MEASUREMENT OF SKIN DOSE AND RADIATION-INDUCED CHANGES IN SKIN MICROCIRCULATION IN CHRONIC TOTAL OCCLUSION PERCUTANEOUS CARDIAC INTERVENTIONS (CTO-PCI)

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Measurement of skin dose and radiation-induced changes in skin microcirculation in chronic total occlusion percutaneous cardiac interventions (CTO-PCI)

Erik Tesselaar[1], Petra Macková[2], Christos Pagonis[3], Samuel Saers[4], Margareta Ahle[2], Michael Sandborg[1]

1.Department of Medical Radiation Physics, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden.
2. Department of Radiology in Linköping, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden
3. Department of Cardiology in Linköping, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden
4. Department of Thoracic and Vascular Surgery in Östergötland, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Short title

Radiation effects in the skin after PCI-CTO

Corresponding address
Erik Tesselaar
Department of Medical Radiation Physics
Linköping University
SE-58183 Linköping
Sweden
tel. +46 10 1038059
email: erik.tesselaar@liu.se

Abstract

Skin injuries may occur when radiation doses to the skin exceed 2 Gy. This study aimed to measure changes in skin microcirculation in patients undergoing chronic total occlusion percutaneous coronary interventions (CTO-PCI). In fourteen patients, peak skin dose (PSD) was estimated with radiographic films and skin microcirculation was assessed with laser Speckle Contrast Imaging (LSCI), before, one day after the intervention, and 4-6 weeks later. The mean PSD was 1.8±0.9 Gy. Peak skin microcirculation increased by 12% from 45±6 PU before to 50±9 PU one day after the intervention ($p=0.01$), and returned to 46±8 PU after 4-6 weeks ($p=0.15$). There was no significant correlation between PSD and the change in perfusion, neither one day ($r=-0.13$, $p=0.69$) nor 4-6 weeks after the intervention ($r=0.33$, $p=0.35$). These results suggest that there are no radiation-induced microvascular changes in the skin after CTO-PCI at skin doses below 2 Gy.

Introduction

Radiation induced skin injuries after fluoroscopically guided procedures are relatively uncommon nowadays, mostly as a result of improvements in equipment and better dose awareness. In patients who undergo long and complicated procedures, the radiation dose to the skin may however locally exceed the threshold for deterministic radiation effects, which is considered to be approximately 2 Gy[1]. Chronic Total Occlusion Percutaneous Coronary Intervention (CTO-PCI) is a complex procedure, which requires long fluoroscopy times and causes relatively high radiation exposures, up to 14 Gy[2].

Peak skin dose is not measured routinely in patients undergoing fluoroscopically guided procedures, as direct measurement involves physical dosimeters such as radiographic film or thermoluminescent detectors. Instead, the absorbed dose to the skin is usually estimated by the x-ray equipment using the air kerma in the reference point (Kref). In modern x-ray systems, an estimate of the spatial distribution of the entrance surface air kerma (ESAK) is also available, taking into account the position of the patient relative to the x-ray source, the projection angle, the dose rate and the x-ray spectrum. However, previous studies have shown that skin dose estimates can differ significantly from the measured peak skin dose[3,4].

Prompt radiation induced skin reactions occur less than 2 weeks after irradiation. The most frequently reported prompt reaction is the so-called early erythematous reaction, which typically occurs from a few hours up to 24 hours after a radiation dose of more than 2 Gy. The absence of early erythematous reactions does not preclude the occurrence of later reactions. The early response is believed to be mediated by an acute inflammatory reaction with an associated increase in vascular permeability[1].

Early reactions occur 2–8 weeks after exposure. These effects take place in the basal cells of the epidermis, which are the more rapidly proliferating cells in the skin. The main erythematous reaction is believed to be caused by a secondary inflammatory reaction[5]. Midterm and late effects include prolonged erythema, secondary ulceration due to failure of moist desquamation to heal, telangiectasia, dermal thinning and necrosis.

