

## IODINATED CONTRAST MEDIA CONSIDERATIONS IN BODY COMPUTED TOMOGRAPHY

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### INTRODUCTION

Iodinated agents are universally used for a variety of radiology examinations because they are water soluble and easy to administer intravascularly. Intravascular contrast media are administered to more than 6 million patients annually in the United States alone.<sup>1</sup>

Intravenous (IV) contrast material is an essential tool for computed tomographic (CT) scanning of the body. The ability to identify and characterize pathology in the liver, spleen, pancreas, and kidney is improved by the use of intravenous contrast media. Retroperitoneal structures are better defined by enhancement of the aorta and inferior vena cava, and the detection of iliac lymphadenopathy is improved by delineating the pelvic vessels with iodinated contrast media. The differentiation of disease in the chest, including the mediastinum and hilar regions, is best accomplished when IV contrast material is used.

Although the utility of iodinated contrast agents is not in question, there is no consensus as to the ideal method of injection when performing CT studies. IV contrast agents have been used in CT studies of the body for more than two decades, during which time there has continued to be evolution and controversy in injection protocols. In 1993 Dodd and Baron stated, "Despite nearly fifteen years of research it is hard to find more than a handful of radiologists who can agree on what constitutes the optimal method of contrast administration."<sup>2</sup> New developments, such as the introduction of multidetector row technologies, have further complicated the discussion. Research continues, with dozens of papers published each year looking at what factors produce optimal contrast enhancement.<sup>3-12</sup> However, currently no universally accepted proto-

cols exist.

Despite the still-raging controversy, there are some basic concepts that are generally accepted. They are: (1) rapid injection of contrast material, using a flow-controlled mechanical injector, is preferable to a drip infusion; (2) liver scanning must be completed before the equilibrium phase, and (3) the degree of parenchymal enhancement is directly related to the amount of contrast material administered.<sup>13</sup>

There are many important considerations in developing injection protocols. To obtain the best results, iodinated contrast media must be properly delivered in adequate concentration and volume. In addition, the timing of the scan delay must be adjusted for the region of interest as well as the scan time required by the specific CT system. For many examinations, the scan must be acquired as quickly as possible after the organs reach peak tissue enhancement. General recommendations for injection rates and delay often fail because of the considerable variability of intrinsic patient factors such as cardiac output, patient weight, renal function, state of hydration, and vascular access. The large number of variables requires that each examination be tailored to the patient. Specific clinical questions should be posed to optimize the examination.

This article begins with a review of basic features surrounding the use of iodinated agents in the CT department. From that point, specific components of injection protocols are examined, with special interest regarding how the total volume of a contrast agent is determined.

### BACKGROUND

Contrast agent administration varies significantly from other pharmaceuticals that are administered intravascularly. Unlike other medications, iodinated agents are not used for their therapeutic qualities, but rather, for their distribution and elimination from the body. The difference is even more dramatic when dose and delivery are considered. Therapeutic agents are given in very small quantities at regularly spaced intervals, whereas relatively large quantities of contrast media are typically given in a bolus lasting only a minute or two, with the intention of having no untoward physical effects. To illustrate the disparity, consider the use of

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morphine sulfate, given specifically to alleviate pain, at a typical dosage of 2 to 10 mg diluted in 4 to 5 mL of sterile water, and given at regular intervals of 4 hours. Compare this to iodinated contrast agents that are given in a typical dose of between 100 to 150 mL and often delivered in less than a minute. Because of these dramatic differences, guidelines for the use of other pharmaceuticals are of little value when applied to the use of IV contrast agents.

## THE UTILITY OF USING IODINE

In order to distinguish adjacent tissues on a CT image, the tissues must have different densities. These varying densities will result in distinct attenuation coefficients, which produce an image that clearly displays the different tissues.

In some parts of the body, such as the chest, subject contrast is inherently high. The pulmonary vessels and ribs have significantly different densities from the adjacent aerated lung, which allows easy identification on the image. Unfortunately, not all areas of the body possess this level of tissue contrast. Often, many tissues have quite similar attenuation coefficients. In addition, tumors and other disease processes may have attenuation coefficients that are very similar to their surrounding tissues. Contrast agents are used to enhance or create a difference in attenuation between neighboring structures. The goal is to make differing tissues readily visible on the image.

