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Which Contrast Agent For Coronary CT Angiography?

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Introduction

Although excellent sensitivity has been reported for computed tomography angiography (CTA) in the detection of significant coronary artery stenoses (1, 2), a prerequisite for successful and robust coronary CTA is prominent vascular enhancement. The type and iodine concentration of the contrast agent used in coronary CTA have assumed increasing importance because the attenuation that can be achieved within the vessel lumen greatly affects the diagnostic yield (3, 4). These considerations are particularly important for imaging the coronary arteries because of the small caliber and tortuous anatomy of these vessels, and because of the decreased blood flow in the presence of stenosis or obstruction.

Contrast enhancement in coronary CTA

The pattern of enhancement in coronary arteries can be described by plotting the attenuation values within the vessel against time after intravascular injection of contrast. This curve is also called 'bolus geometry'. The ideal condition for the enhancement curve is a rectangular profile that overlaps the acquisition window exactly. In practice, the enhancement curve has an upslope, a smooth peak resembling a plateau and a wash-out portion (Figure 1). Being aware of the attenuation changes in a vascular territory (and how to modify them) is not trivial because CTA is based on the acquisition of data strictly synchronized with the arterial passage of contrast agent.

How to optimize contrast enhancement in coronary CTA

The minimum intracoronary attenuation to be achieved when performing coronary CTA is 250-300 HU at the lowest (5). Coronary arteries have a small diameter (2-5 mm) and blood flow can be decreased in the presence of a stenosis or obstruction. Roughly, good coronary enhancement requires iodine administration rates of 1.6-2 g/s. An increase in contrast volume increases absolute intravascular attenuation but delays the peak of maximum enhancement (Figure 1B). An increase in the iodine concentration yields proportionally higher intravascular attenuation (6), and so does an increase in the injection rate. However, whereas an increase in injection rate decreases the time to the peak of maximum enhancement, the latter remains unaffected by concentration changes (Figure 1B). It can be argued that the iodine administration rate can be modified more easily by changing the injection rate than by changing the contrast iodine concentration. However, the injection rates that are feasible in routine clinical practice are 4–5 ml/sec. The use of higher injection rates would require larger needles, larger veins, more time for setting the intravenous line and could potentially increase the risk of contrast extravasation. Increasing the iodine concentration is always feasible in any condition. Thus the use of high-concentration (350-400 mgI/ml) contrast agents is preferred over low-concentration ones.

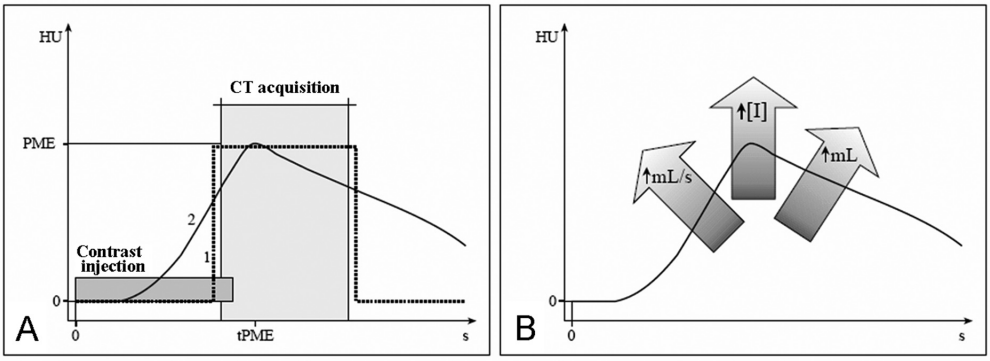

FIGURE 1. Attenuation-time curves after contrast injection. A: in ideal settings, the enhancement curve (dotted line, 1) has a rectangular shape and overlaps exactly the CT acquisition window (light grey rectangle). The real enhancement curve (continuous line, 2) has a steep upslope, a rounded peak and a wash-out downslope. In practice, portions of all the three enhancement phases are imaged. PME = peak of maximum enhancement. tPME = time to peak of maximum enhancement. B: increasing the contrast volume (ml), injection rate (ml/s) and iodine concentration ([I]) increases the PME. The increase in contrast volume increases the tPME; the increase in injection rate decreases the tPME; the tPME is not affected by the iodine concentration.

