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### Abstract

**Background** The contributing effect of contrast media iodine dose on radiation-induced DNA damage in blood lymphocytes during a cardiac CT scan is still unclear. **Methods** This prospective minipig study was approved by the institutional animal care committee. The minipigs were in total 12 times exposed to a fixed cardiac CT scan protocol. A non-contrast, and two contrast injection protocols were considered, the latter with 50% saline diluted (160 mgI/mL) and standard iodixanol. Blood samples were collected, before and after the CT, and radiation-induced DNA double-strand breaks were assessed using  $\gamma$ H2AX immunofluorescent staining of the blood lymphocytes. Significant differences in foci numbers were investigated with an independent sample t-test. In addition, a numerical dosimetry model was applied that simulates the cardiac CT scan with the heart represented by a blood volume containing a mixture of 6 iodine concentrations (0-10-20-30-40-50 mgI/mL). **Results** Compared to the non-contrast enhanced (0 mgI/mL) protocol, the number of  $\gamma$ H2AX foci/cell increased significantly with 56% and 141.1% ( $p < 0.038$ ) for the reduced (160 mgI/mL) and standard iodine dose (320 mgI/mL) protocol, respectively. These in vivo results are confirmed by the dosimetry simulation model, a 78.8% and 133.7% increase in locally absorbed blood dose in the left ventricle were observed for the reduced and standard iodine dose protocol, respectively. **Conclusion** Administration of contrast media during a cardiac CT examination significantly increases radiation-induced DNA damage in blood lymphocytes. Moreover, a lower contrast media iodine dose results in a reduced level of DNA damage, at constant radiation exposure.

<b>Keywords</b>	Cardiac CT; Iodinated contrast media; Patient safety; Radiation-induced DNA damage; Minipigs
<b>Taxonomy</b>	Computed Tomography, Physics, Radiation
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# **The iodine dose of administered contrast media determines the level of radiation-induced DNA damage during cardiac CT scans**

Short title: Iodine dose impact on x-ray induced DNA damage in CTA

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## **Abstract**

### **Background**

The contributing effect of contrast media iodine dose on radiation-induced DNA damage in blood lymphocytes during a cardiac CT scan is still unclear.

### **Methods**

This prospective minipig study was approved by the institutional animal care committee. The minipigs were in total 12 times exposed to a fixed cardiac CT scan protocol. A non-contrast, and two contrast injection protocols were considered, the latter with 50% saline diluted (160 mgI/mL) and standard iodixanol. Blood samples were collected, before and after the CT, and radiation-induced DNA double-strand breaks were assessed using  $\gamma$ H2AX immunofluorescent staining of the blood lymphocytes. Significant differences in foci numbers were investigated with an independent sample t-test. In addition, a numerical dosimetry model was applied that simulates the cardiac CT scan with the heart represented by a blood volume containing a mixture of 6 iodine concentrations (0-10-20-30-40-50 mgI/mL).

### **Results**

Compared to the non-contrast enhanced (0 mgI/mL) protocol, the number of  $\gamma$ H2AX foci/cell increased significantly with 56% and 141.1% ( $p < 0.038$ ) for the reduced (160 mgI/mL) and standard iodine dose (320 mgI/mL) protocol, respectively.

These *in vivo* results are confirmed by the dosimetry simulation model, a 78.8% and 133.7% increase in locally absorbed blood dose in the left ventricle were observed for the reduced and standard iodine dose protocol, respectively.

## **Conclusion**

Administration of contrast media during a cardiac CT examination significantly increases radiation-induced DNA damage in blood lymphocytes. Moreover, a lower contrast media iodine dose results in a reduced level of DNA damage, at constant radiation exposure.

## **Key words:**

Cardiac CT; Iodinated contrast media; Patient safety; Radiation-induced DNA damage; Minipigs

## Abbreviation list

Bpm	Beats per minute
CCTA	Coronary CT angiography
CM	Contrast media
CTDI <sub>vol</sub>	Volume computed tomography dose index
DRL	Dose reference level
DSB	Double-strand break
HU	Hounsfield unit
HR	Heart Rate
NCE	Non-contrast enhanced
PAC	Port-a-cath
SD	Standard deviation

## 1. Introduction

For more than a century, patients are exposed to x-rays in the context of medical imaging. The major contributor to this radiation exposure is CT imaging [1-2]. Stochastic effects after exposure to these diagnostic radiation doses are investigated in large scale and long-term epidemiologic patient studies [3-4]. In another approach, radiation dose impact can be investigated using biomarkers such as DNA double-strand breaks (DSB) to predict cell fate or risk of cancer development [5-7]. These DSBs can be quantified using a  $\gamma$ H2AX immunofluorescent assay, allowing to investigate the relation between radiation dose and the amount of induced DNA damage [8-10].

In CT imaging, the administration of iodine based contrast media (CM) is essential for soft tissue differentiation. They are designed to increase the absorption of x-ray photons and enhance image contrast of blood vessels and well perfused tissues. Although these contrast media are frequently used in medical practice, there is an ongoing discussion about their side effects and the dose dependent incidence of contrast-induced nephropathy [11-13].

In addition, there is an ongoing debate on the impact of these iodinated CM on radiation-induced DNA damage with contradictory results [14-18]. Some CT studies report significantly higher levels of DNA DSBs as a result of the presence of CM both *in vitro* as *in vivo* [14-16]. They hypothesize that the increase of X-ray absorption in the iodinated blood yields an increased local dose deposition by secondary electrons generated by the photoelectric effect. However, other groups with an *in vitro* approach, reported no impact of CM on radiation-induced DNA damage [17-18]. In addition, no publications exist that investigate the effect of the amount of

administered CM on DNA damage. We hypothesize that a reduced amount of CM causes a lower level of DNA damage.

Our study aims to estimate the impact of the administered CM dose on radiation induced DNA DSBs in blood lymphocytes by injecting two iodine dose levels during contrast enhanced cardiac CT scans. These results were compared to the amount of DNA damage from non-contrast enhanced cardiac CT scans with equal scan parameters and radiation dose. This was investigated using an *in silico* Monte Carlo simulation model and an *in vivo* minipigs model. Monte Carlo simulations are computational methods that allows modeling of photon transport to investigate x-ray interaction processes and to determine the radiation dose to the patient [19-20]. In this study, they are performed to determine the absorbed radiation dose in the exposed blood volume of the minipigs. This animal model has similar anatomy, heart function and blood circulation compared to humans [21-23].