Iodine is particularly useful as a contrast agent because it has a relatively high atomic number (ie, 53). Adding an iodinated agent to the bloodstream will temporarily raise the atomic number of the blood, thereby increasing its beam-attenuating ability. This results in structures with an adequate blood supply appearing lighter than surrounding tissues.

The minimal visible detectable difference to identify normal versus pathologic tissue is 10 Hounsfield units (HU). Because different tissues often enhance differently, and because intravascular contrast material is handled differently in normal versus abnormal tissue, contrast agents can serve to widen the difference in attenuation. This difference often allows tissues, tumors, and disease processes to be more easily discernible. The proper administration of contrast media can easily provide a 40- to 75- HU difference, thus placing objects within the visibly detectable range.

## PHASES OF CONTRAST ENHANCEMENT

Three general phases of tissue enhancement are often described following the intravascular injection of iodinated contrast media. Although some variation in name and definition exists in the current literature, these

stages are most commonly called the *bolus phase*, the *nonequilibrium phase*, and the *equilibrium phase*. The difference between these phases is predominantly determined by: (1) the rate at which the contrast material is delivered and (2) the time that elapses between injection and scanning.

The phases can be evaluated using the arteriovenous iodine difference (AVID). This value is computed by obtaining a density measure in HU for the aorta and comparing it to that of the inferior vena cava.

The bolus phase immediately follows a bolus injection. This phase is characterized by an attenuation difference of 30 or more HU between the aorta and inferior vena cava. The nonequilibrium phase follows the bolus phase and demonstrates an AVID of 10 to 30 HU. The last phase is the equilibrium phase, in which the AVID is less than 10 HU.<sup>14</sup>

Optimally, scans should be performed at peak tissue enhancement. This point represents the period of greatest lesion detectability within the intra-abdominal organs. Debate exists regarding the exact time organs reach peak enhancement.<sup>3,5,6,9,11</sup> Despite the question over the ideal timing of scans following a contrast injection, it is commonly held that liver parenchyma should be abruptly elevated by at least 60 HU using a rapid bolus injection.<sup>3,5,8,9,14</sup> Scanning of the liver should be completed while the liver is held at this peak, which lasts only approximately 80 to 100 seconds. Incorporating a delay between the start of a contrast bolus and the initiation of scanning allows time for peak enhancement of both organs and vessels.

The coordination in timing of contrast administration and the start of liver scanning is crucial to enhance both portal vessels and hepatic veins. It is also essential that scans be completed before the equilibrium stage. In this last stage, some lesions will become isodense, which makes them indistinguishable from surrounding tissue. Figures 1A and 1B represent the same anatomic location in the same patient. Figure 1A was acquired when the liver was at peak contrast enhancement, whereas Figure 1B was taken when the liver had reached the equilibrium stage of contrast enhancement. Notice the lesions that are readily identifiable in Figure 1A are nearly invisible in the later stage image. For this reason, it is widely accepted that the equilibrium phase is the worst phase for acquiring body scans, particularly of the liver.



**FIGURE 1A.** *This scan was acquired with contrast at peak liver enhancement.*



**FIGURE 2A.** *This scan was acquired with contrast in the equilibrium phase.*

## SCAN DELAY TIME

The length of delay from injection to scanning depends on scanner speed, flow rate, and the phase of tissue enhancement desired.<sup>11</sup> Scan delay time is particularly important when assessing the liver and pancreas. It is generally agreed that scans should be performed within the window when the liver is at peak enhancement and avoided during the late equilibrium stage. However, there is considerable debate over when, within the peak enhancement window, scans should be obtained. Bader, et al<sup>11</sup> pointed out that, within the liver, hypovascular lesions, like many metastases, are most conspicuous during the hepatic portal venous phase of enhancement. Conversely, hypervascular primary and secondary neoplasms, which receive a large arterial blood supply, show the greatest contrast and conspicuity during the hepatic arterial phase (HAP) of enhancement. Bader et al<sup>11</sup> also pointed out that lesions that are predominantly hypervascular include hepatocellular carcinoma, metastases from endocrine tumors, thyroid, renal cell and breast carcinoma. Therefore, hypovascular lesions are best seen very early in the bolus phase, while hypervascular lesions benefit from a slight delay between injection and scanning. It is because of this dilemma, that Bader et al recommended biphasic scanning, with the first scan obtained during HAP and the second run done 30 seconds after

the first is completed.

