

RESEARCH ARTICLE

Potential increase in radiation-induced DNA double-strand breaks with higher doses of iodine contrast during coronary CT angiography

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Abstract

Purpose: To investigate the contrast media iodine dose dependency of radiation-induced DNA double-strand breaks (DSBs) during a coronary computed tomography angiography (CCTA) scan.

Methods: This prospective patient study was approved by the ethical committee. Between November 2018 and July 2019, 50 patients (31 males and 19 females, mean age 64 years) were included in the study, 45 CCTA and five noncontrast-enhanced (NCE) cardiac computed tomography (CT) patients. A single-heartbeat scan protocol with a patient-tailored contrast media injection protocol was used, administering a patient-specific iodine dose. DNA double-strand breaks were quantified using a γ H2AX foci assay on peripheral blood lymphocytes. The net amount of γ H2AX/cell was normalized to the individual patient CT dose by the size-specific dose estimate (SSDE). Correlation between the administered and blood-iodine dose and the SSDE normalized amount of DNA DSBs was investigated using a Pearson correlation test.

Results: CCTA patients were scanned with a mean CTDI_{vol} of 10.6 ± 5.6 mGy, corresponding to a mean SSDE of 11.3 ± 5.3 mGy while the NCE cardiac CT patients were scanned with a mean CTDI_{vol} of 6.00 ± 1.8 mGy, corresponding to a mean SSDE of 6.6 ± 2.7 mGy. The administered iodine dose ranged from 16.5 to 34.0 gl in the CCTA patients, resulting in a blood-iodine dose range from 5.1 to 15.0 gl in the exposed blood volume. A significant linear relationship ($r = 0.79$, p -value < 0.001) was observed between the blood iodine dose and SSDE normalized radiation-induced DNA DSBs. A similar significant linear relationship ($r = 0.62$, p -value < 0.001) was observed between the administered iodine dose and SSDE normalized radiation-induced DNA DSBs.

Conclusions: This study shows that contrast media iodine dose increases the level of radiation-induced DNA DSBs in peripheral blood lymphocytes in a linear dose-dependent manner with CCTA. Importantly, the level of DNA DSBs can be reduced by lowering the administered iodine dose.

KEYWORDS

computed tomography angiography, contrast media, DNA double-strand breaks, patient safety

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1 | INTRODUCTION

Computed tomography (CT) is an imaging modality of increased importance to diagnose several cardiac pathologies due to recent improvements in CT technology.^{1–2} Although CT exposes patients to ionizing radiation, coronary CT angiography (CCTA) is becoming the clinical standard for imaging of the coronary arteries.³ CT techniques as prospective gating, automatic exposure control system and, iterative image reconstruction techniques, minimize radiation dose to the patient.^{4–6} CCTA examinations require the administration of intravenous iodinated contrast media (ICM) to visualize the coronary arteries. These ICM are not undisputed; adverse effects such as allergic response and contrast-induced nephropathy are associated with the administration of contrast media (CM) and are known to be dose dependent.^{7–9} In addition, some studies report an increase in radiation-induced DNA double-strand breaks (DSBs) in blood lymphocytes with the use of ICM.^{10–12}

ICM molecules are designed to enhance image contrast in blood vessels and well-perfused organs by increasing the absorption of X-ray photons. With each interaction, mainly by photoelectric absorption, secondary electrons are generated. These highly reactive electrons subsequently react with surrounding molecules to regain a stable situation. Interaction with the DNA molecule can result in DNA damage such as DNA DSBs, the most relevant biological damage after exposure to ionizing radiation.¹⁰ Due to the error-prone repair mechanisms of DNA DSBs, they are identified as an increased risk factor for cancer development.^{11,13}

Several dosimetry studies have quantified these DNA DSBs as a biomarker for exposure to ionizing radiation, using a γ H2AX immunofluorescent assay on blood lymphocytes.^{14–19} It is also the preferred technique to investigate the impact of ICM on radiation-induced DNA DSBs.^{10–12} These studies compared the amount of radiation-induced DNA DSBs in patients who received contrast-enhanced CT with non-contrast-enhanced (NCE) CT patients and reported an increase in radiation-induced DNA DSBs with contrast-enhanced CT. A previously published preclinical minipig study compared the amount of DNA DSBs after CCTA scans with three different iodine dose levels.²⁰ The results showed a significant increase in radiation-induced DNA DSBs with the administration of a higher iodine dose during CCTA at constant radiation dose. To our knowledge, no previous research has been reported on the CM iodine dose dependency of the radiation-induced DNA DSBs in clinical routine.