Physical and patient-related factors that affect the expression of radiation induced skin injury include smoking, poor nutritional status, compromised skin integrity, obesity, overlapping skin folds, and the location of the irradiated skin. The anterior aspect of the neck is the most sensitive site. The flexor surfaces of the extremities, the trunk, the back, the extensor surfaces of the extremities, the nape of the neck, the scalp, and the palms of the hands and soles of the feet are less sensitive, in that order[6].

The assessment of radiation induced skin injuries is typically done by visual or tactile inspection. Changes in skin physiology due to radiation exposure may not be visible clinically but can be quantified using measurement techniques. Previously, we have reported the use of laser doppler flowmetry (LDF, laser speckle contrast imaging (LSCI) and polarized light spectroscopy imaging (PLSI) for assessment of skin reactions during radiation treatment in breast cancer patients[7]. We found that these techniques reliably measure changes in erythema and microvascular blood flow in the skin, often before any clinical signs of skin reactions were noted.

The aim of this study was to investigate changes in microcirculation in the skin of patients who have been exposed to relatively high radiation doses to the skin after CTO-PCI. We hypothesized that exposure of the skin of the patient to the x-ray radiation would result in measurable changes in microvascular blood flow in the skin on the day after the intervention and/or at a later stage, 4 to 6 weeks after the intervention.

Methods

Subjects

A total of 14 patients (3 female) with mean age of 71 (range 53-84) years, who were scheduled for CTO-PCI at Linköping University Hospital, Sweden, were included in the study. Patients who were unable to give consent, had received prior radiation therapy to the lungs or breast, or who had existing extensive skin damage on the back were excluded from participation. The study was approved by the Regional Ethical Review Authority in Linköping, Sweden (No. 2018/232-31).

Fluoroscopic intervention (CTO-PCI)

Coronary CTOs were defined as symptomatic coronary lesions with TIMI (Thrombolysis In Myocardial Infarction) grade 0 flow of at least 3-month duration. The duration of the occlusion was estimated based on onset of anginal symptoms, prior myocardial infarction in the region of the target vessels, or by analyzing prior angiograms. Patients were treated in accordance with the hospital's clinical protocol. Interventions were done under fluoroscopic guidance using interventional x-ray systems (GE Innova IGS 520 or 730, GE Healthcare, Buckinghamshire, United Kingdom). Frame rates of 3.75 fps and 15-30 fps were used for fluoroscopy and cine runs, respectively. The systems have a dose mapping function indicating the maximum entrance surface air kerma ($ESAK_{max}$) corrected for backscatter and variation in distance from the reference point to the patient's skin. Detailed procedure data is available by means of radiation dose structured reports. All procedures were performed by the same cardiologist (C.P.)

Film calibration

Ten radiographic films (Gafchromic XR RV3, ISP Technologies Inc., Wayne, USA) were calibrated to measure dose to water, D_w in the range of 0 – 15 Gy[8]. The radiation source was an x-ray tube operated at 80 kV, with a half-value-layer of 3.7 mm aluminum. The films were irradiated at a constant dose rate of 29.5 mGy/s at a focus film distance of 30 cm. A round field with a fixed diameter of 6 cm was used and the films were positioned on top of a 20 cm thick Plexiglas phantom with a surface area of 30 x 30 cm^2. Increasing exposure times between 0-508 s were used to apply increasing dose. A calibration curve was generated relating the red component pixel values (PV_{red}) from the scanned calibration films to the dose in water at the films according to the formula $D_w = a/(PV_{red}-b)+c$, where a, b and c were constants determined using curve fitting.