Similarly, disagreement on injection protocols exists regarding the pancreas. Some author have shown improved tumor conspicuity during the venous phase of enhancement,<sup>15</sup> whereas other researchers have found no difference in detection rate between arterial-phase and venous-phase scanning.<sup>16</sup> Lu and coworkers<sup>17</sup> demonstrated maximum tumor-pancreas contrast during an intermediate phase, referred to as “pancreatic” contrast enhancement.

## INJECTION FLOW RATE

In the past, there has been considerable controversy regarding the choice of injection flow rate. Some researchers have reported that faster injection rates of contrast material result in higher peak liver enhancement,<sup>18,19</sup> whereas other researchers have concluded that incremental increases of the injection rate from 2 to 6 mL/sec had no effect on peak maximum liver enhancement.<sup>20,21</sup>

Newer studies have questioned the methodology of the earlier research. Critics point out that the older studies did not adequately take into account the many variables inherent in the clinical setting. More recent research has been carefully designed to overcome the pitfalls of the older studies. Garcia and coworkers reached the conclusion that, “Higher rates of injection shorten the time to peak liver enhancement but have no effect on maximum liver enhancement.”<sup>20</sup> Consequently, it is now generally accepted that absolute values for and times to peak pancreatic and hepatic enhancement are directly related to the contrast medium injection rate.<sup>6,11</sup>

It is now established that the rate of injection has a marked effect on the enhancement of CT images. However, the literature suggests a wide range of injection flow rates varying from 2 mL/sec to 6 mL/sec. This difference in recommendations can be, in large part, explained by the researcher’s clinical focus. In general, researchers who recommend higher rates are primarily interested in hepatic and pancreatic tumors,<sup>5,6,11</sup> whereas researchers focused on routine abdominal and pelvic CT typically recommend rates on the lower end of the spectrum.<sup>3</sup>

## CONTRAST VOLUME/CONCENTRATION

The beam attenuation abilities of contrast media are directly related to the concentration of iodine. Many concentrations are commercially available. Low osmolality agents are measured in milligrams of iodine per milliliter (mgI/mL) of solution, whereas high osmolality agents are measured in percent weight per volume. When comparing doses between different contrast concentrations and volumes, it is often useful to look at the total grams of iodine delivered. For instance, if 125 mL of an agent is used with a concentration of

240 mgI/mL, then a total of 30 g of iodine is delivered ( $125 \times 240 = 30,000 \text{ mg} = 30 \text{ g}$ ). Similarly, a total of 30 g of iodine can also be delivered using 100 mL of an agent with a concentration of 300 mgI/mL ( $300 \times 100 = 30,000 \text{ mg} = 30 \text{ g}$ ).

The results of two large quantitative studies showed that liver enhancement is directly related to dose.<sup>22,23</sup> A third study evaluated the relative effect of injection rate and volume of contrast medium on aortic portal and hepatic enhancement.<sup>6</sup> Conclusions from this study were: (1) an increase in peak aortic enhancement can be realized by increasing the injection rate, even when the total iodine load is decreased; (2) an increase in the rate of contrast injection does not increase maximum liver enhancement, which is instead related to the total iodine dose injected. Ultimately, researchers involved in this study<sup>6</sup> concluded that a decrease in iodine load cannot be compensated for by increasing the injection rate in contrast-enhanced CT of the liver.

Undoubtedly the dose of iodinated contrast is an essential component in producing examinations of consistently high quality. In most clinical practices, the dose used to perform body CT examinations on pediatric patients is calculated by weight. The most common formula used is 2 mL/kg. It is interesting to note that dose formulas are typically abandoned when it comes to scanning adults, and the same dose is given whether the patient is a 100-pound woman or a 350-pound man. Table 1 demonstrates the dose variation, as measured in mL/kg, when a uniform dose of contrast agent is given to all adult patients. In this example, a 100-pound woman would receive over 3 times the dose per kg as the 350-pound man.