## 2. Methods

### 2.1 Monte Carlo simulation study

Simulations of a cardiac-chest CT were performed using the Monte Carlo transport code MCNPX (LANL) [24]. A simple virtual minipig chest model was designed with water, air and a blood-iodine mixture, respectively representing the thorax wall, lungs and heart. Six blood-iodine concentrations were considered: non-contrast enhanced (NCE) CT (0 mgI/mL) and a range of clinical to high iodine concentrations (10-20-30-40-50 mgI/mL). Both X-rays (100-120 kVp) and gamma rays ( $^{137}\text{Cs}$  with 662 KeV and  $^{60}\text{Co}$  with 1250 KeV) were simulated (Table 1), to investigate the relative contribution of the photo-electric effect [15]. The energy deposited in each volume was normalized to air Kerma. The attenuation coefficient of iodine and blood and the percentage absorbed dose caused by the photoelectric effect for the two x- and gamma rays were obtained from the National Institute of Standard and Technology (NIST) [25] are listed in table 1. Furthermore, the effective atomic number ( $Z_{\text{eff}}$ ) in the blood-iodine mixture for the different iodine concentrations was calculated, following Spiers [26].

### 2.2 *In vivo* study

Prospective study approval was granted by the institutional animal care committee. Two Göttingen minipigs (Ellegaard) with a mean weight of  $41.2 \pm 4.7$  kg were included in the study. Both minipigs were equipped with a port-a-cath (PAC) unit (Power PAC II, Smiths Medical), for controlled and reproducible CM injections. Anaesthesia was induced by an intramuscular injection of an anaesthetic cocktail (500 mg Zoletil-100, 6.25 mg Rompun, 1.25 mL Ketamine and 2.5 mL Dolorex) at a dose of 0.05 mL/kg. Cardiac CT scans were acquired with a fixed scan protocol on a 256 slice CT

(Revolution CT, GE Healthcare) 16 cm coverage axial mode, 100 kVp, 0.35s rotation time and an extended cardiac phase (0-300%) to increase the irradiated blood volume and the radiation dose ( $CTDI_{vol} = 40.8 \pm 3.9$  mGy) (table 2). A non-contrast, and two contrast injection protocols were considered, the latter with 50% saline diluted (160 mgI/mL) and standard iodixanol (Visipaque 320 mgI/mL, GE Healthcare). The two pigs were in total randomly subjected four times to each of the protocols, resulting in 12 acquisitions. An inter-scan delay of one week was respected to avoid an iodine retention bias [27].

### 2.3 Blood sample processing

Before and 15 minutes after each CT scan, blood samples (5 mL) were collected in heparin-containing vials and immediately stored on ice to inhibit all DNA repair activity. Lymphocyte separation was performed according to the Lymphoprep™ solution manufacturer's instructions (Axis-Shield). The isolated lymphocytes were fixed for 10 minutes in 4% formaldehyde and permeabilised for one hour with 0.1% Triton X-100 (Thermo Fisher Scientific) in 3% BSA (Sigma-Aldrich). Samples were incubated overnight with a 1:1000 dilution of the primary rabbit antibody, anti- $\gamma$ H2AX (Abcam) at 4°C. The next day, the samples were incubated with a 1:300 dilution of the secondary antibody, goat anti-rabbit Alexa Fluor 488 antibody (Invitrogen) for 1 hour at room temperature. Also 1:300 dilution of Hoechst stain was added as a background staining. Finally, the samples were mounted with ProLong™ Gold Antifade Mountant (Thermo Fisher Scientific). An Olympus IX81 microscope and CellSens software were used to capture images of all samples. The number of  $\gamma$ H2AX foci on these images was quantified using ImageJ [28] and FociCounter [29] software. Blind sample processing was done for each scan until an average of 500 lymphocytes were analyzed.

## 2.4 Locally absorbed blood dose

The Monte Carlo results were used to calculate locally absorbed blood dose by: 1) mean CT signal measurement in ROI in the left and right ventricle and the aorta in the CT images. 2) conversion of CT signal to iodine concentration by CT scanner specifications with formula (mg iodine per mL=(CT value-26.996)/25.662), obtained from 100 kVp phantom experiments following Buls et al [27]. 3) Conversion of iodine concentration to absorbed blood dose based on Monte Carlo results, using linear extrapolation.

## 2.5 Statistical and data analysis

The presence of correlations was investigated using a Bivariate Pearson Correlation test. Statistical differences in mean numbers of  $\gamma$ H2AX foci and absorbed blood dose were investigated with an independent sample *t*-test, after checking the assumptions. All statistical calculations were performed with SPSS software (SPSS) and differences were considered to be significant *with p*-values smaller than 0.05.

### 3. Results

#### 3.1 Monte Carlo simulation study

The absorbed dose per air kerma in the blood-iodine compartment for the different photon energies and iodine concentrations is displayed in figure 2. A significant increase in absorbed dose is observed with increasing iodine concentrations (Pearson correlation  $p$ -values  $< 0.0001$  for both 100 and 120 kV). With gamma rays, only a marginal increase in absorbed dose of 4% and 1%, for  $^{137}\text{Cs}$  and  $^{60}\text{Co}$ , respectively, is observed. The calculated effective atomic number in the blood-iodine compartment of the different iodine concentrations is displayed in figure 3. By adding iodine to the blood compartment, the effective atomic number ( $Z_{\text{eff}}$ ) increases from 7.7 in the absence of iodine to 11.1 for the reduced (8.7 mgI/mL) and 13.8 for the standard (18.2 mgI/mL) iodine dose protocol of the *in vivo* experiments (concentrations derived from mean CT measurement of the left ventricle). In contrast with the blood-iodine compartment, an increase in iodine concentration resulted in a small but significant decrease in absorbed dose in the air (6,8% for both 100 and 120 kV,  $p=0.003$ ) and water (4,4% for both 100 and 120 kV,  $p=0.029$ ) compartment (Figure 4).

