Title

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Journal

Radiology, 283(3)

ISSN

0033-8419

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Publication Date

2017-06-01

DOI

10.1148/radiol.2017170611

Peer reviewed

Radiology

The Effect of Iodine-based Contrast Material on Radiation Dose at CT: It's Complicated[1]

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In articles published in this issue, Sahbaee and colleagues (1,2) describe their research on the radiation dose consequences when an iodine-based contrast agent is used during a computed tomographic (CT) examination. This research had two parts, and in the first part, the authors describe an elegant, anatomically sophisticated model of the circulatory system through the human body (1). This model allows a realistic depiction of the flow of iodine through the vascular system and can allow prediction of time-density curves for each organ included in this comprehensive model. The second article is about the use of this vascular model to estimate the radiation dose levels both with and without vascular contrast agent by using Monte Carlo techniques (2). The results suggest that the presence of iodine increases radiation dose slightly and to different extents among various organs, with the largest dose increases seen in the kidney and heart.

These studies were well performed, and the results are provocative, but we suggest that there are limitations to all modeling studies and that the results should be considered as only the first chapter in a much longer story about the role of contrast agents on radiation dose at CT. In this editorial, the complications of microdosimetry issues involving the role of iodine-based contrast agents are discussed. On the basis of these observations, we suggest that the dose-enhancement factors described in the second part of Sahbaee et al (2) are probably overestimates.

Implants and Foreign Bodies

When a radiologist evaluates an abdomen-pelvis CT examination of a patient with a metal hip replacement, the metal implant appears bright on the image. Clearly the CT numbers (in Hounsfield units) associated with that metal implant are high, because it is highly attenuating, and it is fair to say that a large amount of the x-ray energy emitted from the CT scanner was absorbed in that implant. Since absorbed dose is the quotient of absorbed energy divided by mass, the dose in the implant is high as well. However, no one would argue that this high dose to the implant has significant biologic consequence to the patient, because the dose was imparted to inert metal and not to biologic tissue. Other metallic implants such as pacemakers or neural stimulators have a similar effect, as do surgical pins and bullet fragments.

Injected iodine-based contrast agent also results in high CT values, and thus the radiation from the CT scanner interacts strongly with iodine as well. Similar to the metal hip implant, iodine is an inert element, and the contrast agent molecules will be eliminated from the body through urination shortly after the CT scan is performed. Essentially, the iodine-based contrast agent is a transient metal implant. So, from the 30 000-foot view, it would appear that radiation absorption in iodine should cause no biologic harm, because it is not biologic (ie, in the context of this discussion, this just means that it does not contain replicating DNA) and only temporarily resides in the body. This viewpoint will be refined later in this article.

Tube Current Modulation

Most modern CT protocols make use of tube current modulation techniques, whereby the tube current is increased to accommodate greater attenuation between the x-ray tube and detector, or it is decreased to accommodate a shorter tissue path. Tube current modulation is an important tool that should be used for radiation

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Study supported in part by grants from the National Institutes of Health (P30 CA093373 and R01 CA181081).

dose reduction in many CT protocols. In some CT scanners, when a large iodine-filled vessel is present during a scan, the tube current is increased to accommodate the additional attenuation of the contrast agent. This is not the topic of the Sahbaee et al part 2 article—the focus is on the dose with the same technique factors (eg, kilovoltage, milliamperage, rotation time, pitch), with and without iodine in the vessel, and this is because the authors properly normalized the results according to the CT scanner output (volume CT dose index).

Energy Deposition and Radiation Dose

If you drink a hot cup of coffee or sit in a hot tub for a few minutes, your body temperature will become slightly elevated. Your body has absorbed the heat energy with which it has come in contact. If this same amount of absorbed energy was in the form of x-rays, it would represent a lethal radiation dose. Why? Thermal energy is distributed broadly over large masses of tissue and causes excitation of electrons, but, in general, this excitation is not sufficient to cause ionization. X-rays, on the other hand, interact at the subatomic scale through direct interactions with electrons and atomic nuclei. The deposition of energy at such a small spatial scale pinpoints the energy deposition to electrons so that they are liberated from the bonds to their parent atom—the very definition of ionization. The energetic electrons produced by x-ray interaction can interact with other electrons along their trajectory, causing additional ionization. These secondary electrons are referred to as delta rays. The weak carcinogenic effect that may be associated with x-ray exposure in medical imaging examinations is due to the ionization of atoms in tissue, leading to single- and double-strand breaks in DNA. While breaks in DNA are often repaired, occasionally they are misrepaired, and this is thought to be the origin of radiation-induced cancers.