An overdose of iodinated contrast media is possible. Deaths have occurred as a result of volumes of 250-300 mL of undiluted ionic media.<sup>24</sup> Due to the risk overdose, most injection protocols set an upper limit on the total volume of contrast media given, regardless of the patient's size. Individual factors, such as a patient's level of hydration, can influence what is a safe dose. Therefore, this upper limit is often quite cautious, typically 200 mL of an agent with a concentration of 320 mgI/mL (64 g)<sup>14</sup>.

**Table 1. Dose Variation When a Uniform Dose of Contrast Agent is Given to All Adult Patients**

Patient weight in kg (lb)	mL/kg with a uniform dose of 100 mL of 300 mgI/mL
46 kg (102.5 lb)	2.17 mL/kg
68 kg (149.6 lb)	1.47 mL/kg
91 kg (200.2 lb)	1.09 mL/kg
114 kg (250.8 lb)	0.88 mL/kg
137 kg (301.4 lb)	0.72 mL/kg
160 kg (352 lb)	0.63 mL/kg

It is difficult to understand how this practice became so well established. Do adult patients handle contrast agents identically, regardless of their size, thereby eliminating the need to adjust the volume? Or did the practice arise from the convenience of using the same dose, via pre-filled syringe, for each patient? Ultimately, the important question is whether this system is best for the patient. Are we underdosing the heavier patients and overdosing the lighter ones? Are we missing important diagnoses? Must examinations be repeated because the quality of the examination was less than ideal?

In a Japanese study,<sup>12</sup> the contrast enhancement of two patient groups was compared. The first group received 100 mL of contrast (300 mgI/mL) independent of patient weight; the second group was given 2 mL/kg. In both groups, contrast material was intravenously administered at a rate of 1.5 mL/sec. Spiral scanning commenced 90 seconds after the start of injection. CT numbers (HU) of the portal vein, hepatic parenchyma of the right lobe, and background were measured on pre- and post-enhanced images; the contrast-to-noise ratio (CNR) as well as increases in CT number of the right hepatic lobe and portal vein were calculated. In the first group, all measurements showed a negative linear correlation with the patient's weight. That is, as the patient's weight increased, the HU of the portal vein and liver, and the CNR declined. No such correlations were observed in the second group.

## MEGIBOW STUDY

A study by Megibow and coworkers<sup>10</sup> was even more enlightening. Because these researchers believed that previously published dose optimization studies provided conflicting conclusions, they created a study design that was unique in two ways. First, previous studies defined "exam acceptability" as a quantitative measure of peak hepatic dose during the data acquisition period. In the Megibow study, the term "acceptable" was defined in a both a qualitative and quantitative fashion. That is, participating radiologists were told that an acceptable study was one in which the overall quality of the study conformed to individual determinations of day-to-day scan quality. An unacceptable scan was defined as a study that might cause the radiologist to abandon the protocol under which the individual patient was studied; or in the extreme case, an unacceptable study might require the patient to return for a second examination. Like previous studies, the quantitative evaluation was based on the difference in HU between similar regions of interest in the unenhanced baseline images and the contrast-enhanced images. Second, in the Megibow trial the dose was based on volume per kilogram of body weight. The trial was performed to assess whether a minimal dose level exists that could produce clinically acceptable study images in most patients. The study was undertaken, in part, to learn if a cost savings could be realized by imple-

menting a weight-based dosing protocol.

The Megibow study included 463 patients at 6 clinical sites. The patients were randomized into one of four weight-based dose categories of 300 mgI/mL iodinated contrast agent: 1.25, 1.50, 1.75, and 2.0 mL/kg. All patients received the contrast agent IV via mechanical flow-controlled injection at a rate of 2.0 mL/sec. A maximum volume of 200 mL was agreed on at the initiation of the trial in the event that a patient weighing more than 100 kg was randomized to the 2.0 mL/kg group. Data acquisition began immediately after the prescribed volume of contrast medium was administered. Therefore, the scanning delay time varied, depending on the dose of contrast medium to which the patient was randomized.

A radiologist at each site determined whether the scans were acceptable without knowing what volume of contrast medium had been administered. Enhancement values (in HU) in regions of interest from the liver, pancreas, aorta, and kidney were obtained at a single time during the scan, although participating radiologists were unaware of these values. Additionally, three nonparticipating site observers (ie, sites that did not scan patients within the study protocol but only reviewed images) assessed the images for acceptability, diagnostic quality, and overall level of confidence.