Measurement of the radiation dose to the skin

Radiographic films were used to measure the spatial distribution of D_w. In each patient, a 35x43 cm^2 film sheet was placed on the patient table between the mattress and the patient's back, with the orange emulsion side facing the x-ray tube below the table. The film was kept in this position during the whole procedure. After the procedure, the films were scanned in a flatbed scanner (EPSON Perfection V600 Photo) in professional mode with all corrections disabled using 48-bit color and 300 dpi. The image was analyzed using the

software tool Fiji [9]. The image was separated into its three color components, and a 3 x 3 pixel spatial mean filter was applied to reduce spurious results due to defect pixels or artefacts. Then, the red component's minimum pixel value was determined to determine the maximum dose to water $D_{w,max}$ using the calibration curve (Figure 1). This measure was used as an estimate for peak skin dose (PSD). The kerma area product, total accumulated air kerma at the reference point (K_{ref}), and the $ESAK_{max}$ were obtained from the skin dose maps and the radiation dose structured reports.

Assessment of microvascular blood flow

Microvascular changes in the exposed skin were measured using Laser Speckle Contrast Imaging (LSCI, Pericam PSI System, Perimed AB, Järfälla, Sweden) on the day after the intervention, and between 4 and 6 weeks after the intervention. LSCI is a microvascular perfusion imaging technique which uses a divergent laser, with a wavelength of 785 nm, to illuminate an area of the skin[10]. The measurement is based on the analysis of the observed laser speckle pattern. At the wavelength in question, variance in the speckle pattern arises mainly due to motion of red blood cells and correlates strongly to the perfusion of the tissue. The method and the image parameters used have been described previously[11]. With each measurement, four 20 x 20 cm images were acquired, covering the four quadrants of the back of the patient (Figure 2).

Data analysis

Because of the inherent heterogeneity of skin perfusion, we measured the mean perfusion by averaging all measurement points within each quadrant of the back. For each patient, this yielded four mean perfusion values for each assessment (before the intervention, one day after, and 4-6 weeks after the intervention). The difference in mean perfusion values between different assessments were analysed using repeated measures analysis of variance (ANOVA). Dunnett's tests were used to correct for multiple comparisons. Correlations were calculated using Pearson's correlation coefficients. Values in text, tables and figures are presented as mean ± SD. Statistical calculations were done using Microsoft Excel 2011 and GraphPad Prism version 8 for MacOS. For all analyses, p-values <0.05 were accepted as significant.

Results

One patient was not physically able to undergo follow-up perfusion measurements, but was kept in the study. In one patient no radiographic film was placed during the procedure, but microvascular changes were assessed anyway. In another patient, the radiation dose map was unavailable. The CTO-PCI procedure was successful in 12 of 14 patients. An overview of the patients and procedure characteristics, radiation doses and perfusion values is given in Table 1. The radiation dose to the skin was typically distributed over the upper back region, and the observed pattern mirrored the variation in the radiographic view angles (Figure 1).

Radiation dose to the skin

The mean kerma area product of the procedures was 131 ± 74 Gycm^2, the mean K_{ref} was 2.4 ± 1.7 Gy and the mean $ESAK_{max}$ was 0.9 ± 0.7 Gy. The mean peak skin dose as estimated using the radiographic films was 1.8 ± 1.0 Gy. The correlation between K_{ref} and peak skin dose ($r=0.88$, $p<0.001$) was strong, as was the correlation between $ESAK_{max}$ and peak skin dose ($r=0.97$, $p<0.001$) although $ESAK_{max}$ underestimated the peak skin dose as measured using radiographic film by 47% (Figure 3).

Changes in skin blood flow

Mean skin perfusion increased by 12% from 45 ± 6 PU before the intervention to 50 ± 9 PU within 24h after the intervention ($p = 0.01$), and then returned to 46 ± 8 PU at 4-6 weeks after intervention ($p = 0.60$). Overall, there was no significant difference in perfusion between different regions on the back at any point in time ($p > 0.05$).

Despite the overall increase in mean skin perfusion after the intervention, there was no significant correlation between the peak skin dose and the change in skin perfusion, neither within 24h after intervention ($r = -0.13$, $p = 0.69$) nor 4-6 weeks after the intervention ($r = 0.33$, $p = 0.35$) (Figure 4). Visual comparison of the radiographic films and the perfusion images showed no spatial correlation between areas with high local radiation doses and areas with increased skin perfusion.

