to CM viscosity and flow rate, and the timing and duration of the CTA acquisition, with a substantial impact on the CTA protocol.\textsuperscript{3–7} Ideally, contrast bolus should have a rectangular shape with instantaneous rise and fall after intravenous administration for infinite bolus compactness and full exploitation of iodine-related enhancement strictly over the CTA scan time. Yet, the time-to-peak enhancement varies as a function of injection rate, with higher injection rates leading to a steeper contrast bolus shape and faster arrival of the enhancement peak, as well as shorter duration of the arterial enhancement plateau (ie, the range of intravascular attenuation values deemed useful for a diagnostic CTA study).\textsuperscript{3,4,9} Thus, administering CM at a higher flow rate with other injection parameters kept constant results in a shorter bolus duration, allowing to achieve good bolus compaction while potentially improving patient safety and reducing overall costs. To this latter purpose, evidence exists that volumes as low as 25 to 40 mL of high concentration CM are sufficient to provide diagnostic quality CTA examinations, for example, of the intracranial arteries (25 mL of iomeprol 400 mg I/mL at 5 mL/s flow rate\textsuperscript{11}), coronary arteries (30 mL of iopromide 400 mg I/mL at 5 mL/s flow rate\textsuperscript{5}), and for the diagnostic workup of noncardiac chest pain (40 mL of iomeprol 400 mg I/mL at 3 mL/s flow rate\textsuperscript{5}). In parallel, low-volume, high-flow rate protocols have been devised with low concentration CM that yield diagnostic CTA image quality, for example, for TAVI (transcatheter aortic valve implantation) planning (down to the bolus shape can be approximated to a pulse function and injection duration does not significantly affect arterial enhancement due to absence of bolus recirculation. Therefore, with a fast protocol, CTA scanning should start approximately 6 to 8 seconds after the CM transit time (as determined, eg, by bolus tracking with a threshold of approximately 100 HU) to reach the peak enhancement and allow for the scan delay of newer-generation multidetector CT scanners.\textsuperscript{3}

Conversely, increasing iodine concentration while keeping other parameters the same does not alter the time-to-peak enhancement, but broadens the duration of the enhancement plateau, which may provide some extra enhancement as a potential safety margin in case of suboptimal bolus timing and can be helpful with slower scan protocols (acquisition time >10 seconds), such as those for CTA of the lower limbs.\textsuperscript{3–5} With slow CTA protocols, it is essential that the duration of CM injection covers the relatively long time needed to scan the entire anatomy up to the most distal arteries to avoid outrunning the CM bolus. In such cases, an increase in injection duration with other parameters kept constant leads to increased and more homogeneous arterial enhancement over the entire acquisition volume due to the cumulative effects of bolus recirculation (contributing to a 10% to 20% increase in peak arterial enhancement), and modern dual-head power injectors allow the usage of a biphasic CM bolus technique that may be beneficial to further prolong and linearize the enhancement plateau.\textsuperscript{3,7,10,11} However, whenever a fast CTA protocol is feasible, the combination of a shorter injection time at constant IDR and a narrower scan window results in higher arterial enhancement due to greater bolus compactness and thus is better than a slower CTA protocol over the entire acquisition volume.\textsuperscript{12}

On the other hand, for a given CM volume, a larger iodine dose (expressed as $[I] \times V$, where $V$ is CM volume) would be delivered using higher concentration CM. Therefore, a lower volume of high concentration CM should be used to keep the same iodine dose and improve bolus compaction while potentially improving patient safety and reducing overall costs. To this latter purpose, evidence exists that volumes as low as 25 to 40 mL of high concentration CM are sufficient to provide diagnostic quality CTA examinations, for example, of the intracranial arteries (25 mL of iomeprol 400 mg I/mL at 5 mL/s flow rate\textsuperscript{11}), coronary arteries (30 mL of iopromide 400 mg I/mL at 5 mL/s flow rate\textsuperscript{5}), and for the diagnostic workup of noncardiac chest pain (40 mL of iomeprol 400 mg I/mL at 3 mL/s flow rate\textsuperscript{5}). In parallel, low-volume, high-flow rate protocols have been devised with low concentration CM that yield diagnostic CTA image quality, for example, for TAVI (transcatheter aortic valve implantation) planning (down to

<table>
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<tr>
<th>Chemical Class</th>
<th>Chemical Name</th>
<th>Trade Name</th>
<th>Iodine Concentration*</th>
<th>Viscosity†</th>
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<td>Monomer, LOCM</td>
<td>Iobitridol</td>
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<td>320  11.8</td>
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* Iodine concentration is expressed in milligram iodine per milliliter.
† Viscosity is expressed in millipascal seconds and is referred to a temperature of 37°C.
CM indicates contrast medium; LOCM, low osmolar CM; IOCM, iso-osmolar CM.