#### 3.2 *In vivo* study

The mean  $\gamma\text{H2AX}$  background (pre-CT samples) is 0.06 foci/cell, with no significant difference between the three groups ( $p>0.261$ ) (figure 5 and table 4). In the post-CT samples, a significant increase in the number of  $\gamma\text{H2AX}$  foci/cell was observed for the standard ( $0.158\pm0.035$  foci/cell,  $p$ -value of 0.001) and reduced ( $0.102\pm0.026$  foci/cell,  $p$ -values of 0.038) iodine dose protocols compared to the NCE protocol ( $0.066\pm0.009$  foci/cell). Also, a significant increase in mean  $\gamma\text{H2AX}$  foci/cell was observed when the

standard protocol was compared to the reduced iodine dose protocol ( $p=0.035$ ) (figure 6).

### 3.3 Locally absorbed blood dose

Locally absorbed blood dose was calculated based on CT enhancement and results of the Monte Carlo study (Table 5). The mean CT signal in the left ventricle was  $249.4 \pm 30.2$  HU and  $493.9 \pm 37.7$  HU for the reduced and standard iodine dose protocol, respectively corresponding to an iodine blood concentration of  $8.7 \pm 0.12$  mgI/mL and  $18.2 \pm 0.42$  mgI/mL. At these iodine levels, a significant increase in absorbed blood dose of respectively  $78.8 \pm 16.3\%$  ( $p=0.002$ ) and  $133.7 \pm 18.7\%$  ( $p=0.001$ ) compared to the absorbed blood dose of a simulated NCE CT scan. Similar results were obtained for the right ventricle and aorta. The relative increase in  $\gamma$ H2AX foci numbers between the two considered injection protocols were also calculated (Table 5).

#### 4. Discussion

This study investigated the impact of different CM iodine dose levels on radiation-induced DSBs after a cardiac CT scan in a Monte Carlo and porcine model. The results of the Monte Carlo model indicate that the absorbed dose in the blood-iodine mixture of the heart increases with higher iodine concentrations (Figure 2). This increase in absorbed blood dose with higher iodine concentrations created a dose shadow in the surrounding air and water volumes, decreasing the absorbed dose with 6.8% and 4.4%, respectively (Figure 4). By adding iodine to the blood compartment, the effective atomic number ( $Z_{\text{eff}}$ ) increases (Figure 3) with 42.9% and 78.3% for the reduced and standard iodine dose protocol compared to the NCE protocol of the *in vivo* experiments. These higher  $Z_{\text{eff}}$  levels implicate an increase in attenuation coefficient and contribution of the photoelectric effect to the absorbed dose, especially for the photon energies used in CT imaging (Table 1) [30]. The dominance of this photoelectric effect is confirmed by the marginal increase of 4% and 1% in absorbed dose, for high energy gamma rays of  $^{137}\text{Cs}$  and  $^{60}\text{Co}$ , which are outside the energy window of the photoelectric effect.

The results of the *in vivo* study showed a relative increase of 56.1% and 141.1% in  $\gamma\text{H2AX}$  foci/cell after a contrast enhanced CT scan with the reduced and standard iodine dose protocol compared to the NCE protocol. Also, a 54.5% increase in  $\gamma\text{H2AX}$  foci per cell was observed with the standard compared to the reduced iodine dose protocol. These significant increases in  $\gamma\text{H2AX}$  foci with increasing iodine dose can be explained by the higher levels of secondary electrons generated with each photoelectric interaction [16]. When combining the Monte Carlo with the *in vivo* study results by calculating the relative *in vivo* absorbed blood dose, we found an increased absorbed blood dose in e.g. the left ventricle of 78.8% and 133.7% for the

reduced and standard iodine dose protocol, respectively, compared to a simulated NCE CT scan.

Both results of the Monte Carlo and *in vivo* study confirm the findings of previously published studies reporting an increase in DNA damage in blood lymphocytes in the presence of iodine compared to NCE CT [14-16]. Moreover, our study adds that the level of DNA damage depends on the amount of administered CM dose. Dissimilarity with results of Beels et al (17) and Jost et al (18), who found no effect of CM on DNA damage, can be due to differences in study design. Both groups investigated the impact of iodine on radiation-induced DNA damage in *in vitro* blood samples in which the cellular response on radiation-induced DNA damage can be different compared to *in vivo* exposed blood lymphocytes.

Iodinated CM are generally considered to be safe and among the most commonly prescribed agents in current medical practice, with more than 30 million doses administered annually [11]. Still there is controversy on the side effects caused by contrast media. Several studies reported cytotoxic and nephrotoxic side effects of CM, although recently some studies reported no increased risk of contrast media-induced nephrotoxicity [11-13]. In absence of radiation, CM have no direct effect on DNA damage [15]. Considering these data and the impact of iodinated CM on radiation-induced DNA damage, a conservative approach on the administered iodine dose is advised in the context of patient safety.

Reported *in vivo* studies on the impact of iodine based CM on radiation-induced DNA damage are based on patient studies [14-16]. A limitation of studying this effect in a patient population is to assess the impact of multiple parameters on the results: medical history of the patient, irradiated blood volume, iodine concentration in

exposed blood volume, physiology of the patient, inter-individual differences in DNA repair capabilities, ... [14-16]. All these variables are controlled in our porcine model offering the opportunity to consider the impact of iodine within one subject, eliminating the inter-patient variability bias of a patient study. This allows us to study the net effect of the iodine dose on the radiation-induced DNA damage in a clinical setting. It would be unethical to perform such a within subject study design with patients. Moreover, the reproducibility of the injection protocols was maintained by equipping the minipigs with a PAC unit. Göttingen minipigs have been reported as a suited animal model for  $\gamma$ H2AX-based dosimetry with a comparable radiation sensitivity to humans [21]. Nonetheless, validation of the results in humans is still necessary.

Our study has some limitations. First, the higher radiation dose compared to clinical doses. The  $CTDI_{vol}$  ( $40.8 \pm 3.9$  mGy) is high compared to recently published radiation doses (4.6-10.3 mGy) [31] but still well within the range of reported dose reference levels (DRLs) (26-70 mGy) [32] in coronary CT angiography (CCTA). In the blood circulation, the irradiated blood volume is mixed with non-irradiated blood, 'diluting' the observable number of  $\gamma$ H2AX foci. From the segmented blood volume and cardiac output, determined from the CT scan images, we estimate that 20.7% of the total blood volume of the minipig is irradiated. This can be different compared to the irradiated blood volume of a standard sized cardiac CT patient. For example, from the segmented blood volume of a clinical CCTA of a 70 kg male patient (HR: 60 bpm), we estimate that the irradiated blood volume is 12% of the total blood volume.