This study aims to investigate the CM iodine dose dependency of radiation-induced DNA DSBs in blood lymphocytes during a clinical CCTA scan. This relationship between iodine dose and radiation-induced DNA

TABLE 1 Patient characteristics and computed tomography (CT) radiation dose parameters

	CCTA	NCE cardiac CT for calcium scoring
Number of patients (male/female)	45 (29/16)	5 (2/3)
Age (y)	62.7 ± 14.7	78.8 ± 8.5
Weight (kg)	82.6 ± 17.9	82.7 ± 3.1
Height (cm)	172.8 ± 11.1	167.0 ± 11.1
Administered iodine dose (gl)	24.7 ± 4.9	0
Exposed volume of blood-iodine mixture (cm ³)	690.5 ± 122.5	NA
Iodine dose in exposed blood-iodine mixture (gl)	8.51 ± 3.03	0
CTDI _{vol} (mGy)	10.6 ± 5.6	6.0 ± 1.8
SSDE (mGy)	11.3 ± 5.3	6.6 ± 2.7
DLP (mGy·cm)	180.1 ± 108.2	93.4 ± 31.1

Abbreviations: CCTA, coronary CT angiography; CTDI_{vol}, volume computed tomography dose index; DLP, dose length product; NCE, noncontrast-enhanced; SSDE, size-specific dose estimate.

Values represent mean values ± standard deviation (SD).

DSBs was investigated for the first time in a clinical setting.

2 | MATERIALS AND METHODS

2.1 | CCTA scans

This prospective study was approved by the institutional ethical committee and written informed consent was obtained from all patients. Forty-five patients (29 males and 16 females, mean age 63 years, range 18–88 years, scanned between November 2018 and July 2019) scheduled for a routine clinical CCTA were included in the study (Table 1). Five additional patients (two males and three females, mean age 79 years, range 70–92 years, scanned between May 2019 and September 2019) scheduled for a calcium scoring scan were added to the study to provide data on NCE cardiac CT. Exclusion criteria contained other X-ray exposure or scintigraphy and radio- or chemotherapy 1 week prior to enrollment in the study (two patients excluded). All scans were performed on a Revolution CT scanner (GE Healthcare) with the following scan parameters: an axial electrocardiogram (ECG) gated scan protocol was used with a tube voltage 100 or 120 kVp, rotation time 0.28 s, collimation 16 cm. Based on a localizer scan of the patient, the lowest kVp is automatically selected for which the automatic exposure control ensures a pre-determined noise index. The CM injection volume and speed are determined by a patient-tailored CM injection model, considering the patient's physiology, tube voltage,

and CM iodine concentration, allowing to preset a targeted enhancement CT value of 475 HU in the coronary arteries. Throughout the inclusion period, three different CM products were used: Iopromide 370 mgI/ml (Ultravist, Bayer), Iobitridol 350 mgI/ml (Xenetix, Guerbet), and Iomeprol 350 mgI/ml (Iomeron, Bracco).

2.2 | Blood sample processing and lymphocyte separation

Before and 15 min 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 before further processing. Lymphocyte separation was performed according to the PBMC Spin Medium manufacturer's instructions (PluriSelect).

2.3 | Immunofluorescence analysis

A full detailed protocol description is provided in the addendum. The isolated lymphocytes were fixed for 10 min in 4% formaldehyde, followed by three washing steps of 10 min in PBS (Thermo Fisher Scientific). The cells were permeabilized for 1 h with 0.1% Triton X-100 (Thermo Fisher Scientific) in 3% BSA. Samples were incubated overnight with a 1:1000 dilution of the primary rabbit antibody, anti- γ H2AX (Thermo Fisher Scientific) at 4°C. The next day, the primary antibody was washed away and samples incubated with a 1:300 dilution of the secondary antibody, goat anti-rabbit Alexa Fluor 488 antibody (Invitrogen) for 1 h at room temperature. Also, 1:300 dilution of Hoechst stain was added as a background staining. Finally, the samples were washed and mounted with ProLong Gold Antifade Mountant (Thermo Fisher Scientific). A fluorescence microscope (Leica), a charge-coupled camera, and EUROPicture software²¹ were used to capture images of all samples. The number of γ H2AX foci on these images was quantified using ImageJ²² and FociCounter²³ software (Figure 1). Monocytes and granulocytes were identified by using morphologic criteria and were excluded from the analysis. Blind sample processing was done, and an average of 3400 lymphocytes were analyzed for each sample.