**TABLE 1.** Nonionic Iodinated CM Currently Available for Intravascular Administration

FIGURE 1. How it is possible to select different combinations of flow rate and iodine concentration values to get the desired IDR (eg, 1.6 gI/s). IDR values in the matrix are expressed in terms of gI/s.
In practice, the actual relationship between CM injection parameters and degree of arterial enhancement that can be obtained is more complex than predicted by IDR alone, and the level of vascular attenuation needed for a CTA examination to be of diagnostic quality can vary depending on the available CT technology and acceptable contrast-to-noise ratio (CNR), as discussed later.

**CTA and Iodine Concentration: Higher or Lower?**

Which Concentration for a Given IDR?

As mentioned previously, one advantage of high concentration over low iodine concentration CM is the possibility to achieve the same degree of arterial enhancement with a lower flow rate or, equivalently, greater arterial enhancement with the same flow rate in CTA. This is a logical consequence of the IDR definition, and there is wide agreement on this point in the literature regarding CTA of several arterial territories, ranging from CTPA to chest CT including CTA of the thoracic aorta, CT of the infrarenal aorta and runoff vessels, CT coronary angiography, and CTA of the abdominal vasculature for planning of pancreatic surgery and evaluation of renal transplant donors.

In all of the aforementioned listed papers, high and low iodine concentration CM were compared using the same flow rate and CTA scanning technique, expectedly resulting in greater arterial enhancement with higher concentration CM, as well as greater subjective image quality and preserved diagnostic accuracy where assessed. Of interest, a partial exception was reported in the work by Cademartiri et al, where iodixanol 320 mg I/mL (a dimeric, iso-osmolar CM) was found to yield vascular attenuation comparable to that of monomeric, low-osmolar 350 mg I/mL CM injected at the same flow rate of 4 mL/s, likely due to its different physicochemical properties. In general, the use of high concentration CM allowed for a reduction of injected volumes compared with lower concentration CM administered with the same flow rate and iodine load, along with up to 5.5% cost savings and increased bolus compaction due to a shorter bolus duration. Furthermore, CM administration at a lower flow rate allows the usage of smaller-bore needles for intravenous injection, which may be beneficial in patients with a poor venous access (eg, after chemotherapy), provided that CM viscosity be kept reasonably low by preheating contrast before introduction.

Conversely (and in agreement with theory), there is extensive evidence that when CM at different iodine concentration and matched IDR are compared, injection of lower concentration CM leads to comparable, or even greater arterial enhancement than higher concentration CM without an increase in iodine load. Mühlenbruch et al compared intravascular attenuation of the aorta and pulmonary vessels.
in 300 chest CTA examinations obtained by administering 3 different CM (iopromide 300 mg I/mL, iopromide 370 mg I/mL, and iodopaque 400 mg I/mL) at matched IDR of 1.3 g I/s and iodine load of 33 g I via a 18-gauge needle placed in a cubital vein. In this setting, no statistically significant differences were found in terms of arterial enhancement, image quality, and discomfort during CM injection.27 Yet, Behrendt et al28 compared equi-IDR, equi-iodine dose injections of the same CM for CTA of the pulmonary arteries and thoracic aorta and showed that significantly greater vascular enhancement could be achieved with the lowest iodine concentration. Similarly, Behrendt et al29 showed as well that higher vascular enhancement could be obtained for abdominal and chest CTA with iopromide 300 mg I/mL than with iopromide 370 mg I/mL using an equi-IDR, equi-iodine dose protocol. These findings can be explained by the lower viscosity of lower concentration CM, allowing for reduced flow resistance and injection pressure. Therefore, CM with lower viscosity would distribute more easily and more evenly in the vessels, potentially resulting in higher vascular attenuation during the arterial first-pass of CM.28,30,31

As a matter of fact, a greater bolus compactness is relevant for CTA regardless of iodine concentration because it allows the contrast bolus to be fully exploited. To this latter respect, it may be interesting to mention the finding by Matoba et al14 that, whereas higher arterial enhancement can be obtained in liver CT for depiction of hyper-vascular hepatocellular carcinoma using 300 mg I/mL rather than 370 mg I/mL CM administered with the same iodine load and injection duration without saline flush, the addition of 40 mL of saline solution after the CM bolus negates the enhancement gain with the 300 mg I/mL CM. This was presumably due to the increased bolus compactness and clearance of the “dead space” between the brachial vein and superior vena cava provided by the saline flush, which should regularly be administered after CM injection using modern dual-head power injectors.