Discussion

The incidence of skin injuries in patients undergoing cardiac interventions is reported to be low, between 0.03% and 1.5%[12,13]. However, skin injuries may be commonly overlooked clinically, because the skin changes are slight and erythema may not be visually observed for hours to days following the intervention. Most previous studies have defined skin reactions as mild deterministic effects such as visual transient erythema and temporary hair loss. Skin reactions in these studies are commonly defined by subjective measures, such as redness or desquamation. This makes it hard to quantify the severity of the skin reactions and to compare results between different studies.

Very few studies have used objective measurements to quantify skin reactions. Reflectance spectrophotometry has been used to measure the change in skin color during radiation therapy[14]. Ultrasonic imaging has been proposed for evaluation of post-radiation changes in epidermal thickness[15] and near-infrared spectroscopy, laser Doppler perfusion imaging, and digital photography have all been found to provide measures of erythema that correlated with the radiation dose to the skin[16].

Previous studies have found that a peak skin dose of 2 Gy is a safe threshold for radiation-induced skin reactions in the average patient population and that temporary injury of the skin is not expected at peak entrance skin doses up to 6 Gy. However, changes in microcirculation in the skin as a result of exposure to radiation may occur before any clinical signs of skin damage are visible[7]. In this study, we therefore used laser speckle contrast imaging to measure changes in microcirculation in the skin after CTO-PCI. This technique is already clinically used for the assessment of skin burns, where changes in skin perfusion during the first week after the injury accurately predicts the healing time of the wound[18].

We found that microvascular perfusion on the back of patients was increased on the day after CTO-PCI, and that it had returned to baseline levels 4-6 weeks after the intervention. Although it could be speculated that the observed increase in perfusion is related to irradiation of the skin, we could not detect a correlation between the increase in perfusion and the radiation dose to the skin, at least not for the peak skin doses up to 2.7 Gy as observed in this study.

This lack of correlation between skin dose and perfusion increase suggests that the observed effects may be related to other factors. One possible explanation is that skin perfusion in patients undergoing a successful CTO-PCI is acutely improved as a result of the improvement in cardiac and macrocirculatory function. On the other hand, most patients had adequate left ventricular function at baseline, and in only two patients this function was improved after the intervention. Another explanation may be that there is a lasting effect of the vasodilatory substances, including nitroglycerine and verapamil, which were used during the intervention. Finally, an upregulation of systemic vasodilatory function due to improved coronary flow may explain the general perfusion increase observed on the day after the intervention.

The mean air kerma observed in this study (K_{ref}, 2.4 Gy) was comparable to those found in a previous study investigating the effect of dose-limiting equipment on radiation dosage during CTO-PCI, in which air kermas between 1.8 and 3.4 Gy were reported depending on the equipment configuration used[19]. Christakopoulos et al. reported a mean air kerma of 4.0 Gy[2]. This can be explained by the higher complexity of the procedures, as indicated by mean JCTO-score, in that study (2.5) compared to the current study (1.6).

This study has a number of limitations. The highest peak skin dose observed in this study where both follow-up perfusion measurements were performed was 2.7 Gy. It would be interesting to investigate microvascular effects in patients that are exposed to higher skin doses. We plan to measure changes in skin perfusion after other types of fluoroscopy guided interventions such as endovascular aortic repairs (EVAR) and other procedures that may result in relatively high doses.

Another limitation is the difficulty of matching the spatial distribution of the skin dose, as visible on the films, with the perfusion maps, since they were obtained at different points in time and in different body positions. Although we were careful to position the radiographic films in a standardized way, the exact location of a dose peak on the skin is hard to determine. We therefore chose to relate the maximum skin dose as measured by radiographic film, to the maximum observed perfusion change in the perfusion maps,

without further assessment of the spatial distribution. However, in the absence of any clear local hyperemic areas in the perfusion maps, we think that this approach is acceptable.
The study population was too small to analyze the effect of comorbidities or the complexity of the procedure on the changes in skin microcirculation after the intervention. Although we measured blood pressure at baseline, we did not measure blood pressure during follow-up measurements. We can therefore not rule out the effect of changes in blood pressure or other hemodynamic changes on the microvascular perfusion in the skin after the procedure.