The biological impact of the radiation-induced DNA DSBs in blood lymphocytes is limited, due to the high turn-over rate of blood cells. In our study we quantified DNA DSBs in blood lymphocytes because they are readily accessible with minor



discomfort to the minipigs. They can also be used as a biomarker for biological effects after radiation exposure [14]. Being present in the blood pool, the lymphocytes are exposed to higher iodine concentrations compared to cells of solid organs like liver tissue.

## **5. Conclusion**

We observe that DNA DSB levels in blood lymphocytes increases with the administered iodine dose during a contrast enhanced CT scan. Conventional patient dosimetry, based on the estimated radiation dose from the radiologic device, does not take this synergistic effect of radiation -and iodine dose on DNA damage into account. An individual patient dosimetry model based on  $\gamma$ H2AX foci as a biomarker for the radiation-induced DNA damage or an iodine dose based coefficient to correct for the underestimation of the radiation dose might be a more suitable approach. Given the debate on nephrotoxic side effects of contrast media, the impact of iodine dose on radiation-induced DNA damage is an extra reason for CM dose reducing measures in the interest of patient safety. CT protocol optimization should balance between diagnostic image quality and the lowest radiation -and CM dose necessary to achieve this.

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## Figure legends

### Figure 1. Geometric Monte Carlo model

Geometric Monte Carlo model (right) based on standard iodine dose cardiac CT image of the porcine model (left). The lateral heart position of the Monte Carlo model mimics the minipig anatomy.

### Figure 2. Absorbed dose of the different iodine concentrations in the heart

Absorbed dose per air kerma of the different iodine concentrations in the blood-iodine compartment for the different X-and  $\gamma$ -ray energies.

### Figure 3. Effective atomic number of the different iodine concentrations in the heart

The increasing  $Z_{\text{eff}}$  in function of the iodine concentration in the blood-iodine mixture. In yellow is the effective range of iodine concentrations derived from CT images of the *in vivo* study, going from 5.5 mgI/mL to 12 mgI/mL for the reduced and standard iodine dose protocol, respectively.

### Figure 4. Absorbed dose of the different iodine concentrations in the air and water volume

The absorbed dose per air kerma of the different iodine concentrations in the air (left) and water (right) compartment of the Monte Carlo model for the different X-and  $\gamma$ -ray energies.

### Figure 5. Mean pre- and post-CT $\gamma$ H2AX foci/cell for the different iodine dose injection protocols

Mean pre (blue) and post (red) CT  $\gamma$ H2AX foci/cell are displayed for the different iodine dose injection protocols with the error bars representing the standard deviation. Significant differences are indicated with an \* ( $p$ -values < 0.05).

Figure 6. Example of  $\gamma$ H2AX foci in blood lymphocytes

Example of increase in  $\gamma$ H2AX foci (red arrows) in blood lymphocytes after cardiac CT when the standard protocol (right) was compared to the reduced (left) iodine dose protocol.



## Tables

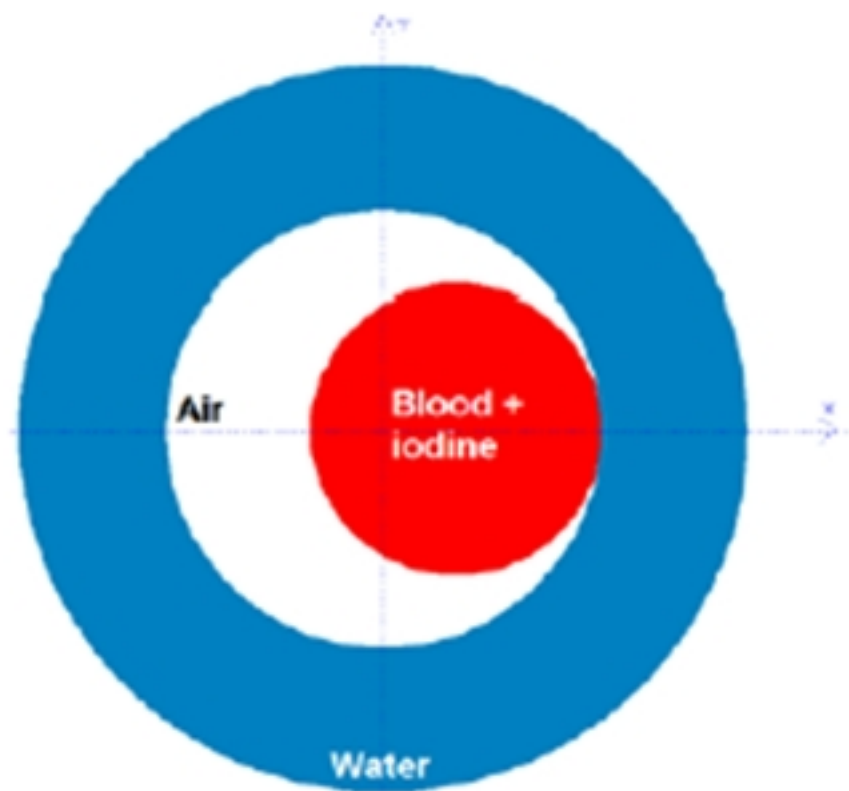
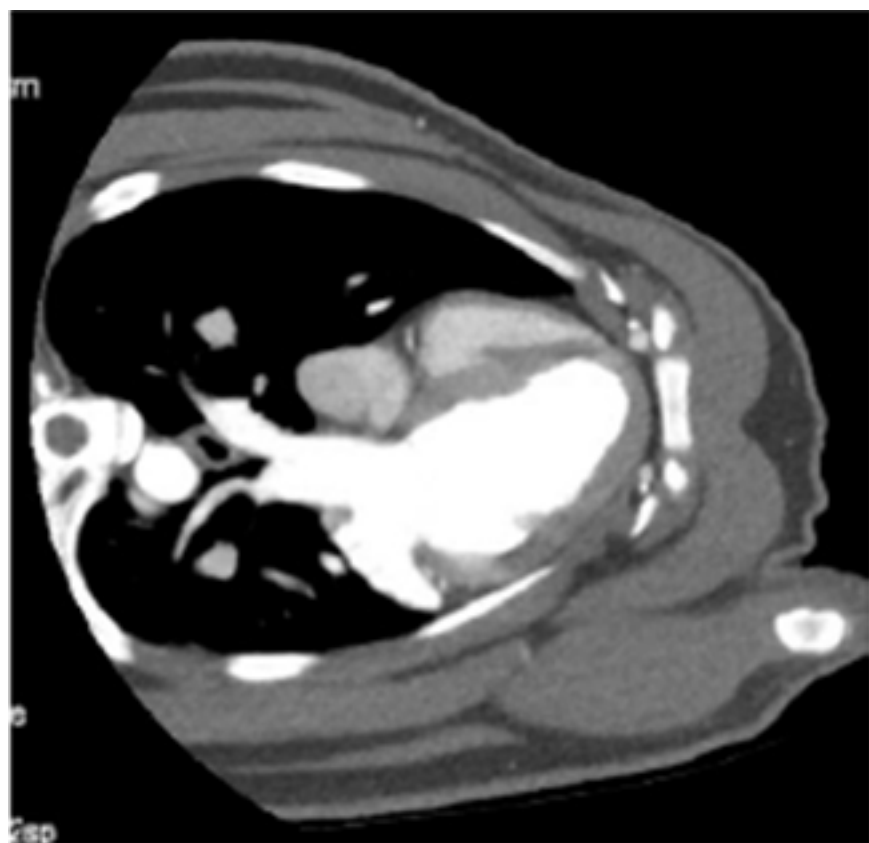
Table 1. Simulated CT kVp spectra and gamma energies with according mean photon energy. Attenuation coefficients and percentage of absorbed dose by the photoelectric effect were calculated for blood and iodine for the different photon energies.