Iodine Concentration and CM Viscosity: A Closer Look

With the evolution of CT and power injector technology, as well as the introduction of PACS-connected hardware and software platforms for automated monitoring of CM administration protocols,25,26 interest has arisen on the development of CTA protocols based on the injection of ultralow (ie, less than 300 mg I/mL) iodine concentration CM at very fast flow rates, provided that a valid venous access is available.30,31,32 This is possible owing to the decreased viscosity of lower concentration CM compared with a higher concentration CM passing through a tube (eg, a venous access or a vessel) at a given flow rate according to Poiseuille’s law:

\[ Q = \pi \Delta p r^4/8\eta l \]  
(Equation2)

where \( Q \) is the flow rate, \( \Delta p \) is the pressure gradient, \( r \) is the radius of the tube, \( \eta \) is the viscosity, and \( l \) is the tube length.35 In particular, Mihl et al showed that CT coronary angiography is feasible using iopromide with an iodine concentration as low as 240 mg I/mL injected at 9 mL/s via a 18-gauge needle (ie, a commonly used needle size for CTA). In their experience, subjective and objective image quality as well as peak pressures as measured by an injector-connected monitoring system were comparable to those achieved by administering an iodine-equidose of iopromide 300 mg I/mL at the same IDR of 2.16 g I/s (resulting in a flow rate of 7.2 mL/s), opening a doorway toward applicability of a broad variety in flow rates and IDRs and subsequently more individually tailored injection protocols29 (Fig. 3). Interestingly, in a previous study, Behrendt et al31 compared the arterial enhancement obtained in pigs by injecting iopromide over a wide range of iodine concentrations (ranging from 150 to 370 mg I/mL) at the same iodine dose and IDR, and found that contrast enhancement was significantly improved using iodine concentrations between 240 and 300 mg I/mL. In the authors’ opinion, this finding may be explained by the fact that too low an iodine concentration results in poor compactness and excessively low concentrated flow pattern of the contrast bolus, whereas a moderate concentration CM would distribute faster and more homogeneously in the vessels than high concentration CM. Moreover, administration of iodinated CM with lower viscosity (and hence, iodine concentration for a given molecule) may potentially limit the risk of acute kidney injury compared with higher viscosity CM by preventing renal hyperfusion and hypoxia induced by excessive tubular fluid viscosity.36

As to the risk of contrast extravasation related to high speed injection, there is no evidence in the literature of a correlation between injection rate and extravasation events, especially if intravenous needles with a diameter larger than 22 gauge are used.37 The availability of modern power injector technology is certainly beneficial, as state-of-the-art systems allow to accurately calibrate flow rate within a wide range of injection speeds, monitor CM injection pressure, and keep track of injection parameters and potential adverse events (such as extravasation or flow limitation issues).33

However, pushing things to the extreme, it is unlikely that an injection rate higher than 10 mL/s would further increase the magnitude of arterial enhancement because of CM dispersion and reflux from the right atrium, the pressure performance envelope of power injectors, and the risk of stressing the venous injection site at such high flow rates.4 Thus, whenever high flow injection is impossible for any reason (eg, poor venous access), increasing CM iodine concentration remains an option to keep IDR up.

Does IDR Always Need to Be “So” High for CTA?

A high IDR for CTA allows to generate a vascular attenuation (ie, signal) high enough to obtain a sufficient signal-to-noise ratio and CNR for optimal depiction of the arterial system and postprocessing of CTA data sets. More generally speaking, maximizing image contrast plays a pivotal role in technical optimization of CTA examinations (where high-contrast objects such as iodine-enhanced blood into the vessel lumen versus the vessel wall are the diagnostic focus), with the target being to produce CTA images of diagnostic quality with the least amount of ionizing radiation (especially in younger patients) and/or iodinated CM. This latter issue is especially important in patients at higher risk for contrast-induced nephropathy (making up a substantial fraction of those referred for CTA), and despite recent reports that such risk for all patients receiving intravenous iodinated CM may be overstated,38 up-to-date guidelines recommend usage of the lowest dose of CM consistent with a diagnostic result.39

To this purpose, image acquisition at a tube voltage as low as 80 to 100 kV or even less on newer-generation CT scanners (low kV scanning) is a common strategy to improve vascular attenuation and CNR while substantially lowering radiation exposure in CTA examinations of nonobese patients, with other scanning parameters kept unchanged.40–43 In fact, x-rays generated by a lower tube voltage have a lower average energy, closer to the k-edge of iodine (33.2 keV), resulting in greater photoelectric effect as well as greater noise and susceptibility to photon starvation artifacts.40,44 which, however, can usually be tolerated unless unacceptably severe (such as in obese patients or patients with metal hardware) owing to the net increase in CNR.45 In this setting, high concentration CM can be advantageous over low concentration CM injected at the same flow rate to improve vessel contrast and actually reduce radiation dose in low kV CTA studies. In particular, Leizzi et al46 showed that compared with a 300 mg I/mL CM, 120 kV protocol for CTA assessment of abdominal aortic aneurysms after endovascular repair, the combination of low kV scanning and the same iodine dose (36 g I) of high concentration CM (400 mg I/mL) yielded comparable subjective and
objective image quality along with substantially reduced radiation exposure.