Conclusion

The results of the current study add to the evidence found in previous studies that a peak skin dose of 2 Gy is a safe threshold for radiation-induced skin reactions after cardiac interventions. Furthermore, we could not detect any radiation-induced, subclinical, microvascular changes in the skin at these dose levels, neither one day nor 4-6 weeks after the intervention. Future studies in patients exposed to skin doses > 2 Gy are needed to further investigate the possible effects of x-ray radiation exposure on the microvascular perfusion in the skin.

Funding

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Figure legends

Figure 1. Estimation of peak skin dose (PSD) using GafChromic radiosensitive films. A. 48-bit color image of the scanned film showing several overlapping irradiated fields; B. 16-bit image of the red channel of A; and C. Histogram of the red channel of the image, indicating the minimum pixel value. This was converted to PSD using a dose-pixel value response curve determined using a separate calibration experiment.

Figure 2. Typical example of a perfusion image obtained by Laser Speckle Contrast Imaging. Microvascular perfusion in the skin was measured in 4 adjacent areas of approximately 20 x 20 cm, Measurements were made before the intervention, the day after, and 4-6 weeks after the intervention.

Figure 3. Top panel: kerma area product (KAP), air kerma in the reference point (K_{ref}), maximum entrance surface air kerma ($ESAK_{max}$) and peak skin dose (PSD) as measured using radiographic film for each patient. There was a strong correlation between KAP and PSD (lower left panel), between $ESAK_{max}$ and PSD (lower middle panel) and between K_{ref} and PSD (lower right panel), although $ESAK_{max}$ underestimated PSD and K_{ref} overestimated PSD, particularly for procedures with higher doses.

Figure 4. Absolute change in perfusion (PU) in the skin one day (left panel) and 4-6 weeks (right panel) after the intervention, as a function of peak skin dose. The perfusion was significantly increased after one day, but there was no correlation between peak skin dose and the change in perfusion, neither after one day nor after 4-6 weeks.

Table 1. Overview of the patients and procedure characteristics, radiation doses and perfusion values.

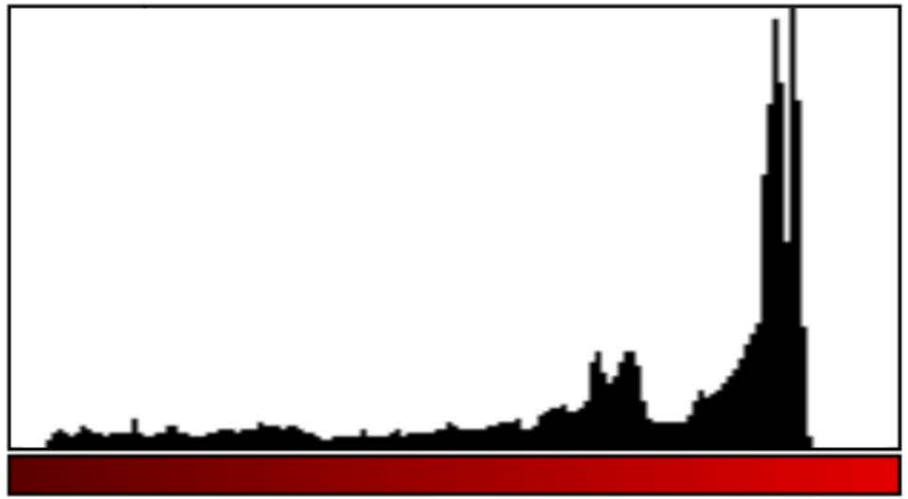
Patients	
Age (y)	71 (8)
Sex (m/f)	11/3
BMI (kg/m^2)	26.9 (4.3)
Procedure	
Successful procedures	12/14
AWE/RDR/ADR	6/4/2
JCTO-score	1.6 (0.9)
Fluoroscopy time (min)	65 (40)
KAP (Gycm^2)	131 (74)
K_{ref} (Gy)	2.4 (1.7)
$ESAK_{max}$ (Gy)	0.9 (0.7)
PSD (Gy)	1.8 (0.9)
Perfusion (PU)	
before	44 (7)
one day after	51 (8) *
4-6 weeks after	46 (8)