2.4 | Data and statistical analysis

To take the individual background signal of each patient into account, the amount of γ H2AX foci/cell of the pre-CT sample was subtracted from the amount of γ H2AX foci/cell of the post-CT sample. The resulting net amount of γ H2AX foci/cell was normalized to the individual CT scan dose, to compensate for the different patient radiation doses. To account for the different patient sizes, the patient dose descriptor size-specific dose estimate

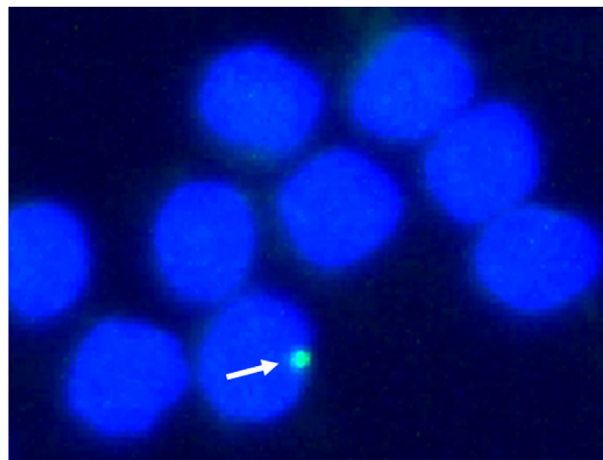


FIGURE 1 Example of a microscopy image of peripheral blood lymphocytes to quantify the amount of γ H2AX foci. The green spot (white arrow) indicates a γ H2AX foci while the blue color is a Hoechst background staining of all genetic material of the lymphocytes

(SSDE) was the preferred metric above $CTDI_{vol}$, as the latter reflects the dose in a cylindrical polymethylmethacrylate phantom with a fixed diameter.^{24–26} The SSDE was calculated by multiplying the $CTDI_{vol}$ with coefficients based on the effective diameter of the patient in the center of the field of view.

To investigate the iodine dose dependency of the radiation-induced DNA DSBs, we considered the exposed blood-iodine dose mixture within the CT-scan volume. In addition, the correlation of radiation-induced DNA DSBs with the administered iodine dose of the CM was also investigated. The exposed blood-iodine dose was derived from the CT images. The blood-iodine volume was segmented on an Advantage Workstation 4.7 (GE Healthcare) from the clinical CT images of each patient using a two-step segmentation process. First, all bone structures were removed by the "auto-remove bone"-function of the workstation and in a second phase, all noniodine-containing tissues were removed by applying a threshold of 85 HU (Figure 2). The mean CT value of this segmented volume was determined and the corresponding iodine concentration (I in mgI/ml) was derived using known CT value to iodine calibration curves of the CT scanner (100 kV: $I = (CT \text{ value} - 26.996) / 25.662$ and 120 kV: $I = (CT \text{ value} - 3.19) / 24.13$), according to the technique described by Buls et al.²⁷ The total exposed blood-iodine dose is the product of the segmented blood-iodine volume and the mean iodine concentration in the segmented volume. The administered iodine dose was calculated as the product of the CM injection volume and the CM iodine concentration.

The increase in radiation-induced DNA DSBs between the CCTA scans compared to the NCE cardiac CT scans was converted in percentages (Tables 2 and 3). We considered the increase in radiation-induced