Table 2. Scan protocol details

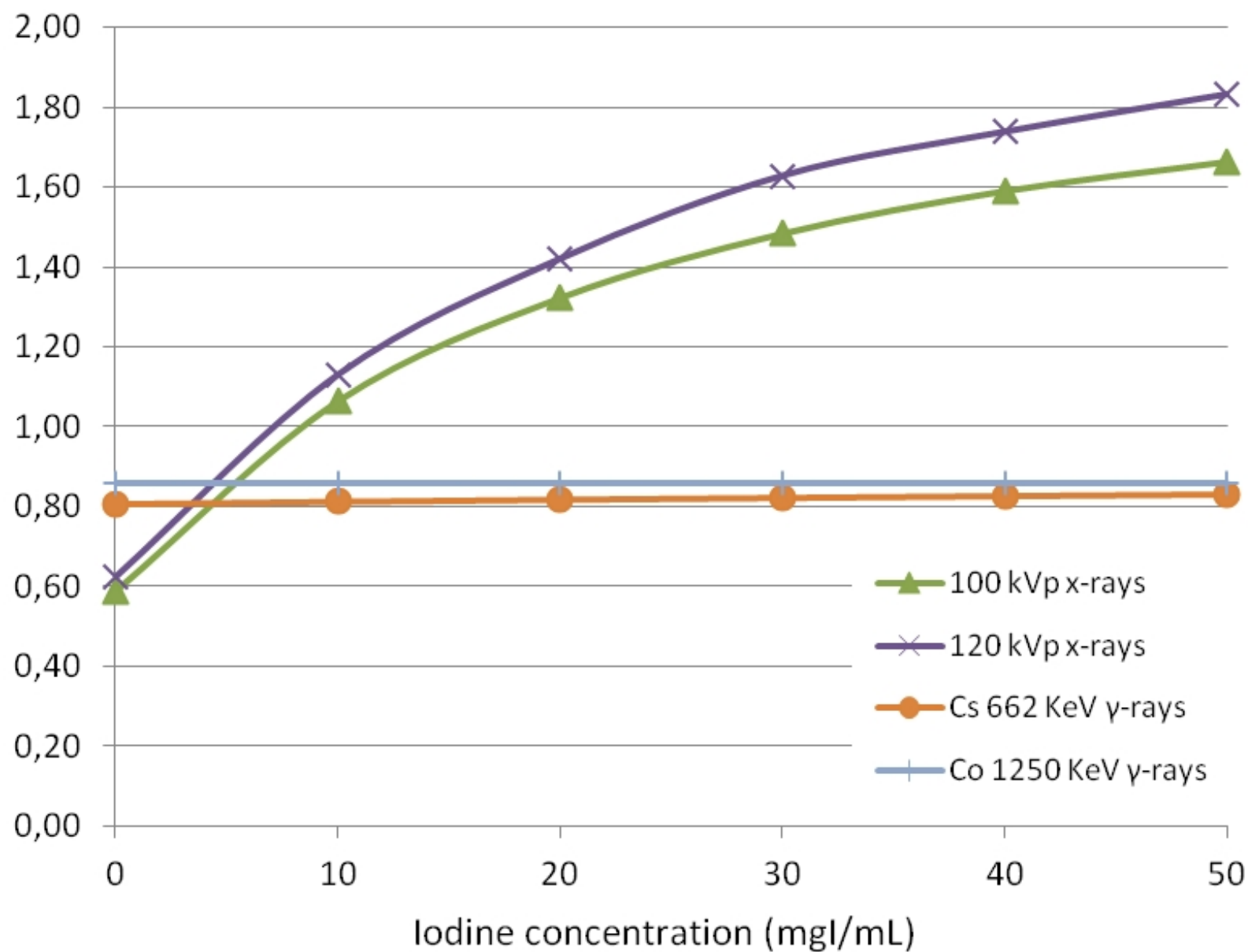
Table 3. Injection protocol details

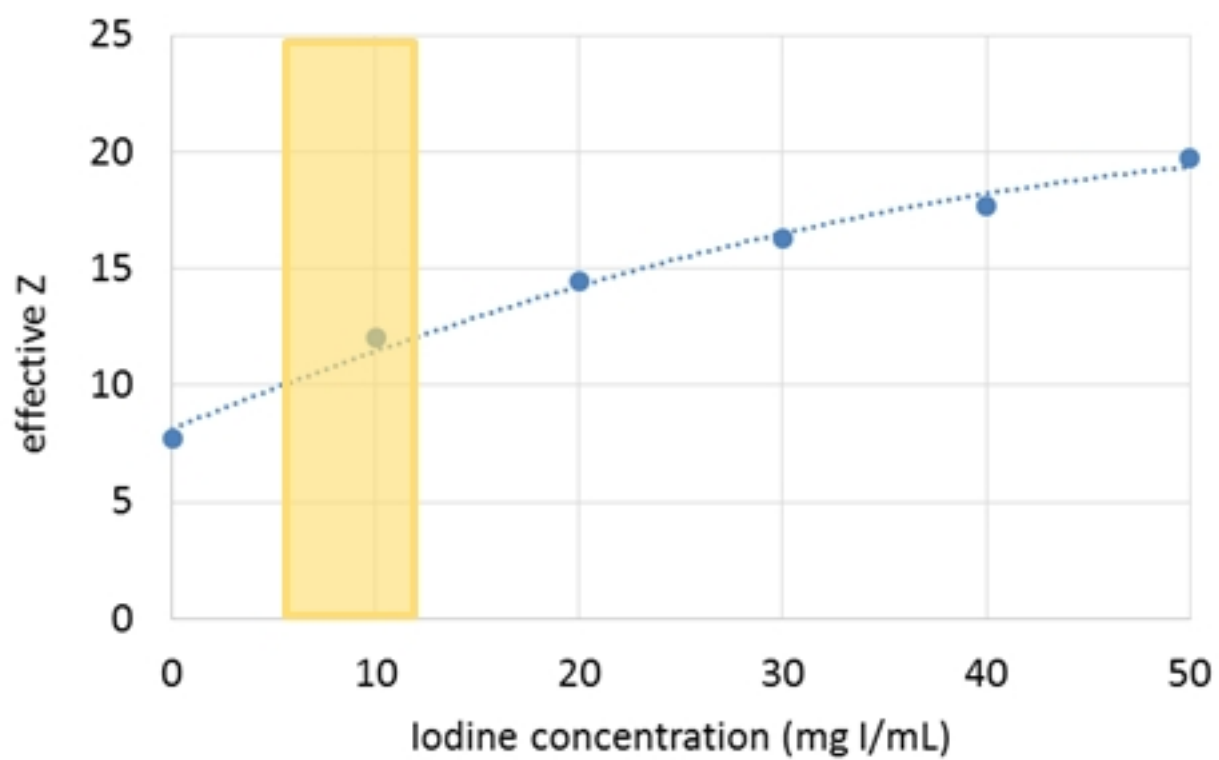
Table 4. Mean  $\gamma$ H2AX foci/cell with standard deviation, pre and post CT, for the different iodine dose injection protocols. Significant