*Values are given as mean (SD). AWE: antegrade wire escalation; RDR: retrograde dissection and re-entry; ADR: antegrade dissection re-entry; JCTO-score: Japan-CTO score indicating complexity of the procedure (between 1-5). KAP: Kerma Area Product; K_{ref}: Air kerma in the reference point; $ESAK_{max}$: Maximum Entrance Surface Air Kerma; PSD: Peak Skin Dose as estimated using radiographic film; PU: Perfusion Units. * indicates a significant change from the perfusion before the intervention.*

A

B

C



22149 52661

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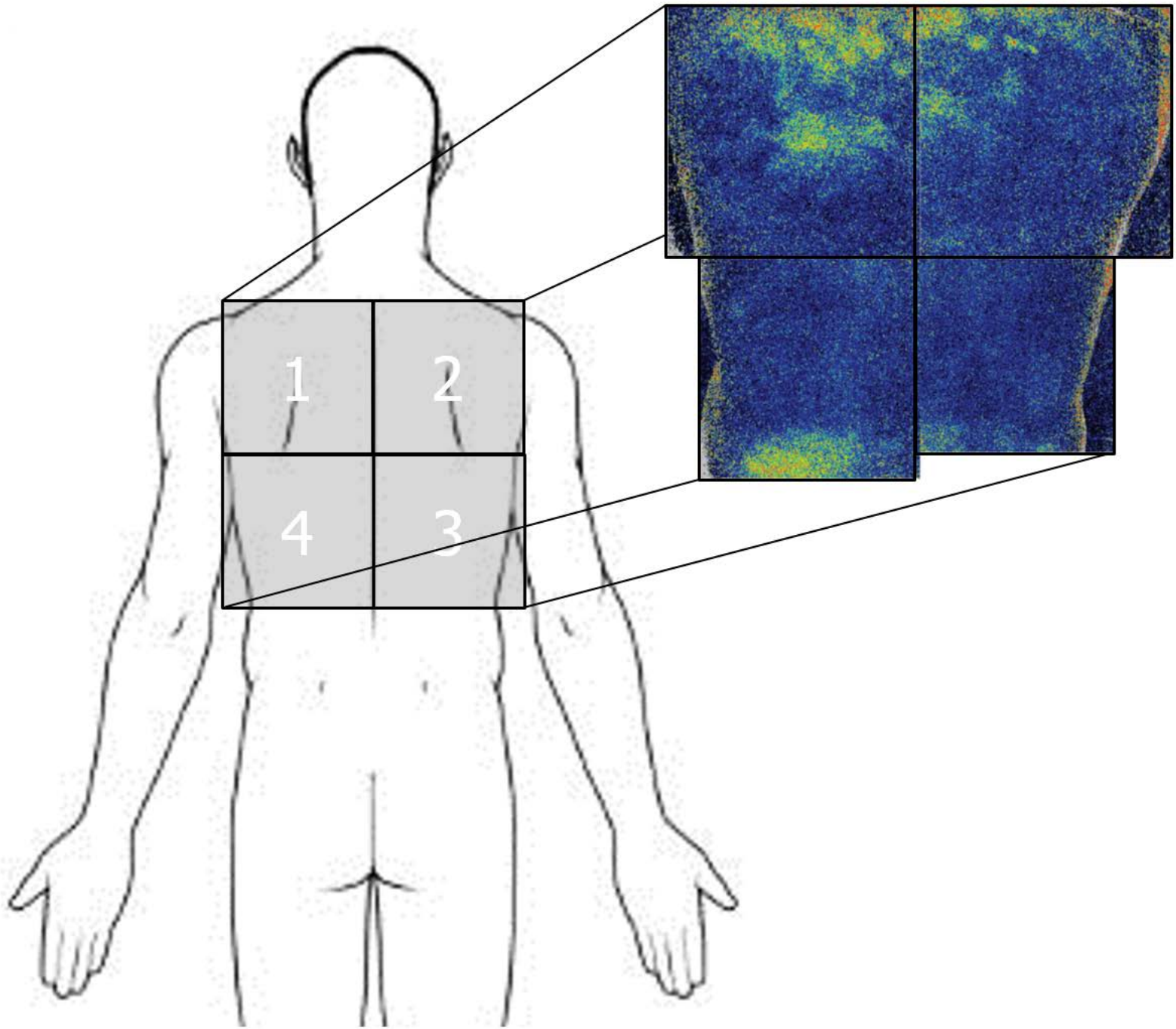
1
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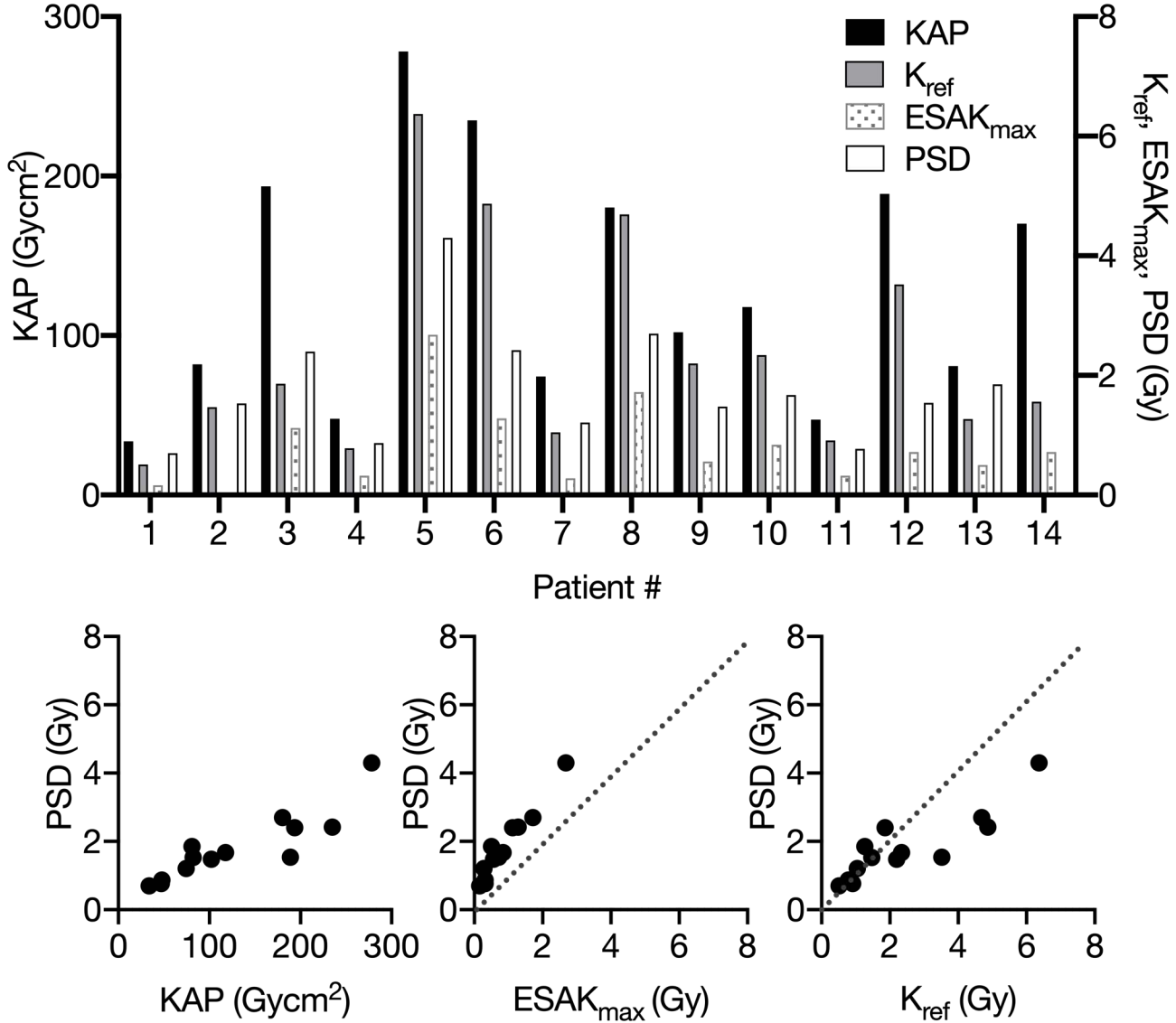