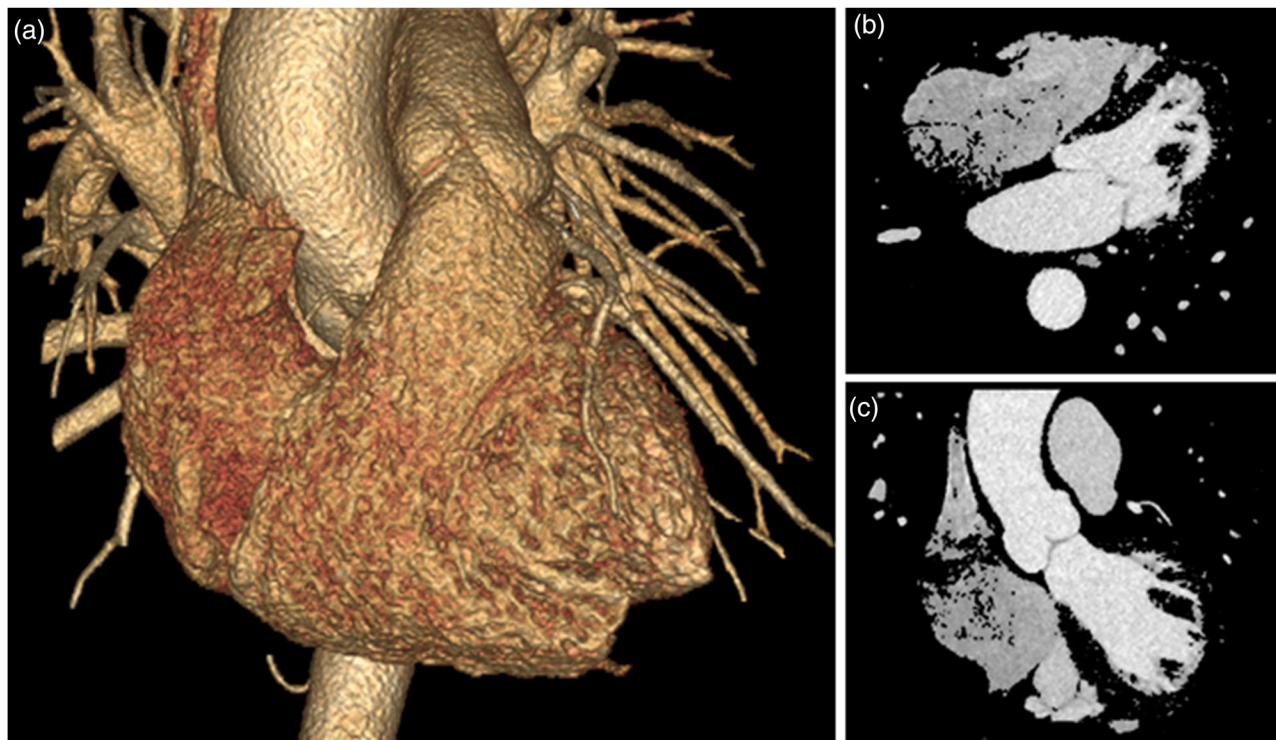


FIGURE 2 Example of a segmentation of the blood-iodine volume from a coronary computed tomography angiography (CCTA) scan of a 65-year-old female patient. The image contains a volume rendering (a), an axial (b), and a coronal image (c) of the segmentation

TABLE 2 Blood-iodine dose and linear model-based level of radiation-induced DNA double-strand breaks (DSBs)

		Amount of radiation-induced DNA DSBs (γ H2AX foci/cell)	Percentage of increase in DNA DSBs compared to NCE cardiac CT scan
Noncontrast-enhanced cardiac CT scan	0 gl	0.0006	/
Mean blood-iodine dose – 1 SD	6.78 gl	0.0023	285.9%
Mean blood-iodine dose	8.91 gl	0.0028	393.1%
Mean blood-iodine dose + 1 SD	11.04 gl	0.0035	500.2%

Abbreviations: CT, computed tomography; NCE, noncontrast-enhanced.

TABLE 3 Administered iodine dose and corresponding level of radiation-induced DNA double-strand breaks (DSBs)

		Amount of radiation-induced DNA DSBs (γ H2AX foci/cell)	Percentage of increase in DNA DSBs compared to NCE cardiac CT scan
Noncontrast-enhanced cardiac CT scan	0 gl	0.0006	/
Mean administered iodine dose – 1 SD	19.8 gl (or 53.5 ml of 370 mg/ml CM)	0.0024	319.0%
Mean administered iodine dose	24.7 g l (or 66.8 ml of 370 mg/ml CM)	0.0029	393.3%
Mean administered iodine dose + 1 SD	29.6 gl (or 80.0 ml of 370 mg l/ml CM)	0.0033	467.6%

Abbreviations: CM = contrast media; CT, computed tomography; NCE, noncontrast-enhanced.

DNA DSBs for the mean iodine dose ± 1 SD.

The presence of a correlation between the SSDE normalized amount of γ H2AX foci/cell and the iodine dose was investigated using a Pearson correlation test. Statistical calculations were performed with SPSS software, and differences were considered to be significant with p -values < 0.05 .