The influx of contrast of very high concentration may cause high-density artefacts. A saline bolus following the contrast bolus may compensate for this. Moreover, contrast viscosity increases with iodine concentration and decreases with rising temperatures. Hence high concentration contrast agents should be administered after appropriate heating at 38°C.

For the synchronization of the CT scan with the peak of maximum enhancement within the coronary arteries (Figure 1), protocols such as bolus tracking (smart prep) or test bolus are routinely used.

Contrast concentration

Several studies have discussed the role of contrast with high iodine concentration for coronary CTA (5, 7-9). In a study comparing several contrast agents with differing iodine concentrations (iohexol 300 mgI/ml, iodixanol 320 mgI/ml, iohexol 350 mgI/ml, iomeprol 350 mgI/ml, and iomeprol 400 mgI/ml), it was shown that significantly higher vascular attenuation was achieved with the highest iodine concentration, and significantly lower attenuation was achieved with the lowest iodine concentration (8) (Figure 2). Another study (7) aimed at further defining the benefits of contrast agent with high iodine concentration by comparing the attenuation achieved in the coronary arter-

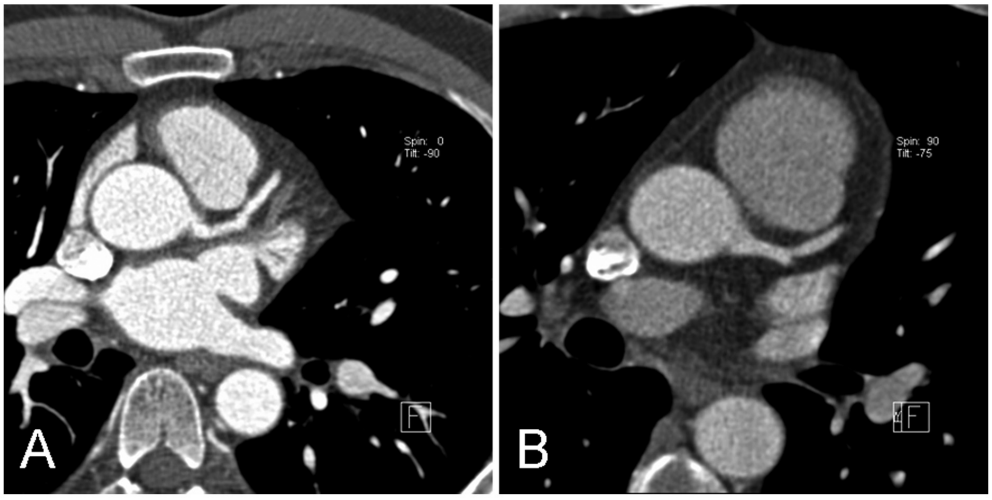

FIGURE 2. Comparison of blood attenuation after injection of contrast agents with different iodine concentration, both injected at 4ml/sec. A: attenuation obtained with an iodine concentration of 400 mgI/ml, and B: attenuation obtained with an iodine concentration of 320 mgI/ml. Notice the differences in attenuation at the level of the aorta, left main and left anterior descending arteries.

ies and great vessels of the thorax after administration of 2 contrast agents with high iodine concentration (iopromide 370 and iomeprol 400). With all other injection variables (volume, injection rate) and scan parameters (kV, mA) kept constant, significantly higher attenuation was found in all vessels with the contrast agent with the highest iodine concentration (400 mgI/ml).

Contrast induced nephropathy (CIN) and contrast agent safety

Contrast induced nephropathy (CIN) is generally defined as an increase in serum creatinine of more than 25%, or 44 μmol/l [0.5 mg/dl] within 3 days after the intravascular administration of a contrast agent (10) . The highest risk for CIN is seen in patients with preexisting kidney disease (serum creatinine >132 μmol/l [1.5 mg/dl], glomerular filtration rate <60 ml/min), particularly when due to diabetic nephropathy (10, 11). Diabetes mellitus without renal impairment is not considered a risk factor (10). The route of contrast administration is also important. Contrast agents seem less nephrotoxic when administered intravenously than when given intraarterially into the renal arteries or the aorta proximal to the origin of the renal arteries (12).