differences are indicated with \* or † ( $p$ -values<0.05).

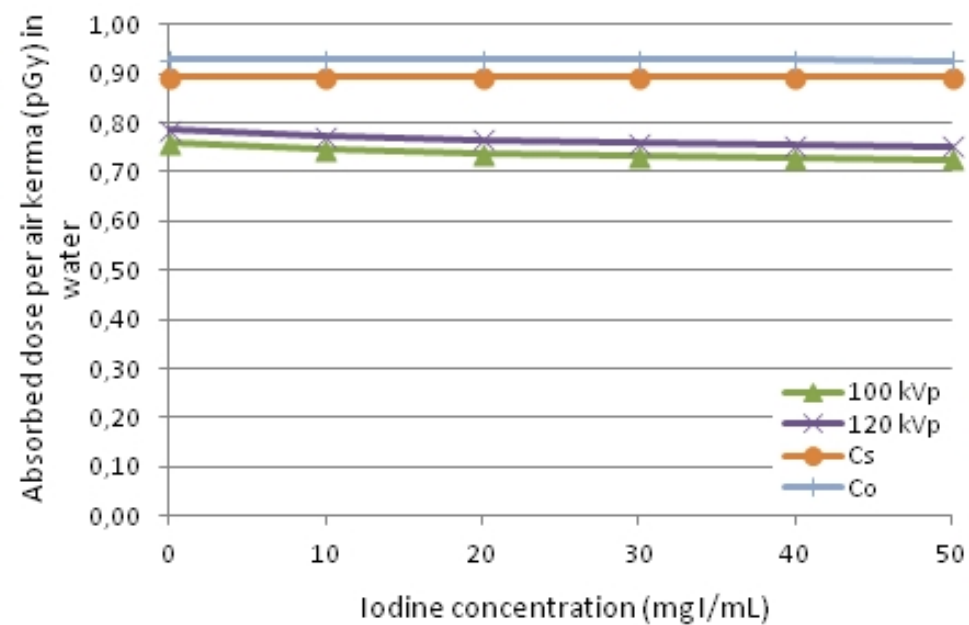
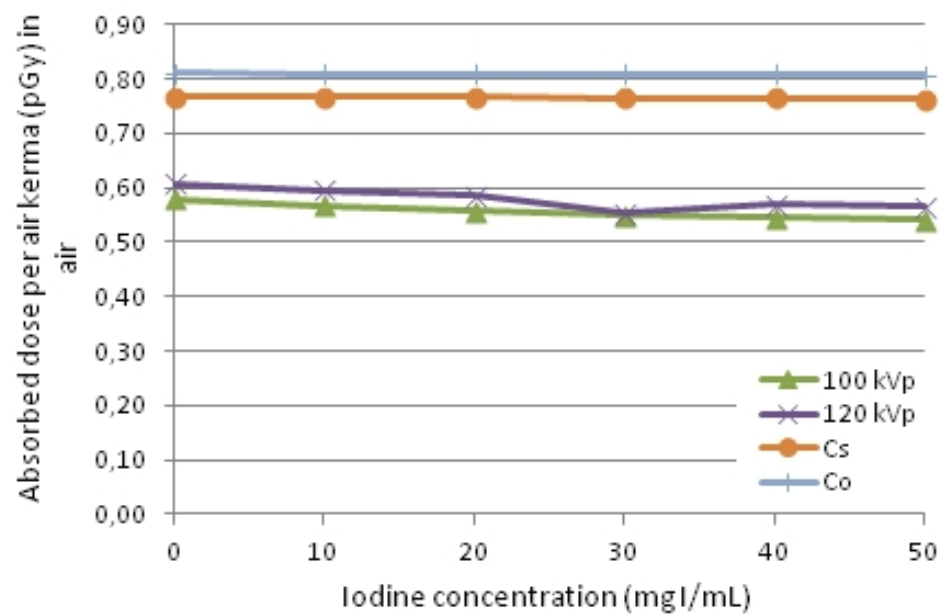
Table 5. Relative increase with standard deviation in absorbed dose and  $\gamma$ H2AX foci/cell for the different injection protocol combinations.