3 | RESULTS

The mean $CTDI_{vol}$ of the CCTA scans was 10.6 ± 5.6 mGy, corresponding to a mean SSDE of 11.3 ± 5.3 mGy (Table 1). The NCE cardiac CT scans resulted in a mean $CTDI_{vol}$ of 6.0 ± 1.8 mGy, corresponding to a mean SSDE of 6.6 ± 2.7 mGy. The mean amount of γ H2AX foci/cell in the pre-CT samples was 0.0034 ± 0.0010 for the CCTA scans and 0.0036 ± 0.0006 for the NCE cardiac CT scans. The mean amount of γ H2AX foci/cell in the post-CT samples was 0.0061 ± 0.0017 for the CCTA scans and 0.0040 ± 0.0007 for the NCE cardiac CT scans resulting in a mean difference of 0.0028 ± 0.0014 γ H2AX foci/cell for the CCTA scans and 0.0004 ± 0.0001 γ H2AX foci/cell for the NCE cardiac CT scans. After normalizing the amount of DNA DSBs to the radiation dose, an SSDE normalized mean γ H2AX foci/cell of 0.00026 ± 0.00010 m/Gy was observed for the CCTA scans and 0.000054 ± 0.000009 m/Gy for the NCE cardiac CT scans. The segmentations showed that the mean exposed volume of the blood-iodine mixture of the CCTA scans was 690.5 ± 122.5 cm³. In this volume, the mean blood-iodine dose was 8.9 ± 2.1 gl, ranging from 5.1 to 15.0 gl. The mean administered iodine dose was 24.7 ± 4.9 gl, ranging from 16.5 to 34.0 gl. A strong linear correlation ($y = 2.41E-5 + 2.71E-5 \times x$, where y = SSDE normalized amount of γ H2AX foci/cell and x = the blood-iodine dose) between the blood-iodine dose and radiation-induced DNA DSBs was found with a correlation coefficient of 0.79 (p -value < 0.0001) (Figure 3 and Table 2). A good linear correlation ($y = 6.39E-5 + 8.17E-6 \times x$, where y = SSDE normalized amount of γ H2AX foci/cell and x = the administered iodine dose) was observed between the administered iodine dose and radiation-induced DNA DSBs with a correlation coefficient of 0.62 (p -value < 0.0001) (Figure 4 and Table 3).

4 | DISCUSSION

The aim of the study was to investigate the CM iodine dose dependency of radiation-induced DNA DSBs in blood lymphocytes during a clinical CCTA. An increase of radiation-induced DNA DSBs due to the administration of ICM implicates an increased risk of cancer development.^{11,12} Our results demonstrate for the first time the linear correlation between both the admin-

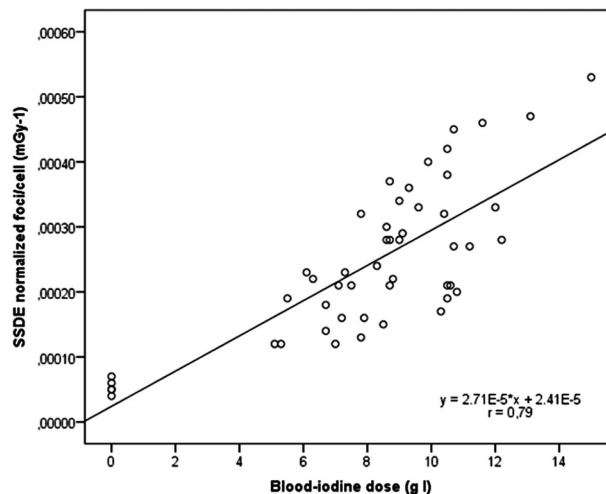


FIGURE 3 Strong linear correlation between blood-iodine dose and size-specific dose estimate (SSDE) normalized amount of γ H2AX foci/cell with a correlation coefficient of 0.79 (p -value < 0.0001)