Yet, when comparing high (370 mg I/mL) and low (300 mg I/mL) concentration CM injected with the same volume (110 mL) and flow rate (5 mL/s) for CTA of the renal arteries performed at 120 kV and 80 kV, respectively, the combination of low concentration CM and 80 kV was associated with significantly higher arterial enhancement and superior image quality along with a smaller amount of iodine in a lower radiation dose, underscoring the prevailing impact of kV reduction on boosting iodine signal. Of interest, some modern power injectors can actually reduce both IDR and iodine load without changing CTA timing strategy by simply mixing saline to high concentration CM, potentially improving individualization of CTA protocols and workflow with a single iodine concentration.

**How Conservative CM Technology Can Keep Up With Fast-Changing CTA Technology**

More recently, the development and increased availability of novel CT technology including iterative reconstruction (IR) algorithms, dual-energy imaging, and ultrafast CT scanners have opened new perspectives toward a more and more aggressive reduction of iodine and radiation exposure, progressively pushing the limit at which diagnostic CTA images can be acquired with low kV, low iodine concentration CM, potentially improving individualization of CTA protocols and workflow with a single iodine concentration.
protocols, even in larger patients. In fact, the extremely short acquisition time of newer-generation CT scanners (in the order of a couple of seconds for prospectively electrocardiographically-triggered CTA of the entire aorta), combined with the availability of tube settings as low as 70 kV and state-of-the-art IR algorithms enabling maximization of signal-to-noise ratio and CNR via a strong reduction of image noise, can naturally be matched and even strengthen all of the previously discussed concepts of maximum bolus compaction, as low as possible iodine dose, and as low as possible radiation exposure for CTA. As a potential additional tool, dual-energy scanning coupled with IR techniques allows to even halve iodine exposure by reconstructing low-energy monochromatic images (hence with dramatically improved photoelectric effect), allowing flexibility in optimizing image contrast.

In this context, several papers have recently been published showing the feasibility of submillisievert CTA examinations with modest amounts of iodine, both from high- and low-concentration CM. For instance, Zhang et al.14 obtained diagnostic quality high-pitch ECG-triggered CTA examinations of the aorta on a dual-source CT scanner with only 30 mL of 370 mg I/mL at 70 kV tube voltage. On the other hand, Zheng et al.11 compared a high iodine concentration (370 mg I/mL) 100 to 120 kV protocol without IR and a low concentration (270 mg I/mL), 80 to 100 kV IR protocol for prospectively ECG-triggered dual-source CT coronary angiography, showing that this latter protocol yielded comparable arterial enhancement and image quality along with reduced radiation dose. As for dual-energy scanning, it may be worthwhile reporting the finding by Xin et al.13 of better image quality for upper abdominal CTA examinations performed with 28% less iodine load and reduced radiation burden using 270 mg I/mL CM and monochromatic dual-energy scanning, compared with 350 mg I/mL and conventional 120 kV scanning. Of course, the advantages seen with the lower concentration protocols in the 2 papers mentioned previously are not due to the lower iodine concentration itself but rather to the higher inherent image contrast of the improved CT scanning techniques, leading to a more efficient use of iodine.

CONCLUSIONS

Image quality and overall diagnostic performance of CTA examinations in the various areas of the arterial tree are a function of multiple variables related to patient characteristics, available CT technology, and CM properties. Out of these latter, iodine concentration is one of the main determinants of arterial enhancement and plays a major role in the optimization of CTA protocols in terms of diagnostic quality, iodine exposure, and radiation dose. To the best of our knowledge, there is currently no evidence that any given iodine concentration is in itself superior to the others as to the overall optimization of CTA protocols. Rather, it is the operators’ duty to make any effort to choose the most appropriate CTA protocol (ie, scanning and CM injection parameters, including iodine concentration), tailored to any single patient for any single diagnostic query by leveraging the wide variety of available iodine concentrations and scanning techniques and the flexibility of modern power injectors, in line with the ALARA (as low as reasonably achievable) principle.

REFERENCES