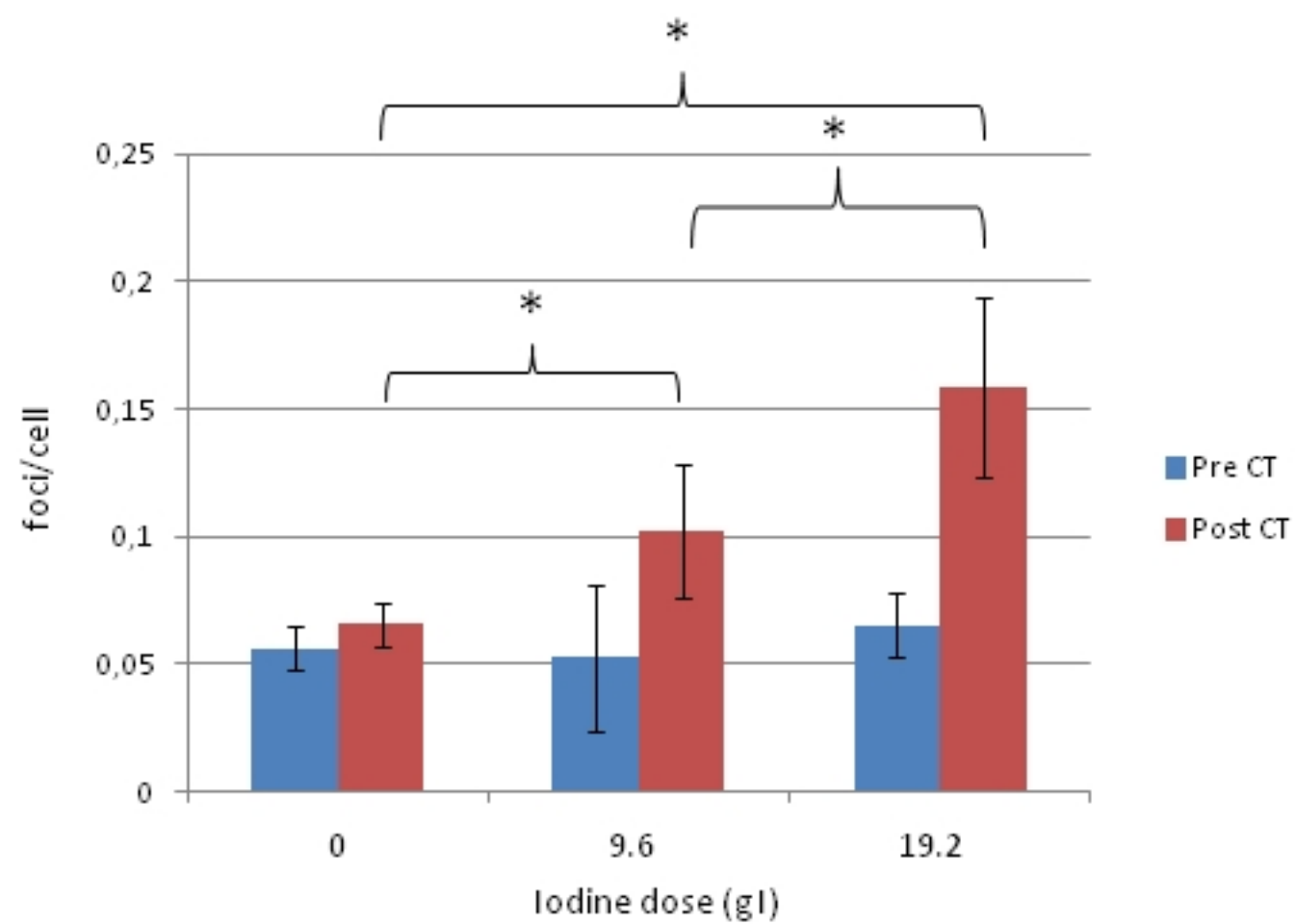


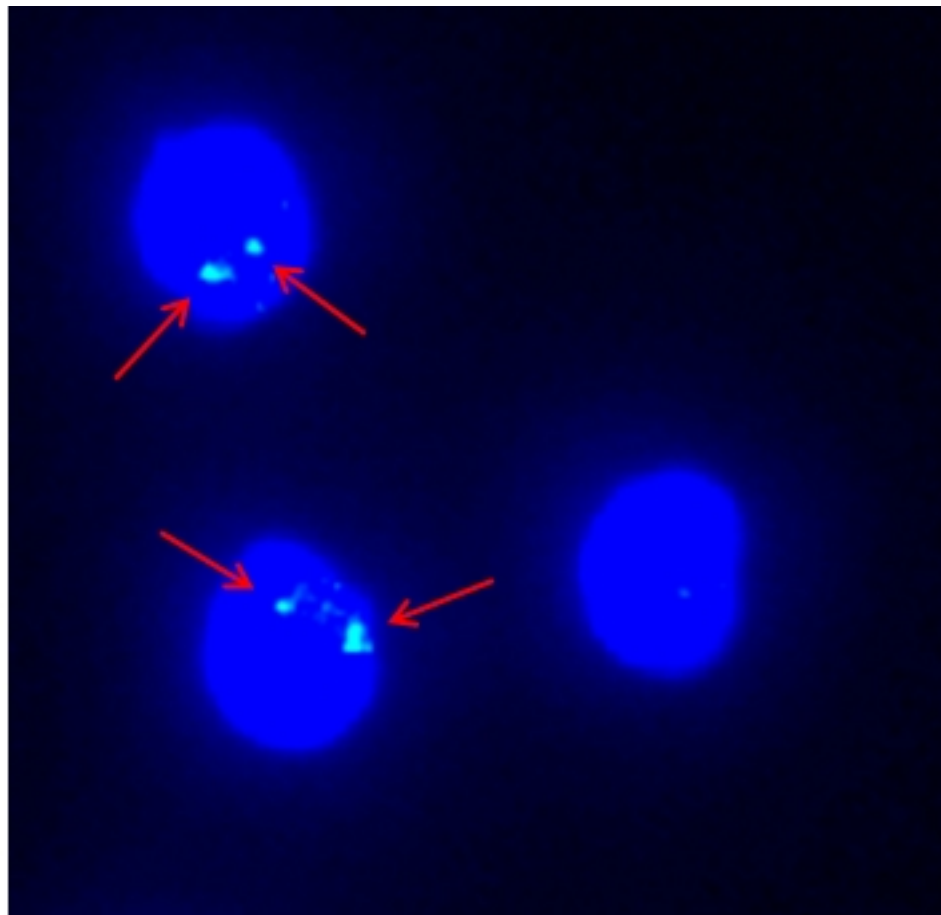
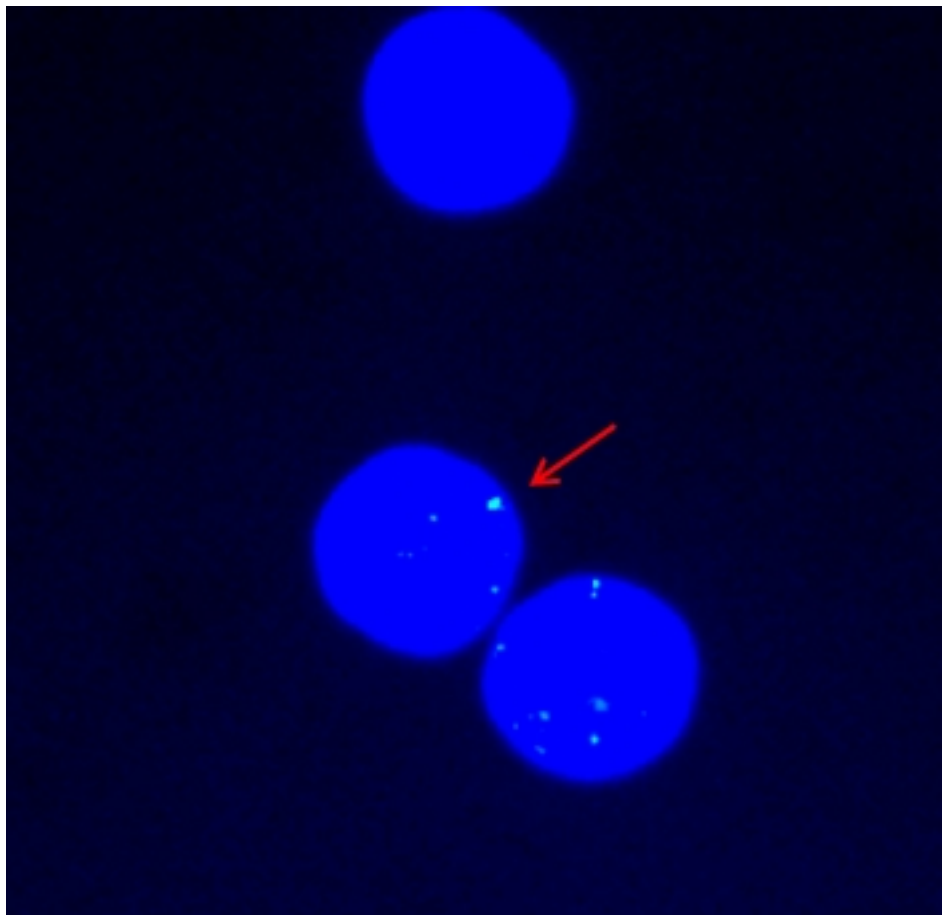
Absorbed dose per air kerma (pGy) inside the heart











		Mean photon energy (KeV)	Blood attenuation coefficient (cm <sup>-1</sup> )  (Percentage absorbed dose by photoelectric effect (%))	Iodine attenuation coefficient (cm <sup>-1</sup> )  (Percentage absorbed dose by photoelectric effect (%))
CT tube voltage spectra	100 kVp	56.9	0.224 (9%)	43.1 (96%)
	120 kVp	62.4	0.214 (7%)	33.6 (95%)
Gamma energies	<sup>137</sup> Cs	662	0.09 (0%)	0.038 (13%)
	<sup>60</sup> Co	1250	0.066 (0%)	0.252 (5%)



Scan protocol	
Scan type	ECG gated axial cardiac scan
Scanned cardiac phase	0-300%
Tube voltage (kVp)	100
Tube current (mA)	435
Rotation time (s)	0.35
Slice thickness (mm)	0.625
Collimation (mm)	160
CTDI <sub>vol</sub> (mGy)	41.3±3.6

	<b>Standard iodine dose protocol</b>	<b>Reduced iodine dose protocol</b>	<b>Non-contrast enhanced protocol</b>
Contrast media iodine concentration (mgI/mL)	320	160	0
Iodine dose (gI)	19.2	9.6	0
Injection speed (mL/s)	3	3	0
Injection volume (mL)	60	60	0
Saline chaser (mL)	12	12	0

	Mean number of foci/cell	
	Pre CT	Post CT
Non contrast enhanced protocol (0 gl)	0.056±0.009	0.066±0.009
Reduced iodine dose protocol (9.6 gl)	0.052±0.028	0.102±0.026*
Standard iodine dose protocol (19.2 gl)	0.065±0.012	0.158±0.035*,†

\* indicates significant difference compared to NCE protocol ( $p$ -value<0.05)