The data were analyzed for each dose in total and by the individual clinical sites. The data were also analyzed after separating the patient into four weight categories:  $\leq 60$  kg, 61-79 kg, 80-99 kg, and  $\geq 100$  kg. HU differences were recorded at each dose level, overall, and within the four weight categories. The researchers also looked at differences in acceptability based on patient sex regardless of body weight. Finally, a cost model was developed comparing incurred charges associated with the weight-based dosing to those incurred with a standard dose of low osmolality contrast medium. The model was based on experience in an additional 303 patients where standard doses were used. This cost model compared the data from the study against standard contrast medium doses of 150 mL and 100 mL.

The results of the Megibow study found no clinically significant difference in acceptability of scans at doses greater than 1.5 mL/kg. Furthermore, when compared to using a standard dose of 150 mL, a significant cost savings can be realized using a weight-based dose. However, the cost was the same for 1.5 mL/kg or use of a standard dose of 100 mL of contrast medium.

It is interesting to note that acceptability was most affected in patients in the lowest weight category (ie, 60 kg or less) and given a dose of 1.25 mL/kg. This effect was not as significant in the other weight classification receiving the 1.25 dose. This phenomenon could possibly be explained by the scan delay, as opposed to the total volume used. As mentioned, the study was designed so that regardless of the dose given, the flow rate was held constant and scanning was initiated at the completion of the

injection. Therefore, in the dose category of 1.25 mL/kg, a patient weighing 50 kg would receive 62 mL of contrast with a scan delay of just 31 seconds. Perhaps this is not enough time for the contrast agent to reach peak enhancement at the injection rate of 2.0 mL/sec that was used in the study.

## OTHER RESEARCH

Other studies have been conducted that show that total contrast dose can be reduced and image quality improved when new software is used to determine the optimum scan delay time.<sup>7,8</sup> These software programs are used in conjunction with a spiral CT system that produces repetitive, low-dose test images to measure the attenuation (in HU) in a pre-selected region of interest. Once a defined HU threshold is reached a diagnostic spiral CT examination is begun automatically.

## CONCLUSION

A large number of intrinsic and extrinsic factors can affect the perfusion of iodinated contrast agents in the organs of the abdomen. Much can be learned from the many studies that have been undertaken to clarify the issues that surround the IV injection of iodinated contrast agents. Despite the wealth of research to date, many questions remain unanswered, which points to the need for continued investigations. Understanding the many variables and how they affect the CT image is the first step in designing and implementing successful injection protocols.

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## IODINATED CONTRAST MEDIA CONSIDERATIONS IN BODY CT POST TEST

Expires: July 15, 2009 Approved for 1 ARRT Category A Credit.

### 1. Iodinated agents are universally used in radiology because they are

1. chemically inert and therefore cannot cause an allergic response.
2. water soluble.
3. easy to administer intravascularly.
  - a. 1 only
  - b. 2 and 3
  - c. 1 and 3
  - d. 1, 2 and 3

### 2. Which is a TRUE statement concerning iodinated contrast agents?

- a. The utility of iodinated contrast agents remains a question.
- b. New developments, such as multidetector row technologies, have simplified the controversy regarding injection protocols.
- c. There are no generally accepted concepts when it comes to contrast media.
- d. Research continues in hopes of defining the factors that will produce optimal contrast enhancement.

### 3. Which of the following is NOT a generally accepted concept?

- a. Rapid injection of contrast material using a flow-controlled mechanical injector is preferable to a drip infusion.
- b. Scanning of the liver must be completed before the equilibrium phase.
- c. Flow rate must be 2.0 mL/sec, total volume 150 mL, and scanning must start 30 seconds following the start of the injection.
- d. The degree of parenchymal enhancement is directly related to the amount of contrast material administered.

### 4. General recommendations for injection rates and delay often fail because

- a. technologists do not follow injection protocols.
- b. of the considerable variability of intrinsic factors.
- c. scanners are not capable of acquiring scans during peak tissue enhancement.
- d. scans must be taken while organs are in the equilibrium phase and this requires too much time.