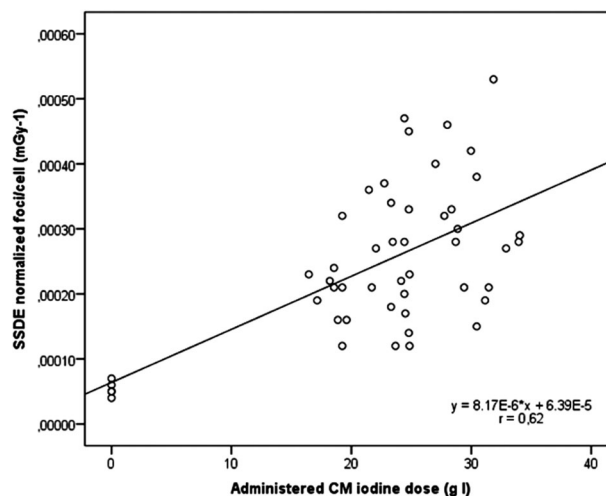


FIGURE 4 Good linear correlation between the administered contrast media (CM) iodine dose and size-specific dose estimate (SSDE) normalized amount of γ H2AX foci/cell with a correlation coefficient of 0.62 (p -value < 0.0001)

istered and blood-iodine dose and SSDE normalized radiation-induced DNA DSBs in CCTA, suggesting that patients with a high administered iodine dose (and thus a high exposed blood-iodine dose) will suffer an increase in radiation-induced DNA DSBs. For example, the mean exposed blood-iodine dose was 8.9 gl \pm an SD of 2.1 gl resulting in a range of 6.8 – 11.0 gl. Over this range, the amount of SSDE normalized DNA DSBs increased from 0.00021 to 0.00032 foci/cell or a 55.5% increase in radiation-induced DNA DSBs. For the administered iodine dose, the mean was 24.7 gl \pm an SD of 4.9 gl resulting in a range of 19.8 – 29.6 gl. Over this range, the amount of SSDE normalized DNA DSBs

increased from 0.00023 to 0.00031 foci/cell m/Gy or a 35.5% increase in radiation-induced DNA DSBs.

Differences in results between the blood and administered iodine dose can be explained due to varying scan timing and patient physiology. Although the patient-specific administered iodine dose targets a predefined enhancement level in the coronary arteries, a similar blood-iodine dose would be expected in all patients. However, differences in cardiac output influence the timing of the scan relative to the CM bolus. A suboptimal scan timing will result in a deviating blood-iodine dose, which will be high when scanned too early or low after a late scan. The significant increase in DNA DSBs with increasing iodine dose can be explained by the higher levels of secondary electrons generated with each photoelectric interaction between X-ray photons and iodine.¹¹ This increased level of secondary electrons is the main cause of radiation-induced DNA DSBs.^{11,12} Results of Grudzinski et al. reported no direct effect of ICM on radiation-induced DNA DSBs in the absence of radiation,¹⁰ indicating that the increase in DNA DSBs is a radiophysics effect instead of a pharmacological cause.

The five NCE cardiac CT scans in our dataset allowed us to compare our results with previously reported contrast-enhanced versus NCE CT patient dosimetry studies. They confirm the findings of these studies, reporting an increase in DNA DSBs in blood lymphocytes with contrast-enhanced compared to NCE CT scans.^{10–12} Grudzinski et al.¹⁰ report an increase of 30%, 0%–58% by Pathe et al.¹¹, and 107%–267% by Piechowiak et al.¹², considerably lower compared to the 393.3% increase reported in Table 3.²⁸ Variation in the reported percentages can be explained by differences in study design: type of scan (cardiac, abdominal, chest, etc.), scan parameters, patient radiation dose, contrast injection protocol, exposed blood volume, results whether or not normalized by radiation dose, and procedure of DNA DSB quantification. Besides observing additional radiation-induced DNA DSBs due to the presence of ICM, we also found that this amount of DNA DSBs is dependent on the iodine dose, with significantly less DNA DSBs after administration of a reduced CM iodine dose. This confirms previously reported results from a preclinical minipig study.²⁰

Not only the delivered radiation- and iodine dose but also the irradiated blood volume has an impact on the number of γ H2AX foci in a blood sample. The mean CTDI_{vol} (10.6 ± 5.6 mGy) and iodine dose (24.7 ± 4.9 gl) of this study were comparable to recently published radiation doses (4.6–10.3 mGy) and iodine doses (25.3 gl) in CCTA.²⁹ The mean exposed blood volume, measured in the CT images, was 683.0 ± 118.3 ml, which is approximately 13.7% of the average adult blood volume of 5000 ml.²⁹ In the blood circulation, the irradiated blood volume is mixed with non-irradiated blood, "diluting" the observable number of γ H2AX foci.