While x-rays can penetrate several tens of centimeters through tissue, electrons have a much shorter range—on the order of 15–100 μm (3), depending on their energy. The extremely short range of electrons and delta rays creates an interesting but complicated situation with respect to dose distribution, since virtually all radiation dose imparted from an x-ray beam is delivered by electron interactions, as we have described. Because of the extremely short range of electrons, proximity matters greatly. Therefore, the shape of a highly attenuating object such as a hip implant or iodinated vessel has a huge effect on the radiation dose to a DNA target. But before we address shape, since the focus is on intravascular iodine-based contrast material, we will briefly discuss the contents of blood.

What is in a Blood Vessel?

The primary constituents of blood are plasma, red blood cells, and white blood cells (4). Plasma represents 55% of the blood volume and is composed of 92% water, along with proteins, minerals, hormones, sugars, and other compounds; none of these components include DNA. Red blood cells make up approximately 45% of whole blood by volume; red blood cells do not have nuclei and do not contain somatic DNA. White blood cells make up approximately 0.7% of blood volume and consist of a wide range of cell types, most of which do not contain somatic DNA. The point is, unlike parenchymal tissue in the body (eg, in the liver or kidney), blood is largely (but not completely) devoid of replicating DNA, and therefore, there is very little biologic effect from ionization events that occur within blood vessels. Thus, for electrons generated by x-ray interaction with vascular contrast agent to produce significant DNA damage, the electrons must propagate beyond the vascular compartment and reach extravascular soft-tissue cells.

Shape Matters

Spheres are shapes that occur frequently in nature, for instance, bubbles in a bathtub or raindrops falling from the sky. Spheres are unique geometric shapes, because they require the smallest amount of surface area to enclose a given volume. A very narrow 5-μm diameter cylinder, such as that used to model an iodine-filled capillary in Sahbaee et al study (2), has a much higher surface area–to-volume ratio compared with a sphere or even a larger-diameter cylinder (eg, an artery or vein). The surface area–to-volume ratio of a vessel is a key parameter pertaining to the microdosimetry of iodine dose enhancement. For example, let us assume that the range of electrons produced by a 120-kV CT x-ray beam averages approximately 20 μm. The effective energy of a 120-kV CT x-ray beam (10-mm Al filtration) is approximately 63 keV (5). A 63-keV x-ray photon interacting with an iodine atom will eject a (K-shell) photoelectron with approximately 30 keV of kinetic energy, since 33 keV is required to overcome the K-shell binding energy of iodine (ie, 63 keV – 33 keV = 30 keV). The range of a 30-keV electron in soft tissue is 18 μm, and we round this to 20 μm (3). In a simplified example for a vessel with a diameter of 5 mm, only electrons produced in the thin 20-μm layer at the very edge of this vessel could propagate into the soft tissue outside of the vascular volume. In reality, only approximately half of the electrons in this surface layer would be directed outside the vessel volume; the other half would be directed inwards and would not reach the intima and other extravascular soft tissue. This 20-μm peripheral layer constitutes less than 2% of the volume of a 5-mm diameter vessel, approximately 4% of the volume of a 2-mm diameter vessel, and still only 8% of the volume for a 1-mm diameter vessel. This example demonstrates how a vessel with

Published online
10.1148/radiol.2017170611 **Content code:** PH
Radiology 2017; 283:624–627

See also the articles by Sahbaee et al in this issue.

a diameter of 5 μm, as modeled in the article by Sahbaee et al (2), represents a worst-case scenario in terms of iodine dose enhancement, where 100% of the electrons would have access to the extravascular space. Since less than 10% of the blood volume in a human (6) resides in capillaries (54% in small vessels, 31% in large vessels, and another 7% in the heart), use of the 5-μm model for the entire vasculature overemphasizes the dose enhancement to extravascular tissues compared with that derived if a more realistic, heterogeneous vessel-size distribution model were used.