### 5. Factors considered intrinsic to contrast injection are

- a. flow rate and scan delay.
- b. patient's weight and cardiac output.
- c. brand and concentration of contrast agent.
- d. osmolality and temperature of the contrast agent.

### 6. Iodinated contrast agent administration varies from other pharmaceuticals in

1. the dose given.
2. the rate of delivery.

3. the reason for administration.

- a. 1 only
- b. 2 only
- c. 1 and 2
- d. 1, 2, and 3

### 7. In order to distinguish adjacent tissues on a CT image, the tissues must

- a. have different densities.
- b. have different functions.
- c. have sharply defined edges.
- d. be abnormal.

### 8. Adding an iodinated agent to the bloodstream will temporarily raise the atomic number of the blood, thereby

- a. providing a radioactive signal that can be measured.
- b. increasing its beam attenuation ability.
- c. inducing a magnetic moment.
- d. producing a small amount of x-ray that is recorded by the CT system's detectors.

### 9. The minimal visible detectable difference to identify normal versus pathologic tissue is

- a. 1 HU
- b. 5 HU
- c. 10 HU
- d. 75 HU

### 10. The difference between the bolus phase, the nonequilibrium phase, and the equilibrium phase of contrast enhancement is primarily determined by the

- a. brand of iodinated contrast agent that is used.
- b. injection rate and scan delay.
- c. type of pathology present.
- d. film processing time.

### 11. The arteriovenous iodine difference can be calculated by

- a. taking an HU measure of the liver before and after the contrast injection.
- b. comparing an HU measure of the pancreas to the liver.
- c. comparing an HU measure of the aorta to that of the inferior vena cava.
- d. dividing the concentration of iodine by the volume used.

### 12. Which is a TRUE statement regarding peak tissue enhancement?

- a. There is universal agreement as to the exact time that organs reach peak enhancement.
- b. Peak enhancement is the worst time for data acquisition and could actually disguise many tumors.
- c. The time required for tissues to reach peak enhancement is not affected by the flow rate, volume of contrast used, or scan delay.
- d. Peak tissue enhancement represents the period of greatest lesion detectability within the intra-abdominal organs.

**13. The liver can be held at peak enhancement for approximately**

- a. 5 to 10 seconds.
- b. 80 to 100 seconds.
- c. 5 to 8 minutes.
- d. 12 to 15 minutes.

**14. The equilibrium phase of contrast enhancement**

- a. is the phase that immediately follows a bolus injection.
- b. is the worst phase for acquiring body scans, particularly of the liver.
- c. occurs when the liver is at peak contrast enhancement.
- d. is characterized by an arteriovenous iodine difference of 30 or more.

**15. For body CT, the range of suggested flow rates is typically**

- a. 0.2 mL/sec to 0.5 mL/sec
- b. 1.0 mL/sec to 2.0 mL/sec
- c. 2.0 mL/sec to 6.0 mL/sec
- d. 15 mL/sec to 23 mL/sec

**16. The contrast medium injection rate affects the**

1. absolute values for peak pancreatic and hepatic enhancement.
2. time to peak hepatic enhancement.
3. time to peak pancreatic enhancement.
  - a. 1 only
  - b. 2 only
  - c. 2 and 3
  - d. 1, 2, and 3

**17. The length of delay from injection to scanning depends on**

1. scanner speed.
2. flow rate.
3. phase of tissue enhancement desired.
  - a. 1 only
  - b. 1 and 2
  - c. 2 and 3
  - d. 1, 2, and 3

**18. If 100 mL of an agent is used with a concentration of 320 mgI/mL, then what is the total amount of iodine given?**

- a. 0.32 gm
- b. 3.2 gm
- c. 32 gm
- d. 320 gm

**19. A common dose for pediatric patients is**

- a. 100 mL.
- b. 0.2 mL/kg.
- c. 1 mL/kg.
- d. 2 mL/kg.

**20. Megibow and coworkers concluded that**

- a. there was no measurable benefit in acceptability of scans at doses greater than 1.5 mL/kg.
- b. a standard dose of 150 mL is cost effective.
- c. weight should not be used to determine contrast dose.
- d. optimal scans resulted from a dose of 2.5 mL/kg.