A meta-analysis of comparative trials (17) showed that high-osmolar contrast agents should be avoided in patients at increased risk of CIN. The question remains as to whether the other available contrast agents, several low-osmolar and one iso-osmolar, differ in terms of nephrotoxicity. Several nonionic monomers (iohexol, iomeprol, iopamidol, iopromide, ioversol, iobiditrol), one ionic dimer (ioxaglate), and one nonionic dimer (iodixanol) (Table 1) are available for intravascular use. In 2003, the results of a randomized trial by Aspelin et al. (11) (NEPHRIC study) suggested less CIN with use of the iso-osmolar nonionic dimer (iodixanol) than with nonionic monomers in 129 patients with moderate chronic kidney disease and diabetes mellitus receiving an intraarterial contrast injection during coronary or aorto-femoral angiography. However other studies (18-21) have not confirmed the results of the NEPHRIC study.

Whereas controversy may exist about differences in nephrotoxicity between iso-osmolar and low-osmolar contrast agents following their intraarterial administration (22), there is no clear advantage of using the nonionic dimer for intravenous injection. Thomsen et al. (20) reported 7% CIN after intravenous injection of 40 gI of the iso-osmolar iodixanol and 0% CIN after the low-osmolar iomeron in patients with reduced kidney function ($P<0.05$). Barrett et al. (23) showed a 2.6% CIN rate after intravenous injection of iodixanol

TABLE 1. Properties of low- and iso-osmolar contrast agents [modified from (26)]

Generic name	Type, ionicity	Trade name	Manufacturer	Iodine Concentration (mg/ml)	Osmolality (mOsm/kg H2O)
Ioxaglate	Low-osmol. Ionic (dimer)	Hexabrix	Guerbet (licensed to Tyco Healthcare/Mallinckrodt)	160 200 320 350	295 370 600 680
Iohexol	Low-osmol. Nonionic (monomer)	Omni-paque	GE Healthcare Biosci-ences/Amersham Health	180 200 240	410
		Omnitrast	Schering	250	520
		Omnigraf	Juste	300 350	640 780
Iopamidol	Low-osmol. Nonionic (monomer)	Isovue	Bracco Diagnostics	150 200	300-340 412-438
		Iopamiro Jopamiro Niopam Solutrast	Bracco Intl Bracco Intl Bracco UK Bracco Altana-Pharma	240 300 350 370	480 616-680 730 796-832
Ioversol	Low-osmol. Nonionic (monomer)	Optiray	Tyco Healthcare/ Mallinckrodt	160 240 300 320 350	355–380 502–550 630 695–720 790
Iopromide	Low-osmol. Nonionic (monomer)	Ultravist	Schering Berlex	150 180 200 240 300 350 370 400	340 390 420 480-500 610-620 730 774-780 880
Iobitridol	Low-osmol. Nonionic (monomer)	Xenetix	Guerbet	250 300 350	585 695 915
Iomeprol	Low-osmol. Nonionic (monomer)	Iomeron	Bracco Intl	150 200 250 300 350 400	301 362 440 521-609 620 730
Iodixanol	Iso-osmol. Nonionic (dimer)	Visipaque	GE Healthcare Biosci-ences/Amersham Health	150 270 320	290 290 290

and 0% after injection of iopamidol in a randomized, multicenter trial (IMPACT). These results were similar to those of a previous study by Carraro et al. (24) in which no difference was found between the iso-osmolar iodixanol and the low-osmolar iopromide in patients with chronic kidney disease. A recent study by Nguyen et al. (25) randomized 117 patients with decreased renal function undergoing contrast-enhanced CT to receive either iodixanol (61 patients) or iopromide (56 patients). Serum creatinine levels were measured one, two, and three days after the exam, and then again after 30 and 90 days. This study found that after one day serum creatinine levels were lower with iodixanol than with iopromide. However, no patients in either group showed contrast-related adverse events at the 30- or 90-day follow-up.

Conclusion

Good coronary enhancement is mandatory in order to perform successful coronary CTA. The minimum intracoronary attenuation to be achieved is 250-300 HU at the lowest. Coronary arteries are small vessels with a tortuous anatomy. Moreover, coronary blood flow can be decreased in the presence of stenosis or obstruction. In order to optimize coronary enhancement, iodine administration rates of 1.6-2 g/s should be used. Contrast injection rate and concentration must be chosen accordingly. The injection rates that are feasible in clinical routine are 4–5 ml/sec. The use of higher injection rates would require larger needles, larger veins and could potentially increase the risk of contrast extravasation. Conversely, the use of high-concentration (350-400 mgI/ml) contrast agents is always feasible and increases coronary enhancement proportionally. High-concentration contrast agents are low-osmolar nonionic monomers. For intravenous injection, these contrast agents can be considered as safe as iso-osmolar nonionic dimers.