Patients might have an increased baseline level of DNA DSBs in case of previous exposure or medical treatment. To minimize the study bias, criteria were formulated to exclude patients who received X-ray exposure, scintigraphy, and radio- or chemotherapy one week before their enrollment. Furthermore, the pre-CT blood samples collected to calculate the difference in the amount of pre- and post-CT γ H2AX foci serve as a control for baseline DNA DSBs.

The results of this study have some clinical implications. Annually, more than 30 million doses of intravenous ICM are administered, making them among the most commonly prescribed agents in current medical practice.⁹ Considering the controversy associated with iodine dose-dependent adverse effects of CM and the synergistic effect of CM iodine dose on radiation-induced DNA DSBs, a conservative approach on the administered iodine dose is advised in the context of patient safety.^{7–9} Several studies already reported the possibility of reducing the administered iodine dose in CCTA without impairing image quality by combining a low tube voltage and advanced image reconstruction techniques.^{27,30,31} Nevertheless, the administration of CM remains essential to correctly diagnose the underlying pathology of the patient, which is more critical from a medical point of view compared to the possible CM-related adverse effects.

Our study had some limitations. First, is the limited amount of five NCE cardiac CT patients in the study. However, the aim of this study was to investigate the dose dependency of radiation-induced DNA DSBs and not to compare the level of radiation-induced DNA DSBs between CCTA and NCE cardiac CT. These NCE patients were added to the dataset to obtain additional information on the level of radiation-induced DNA DSBs in the absence of ICM and to complement our model. The amount of radiation-induced DNA DSBs of the NCE cardiac CT scans was also used to calculate the percentage of increase in DNA DSBs at different iodine dose levels. This allowed us to compare our results with previously published studies, which compared the amount of DNA DSBs after contrast-enhanced with NCE CT. Second, the clinical consequences of an increased level of DNA DSBs in peripheral blood lymphocytes remain unclear at this stage. Due to the high turn-over rate of blood cells, the biological impact of the radiation-induced DNA DSBs in the blood lymphocytes is limited. However, they are the preferred cell type to perform a γ H2AX assay, since they are easily accessible with minor discomfort to the patient. Being present in the blood pool, the lymphocytes are exposed to higher iodine concentrations compared to cells of solid organs. That is why a lower impact of CM iodine dose on radiation-induced DNA DSBs is expected. A recent study by Harbron et al. reported that, although the majority of DNA damage is restricted to blood and the vessel wall, secondary electrons with sufficient kinetic

energy can escape blood vessels and reach the cell nuclei of surrounding tissues.³² This is particularly true in case ICM molecules reach the capillary network of well-perfused organs like the liver, lung or kidneys, or the interstitial fluid during the CT acquisition.³³ Clinical consequences might be limited in peripheral blood lymphocytes, they can be more severe in for example slow dividing liver, lung, or kidney cells and can be an event in the multistep carcinogenic process. Some studies even report an estimated increase in organ dose up to 71% with contrast-enhanced compared to NCE CT scans.³⁴ However, the relationship between radiation-induced DNA DSBs and cancer development is still unknown and will require large-scale epidemiologic studies. Due to direct contact with the iodinated blood, the endothelial cells of the vessel wall will be exposed to ICM secondary electrons which might implicate a potential increased risk of non-malignant circulatory disease. The endothelium has been identified as a critical target in the pathogenesis of the radiation-induced cardiovascular disease (CVD).^{31,35} The underestimation of the blood vessel and endothelium dose by standard dosimetry techniques may have consequences of underestimating the radiation-induced health effects like CVD, especially in interventional fluoroscopy procedures with high radiation and ICM dose.

5 | CONCLUSIONS

In conclusion, we observe a CM iodine dose dependency of radiation-induced DNA DSBs. Our results show that DNA DSB levels increase linearly in blood lymphocytes with the iodine dose during a CCTA. Conventional patient dosimetry, based on the estimated radiation dose from the CT device, neglects this effect of radiation and iodine dose on DNA DSBs. Using γ H2AX foci as a biomarker for the radiation-induced DNA DSBs could allow the development of an iodine dose-based coefficient factor to correct for the underestimation of the radiation dose and could improve individual patient dosimetry. Besides their nephrotoxic and cytotoxic side effects, the impact of iodine dose on radiation-induced DNA DSBs is an extra argument for iodine dose reducing measures in the interest of patient safety. For each CCTA scan, an optimal balance must be pursued between diagnostic image quality and the lowest radiation and iodine dose necessary to achieve this.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article. None of the authors has a relationship with industry.

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