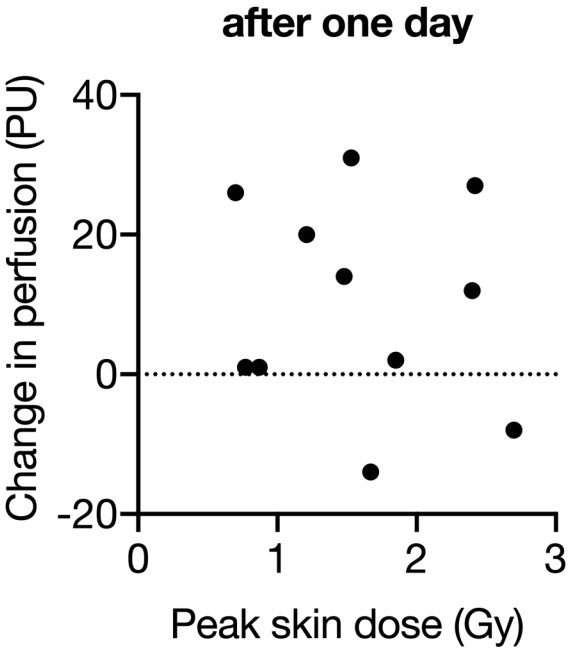
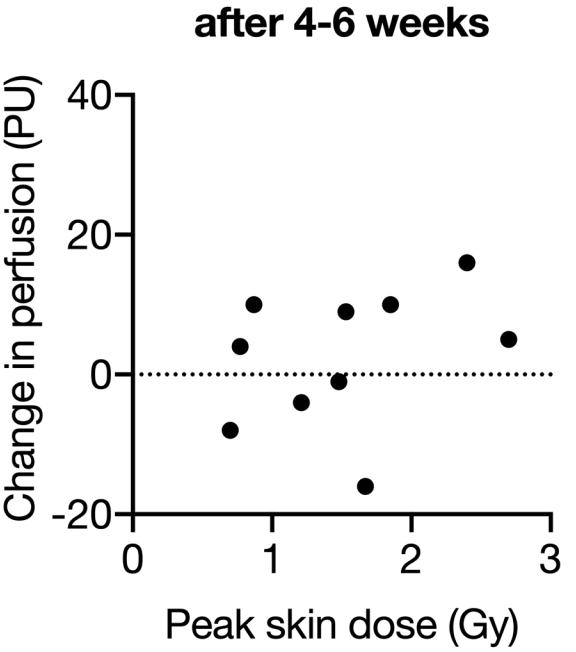

KAP
K_{ref}
$ESAK_{max}$
PSD
KAP (Gycm^2)
K_{ref}, $ESAK_{max}$, PSD (Gy)
Patient #
PSD (Gy)
KAP (Gycm^2)
$ESAK_{max}$ (Gy)
K_{ref} (Gy)


after one day
Change in perfusion (PU)
40
20
0
-20
0
1
2
3
Peak skin dose (Gy)


after 4-6 weeks
Change in perfusion (PU)
40
20
0
-20
0
1
2
3
Peak skin dose (Gy)