References

1. Pugliese F, Mollet NR, Hunink MG, et al. Diagnostic performance of coronary CT angiography by using different generations of multisection scanners: single-center experience. Radiology 2008; 246:384-393.
2. Vanhoenacker PK, Heijenbrok-Kal MH, Van Heste R, et al. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. Radiology 2007; 244:419-428.
3. Bae KT, Heiken JP, Brink JA. Aortic and hepatic contrast medium enhancement at CT. Part I. Prediction with a computer model. Radiology 1998; 207:647-655.
4. Fleischmann D, Rubin GD, Bankier AA, Hittmair K. Improved uniformity of aortic enhancement with customized contrast medium injection protocols at CT angiography. Radiology 2000; 214:363-371.
5. Becker CR, Hong C, Knez A, et al. Optimal contrast application for cardiac 4-detector-row computed tomography. Invest Radiol 2003; 38:690-694.
6. Fleischmann D. Use of high concentration contrast media: principles and rationale-vascular district. Eur J Radiol 2003; 45 Suppl 1:S88-93.
7. Cademartiri F, de Monye C, Pugliese F, et al. High iodine concentration contrast material for noninvasive multislice computed tomography coronary angiography: iopromide 370 versus iomeprol 400. Invest Radiol 2006; 41:349-353.
8. Cademartiri F, Mollet NR, van der Lugt A, et al. Intravenous contrast material administration at helical 16-detector row CT coronary angiography: effect of iodine concentration on vascular attenuation. Radiology 2005; 236:661-665.
9. Rist C, Nikolaou K, Kirchin MA, et al. Contrast bolus optimization for cardiac 16-slice computed tomography: comparison of contrast medium formulations containing 300 and 400 milligrams of iodine per milliliter. Invest Radiol 2006; 41:460-467.
10. Thomsen HS, Morcos SK. Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. Br J Radiol 2003; 76:513-518.
11. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003; 348:491-499.
12. Katzberg RW, Barrett BJ. Risk of iodinated contrast material--induced nephropathy with intravenous administration. Radiology 2007; 243:622-628.
13. Thomsen HS, Morcos SK. In which patients should serum creatinine be measured before iodinated contrast medium administration? Eur Radiol 2005; 15:749-754.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.
15. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol 2002; 13:2140-2144.
16. Blaufox MD, Aurell M, Bubeck B, et al. Report of the Radionuclides in Nephrourology Committee on renal clearance. J Nucl Med 1996; 37:1883-1890.

17. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 1993; 188:171-178.
18. Liss P, Persson PB, Hansell P, Lagerqvist B. Renal failure in 57 925 patients undergoing coronary procedures using iso-osmolar or low-osmolar contrast media. Kidney Int 2006; 70:1811-1817.
19. Solomon RJ, Natarajan MK, Doucet S, et al. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. Circulation 2007; 115:3189-3196.
20. Thomsen HS, Morcos SK, Erley CM, et al. The ACTIVE Trial: comparison of the effects on renal function of iomeprol-400 and iodixanol-320 in patients with chronic kidney disease undergoing abdominal computed tomography. Invest Radiol 2008; 43:170-178.
21. Barrett BJ, Katzberg RW, Thomsen HS, et al. Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol. Invest Radiol 2006; 41:815-821.
22. Thomsen HS, Morcos SK, Barrett BJ. Contrast-induced nephropathy: the wheel has turned 360 degrees. Acta Radiol 2008; 49:646-657.
23. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. N Engl J Med 2006; 354:379-386.
24. Carraro M, Malalan F, Antonione R, et al. Effects of a dimeric vs a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. Eur Radiol 1998; 8:144-147.
25. Nguyen SA, Suranyi P, Ravenel JG, et al. Iso-osmolality versus low-osmolality iodinated contrast medium at intravenous contrast-enhanced CT: effect on kidney function. Radiology 2008; 248:97-105.
26. Davidson C, Stacul F, McCullough PA, et al. Contrast medium use. Am J Cardiol 2006; 98:42K-58K.