† indicates significant difference compared to the reduced iodine dose protocol ( $p$ -value=0.035)

	Relative increase in absorbed dose from Monte Carlo simulations (%)			Relative increase in $\gamma$ H2AX foci from <i>in vivo</i> experiments (%)
	Left ventricle	Right ventricle	Aorta	
Reduced iodine dose protocol (9.6 gl) versus NCE (0 gl)	78.8±16.3	42.9±15.4	86.1±14.4	56.1±28.9
Standard iodine dose protocol (19.2 gl) versus NCE (0 gl)	133.7±18.7	94.0±17.6	137.6±17	141.1±25.9
Standard iodine dose protocol (19.2 gl) versus reduced (9.6 gl)	69.5±14.4	118.9±14.2	59.7±18.4	54.5±34.1

\*NCE: Non-contrast enhanced

## AUTHOR DECLARATION CONFLICTS OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

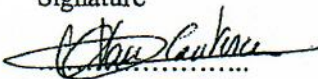
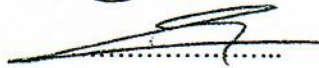





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## **TOC summary**

Despite their known cytotoxic and nephrotoxic side effects, iodinated contrast media are amongst the most prescribed agents in medical practice. Our study investigated a possible impact of the administered contrast media iodine dose on radiation-induced DNA damage. This was studied in vivo in a pre-clinical minipig model after a cardiac CT scan and in silico using a numerical dosimetry simulation model. Both models indicated that presence of iodine can have a significant impact on radiation-induced DNA damage. However, reduction in administered iodine dose reduces the amount of DNA damage which should be taken into account regarding patient safety.