Characteristic Radiation

After x-ray interaction with an iodine atom occurs, in addition to the ejection of an electron as discussed above, a characteristic x-ray photon is emitted as the charge and energy balance in the ionized iodine atom are reassumed. This x-ray photon is approximately 30 keV (the $k_{\alpha 1}$, $k_{\alpha 2}$, $k_{\beta 1}$, and $k_{\beta 2}$ emissions span the energy range from 28.3 to 33.05 keV) and has a median range in tissue of approximately 18.5 mm, defining a ping pong ball–sized sphere in which 50% of the x-rays interact in tissue (and produce more energetic electrons). These fluorescent x-ray photons will deposit a diffuse pattern of radiation dose in tissue surrounding the original interaction site. This is a mechanism for x-ray interactions in vascular iodine to deposit the dose in tissues outside all but the larger vessels; however, the total fluorescent energy is less than half of the kinetic energy imparted to electrons when a 120-kV x-ray spectrum is considered.

It's Complicated

Many factors must be considered in determining whether the presence of iodine-based contrast agent increases or decreases the radiation risk to patients. In this editorial, we have argued that the dose to iodine atoms and to the constituents of blood inside the vascular space has significantly less biologic effect, because there is a limited amount of DNA in blood compared with that in extravascular soft tissues. Further, vessel diameter has an order-of-magnitude influence on radiation dose to extravascular tissue. Many other factors such as the temporal delay between contrast material injection and scanning, the anatomic area that is scanned, the x-ray tube potential, the pattern of dose deposition by means of x-ray fluorescence, and other factors will influence the dose-enhancement factor of iodine.

It is also imperative in radiation dose studies that the heterogeneity of tissue in the body be considered—not just differences in x-ray interaction probabilities—but differences in biologic effect. Radiation deposition in inert materials in the body, which include metal implants, injected vascular contrast agent, cortical bone minerals, urine in the bladder, feces in the intestines and rectum, and most blood components must be considered accurately and realistically if accurate radiation risk estimates are to be produced. This is especially true considering the huge proximity effects of ionizing radiation, where tissue heterogeneity must be considered at spatial resolutions on the scale of the range of the electron (10–20 μm). This is not an easy task in computer modeling or Monte Carlo simulations.

An x-ray beam that strongly interacts with iodine in the 25-mm diameter abdominal aorta is reduced in intensity distal to the aorta, producing an x-ray shadow that reduces dose to those tissues. Because the source rotates around the patient, this shadow rotates as well, and, in fact, all tissues in the same axial plane as the contrast material–filled aorta experience this downstream shadow effect during the scan. If the higher deposition of dose in the aorta has less biologic effect because of the inert nature of iodine and the low DNA content of blood in this large-diameter vessel, the DNA-rich tissues in the x-ray beam shadow will receive a lower dose; and in this scenario, the role of contrast agent may, in fact, reduce radiation risk by redirecting the absorbed dose to less biologically sensitive regions of the body.

What we have discussed is the observation that iodine-based contrast material and its role in increasing the dose of a contrast material–enhanced CT examination is complicated. While "dose" can be accurately quantified in Monte Carlo studies, where this dose is deposited and how it leads to biologic harm requires a more nuanced understanding of the radiosensitivity of biologic and nonbiological structures in the body at high spatial resolution. A slight increase in radiation risk when a contrast agent is used at CT should also be placed in a larger clinical context, which includes the tiny risk of acute contrast material reaction and the long-term effect on kidney function. In the end, the use of iodine-based contrast material adds considerable diagnostic information in many CT examinations, and this benefit must be weighed in the clinical setting against a number of risks associated with the use of iodine-based contrast agents.

Summary

Sahbaee et al have underscored the importance of considering the role of injected contrast material on radiation dose at CT. While their study likely defines the extreme upper bounds of dose enhancement when intervascular iodine contrast material is used at CT, iodine does produce a slight enhancement in dose deposition locally to vascular structures in the body. Given that, on average, more than 200 000 CT scans are performed in the United States each day, the studies by Sahbaee et al should serve to stimulate continued research into the microdosimetry methods and models required to understand the biologic effect and potentially increased radiation risk when iodine-based contrast agents are used.

Disclosures of Conflicts of Interest: J.M.B. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: travel fees as officer of the American Association of Physicists in Medicine, personal fees as consultant for Canadian Organization of Radiologists, royalties from Wolters Kluwer, patent for Breast CT technology. Other relationships: disclosed no relevant

relationships. **A.M.H.** disclosed no relevant relationships.

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