Assessment of thermal sensitivity of CT during heating of liver: an *ex vivo* study

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Objectives: The purpose of this study was to assess the thermal sensitivity of CT during heating of *ex-vivo* animal liver.

Methods: Pig liver was indirectly heated from 20 to 90 °C by passage of hot air through a plastic tube. The temperature in the heated liver was measured using calibrated thermocouples. In addition, image acquisition was performed with a multislice CT scanner before and during heating of the liver sample. The reconstructed CT images were then analysed to assess the change of CT number as a function of temperature.

Results: During heating, a decrease in CT numbers was observed as a hypodense area on the CT images. In addition, the hypodense area extended outward from the heat source during heating. The analysis showed a linear decrease of CT number as a function of temperature. From this relationship, we derived a thermal sensitivity of CT for pig liver tissue of $-0.54 \pm 0.03 \text{ HU } ^\circ\text{C}^{-1}$ with an r^2 value of 0.91.

Conclusions: The assessment of the thermal sensitivity of CT in *ex-vivo* pig liver tissue showed a linear dependency on temperature $\leq 90^\circ\text{C}$. This result may be beneficial for the application of isotherms or thermal maps in CT images of liver tissue.

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Thermal ablation therapy of liver tumours has received much attention as a minimally invasive method for local treatment of solid malignancies [1–5]. Several techniques for thermal ablation therapy [6, 7], such as radiofrequency ablation, laser ablation, microwave ablation and high intensity focused ultrasound, are in clinical practice. During thermal ablation therapy, the tumour should be heated to temperatures $>56^\circ\text{C}$ [8] or its cumulative equivalent minute (CEM), whereas adjacent healthy tissue and blood vessels should stay at $<40^\circ\text{C}$. Thus, the assessment of temperature distribution during thermal ablation therapy is essential for complete tumour necrosis. In order to assess the temperature in the ablation zone, invasive interstitial thermometry can be used. However, invasive thermometry can only be performed at a limited number of points in the liver, owing to several complications [9, 10]. Therefore, several non-invasive techniques for temperature measurement are in clinical use. Most of these non-invasive techniques are based on microwave radiometry [11], MRI [12, 13] and ultrasound imaging [14, 15], but these techniques are sensitive to motion and misregistration artefacts in moving and refilling organs such as the kidney, liver and lungs. Alternatively, CT gained interest by overcoming those limitations and by offering an almost real-time monitoring technique for ablation therapy [16].

A CT scanner yields CT numbers which are proportional to the fractional difference in effective local electron density of the subject material. Any temperature

variation (spatial or temporal) in the subject material scanned will generate a CT number shift in the CT image because of density changes due to thermal expansion. Despite very few assessment studies [16–22] on the thermal shift of CT numbers in various materials using early-stage CT systems, no study has been undertaken on the thermal sensitivity of liver tissue during heat application using current CT systems. Therefore, the purpose of this study was to assess the CT thermal sensitivity of liver tissue during heat application in an *ex-vivo* setting.

Methods and materials

The study was conducted after obtaining approval from the institutional ethical committee for animal care. A liver was extracted within 12 h after sacrifice of a pig. From the liver, three circular tissue discs that were 9 cm in diameter and approximately 5 cm thick were prepared. Each tissue disc was placed into a 9-cm-internal diameter polymethyl methacrylate (PMMA) cylinder (Figure 1). The tissue disc was heated using a hot polytetrafluoroethylene tube. The tube, with a diameter of 9 mm and a thickness of 2 mm, was placed through the central axis of the tissue disc and fixed by centrally drilled holes in two PMMA end plates. The tube was heated from 20 to 90°C by the flow of the hot air. The hot tube subsequently acted as a heat source. Five 1-mm-diameter holes were spaced at 5, 10, 15, 20 and 25 mm distances parallel to the central axis. Five thermally insulated thermocouples (NiCr-Ni; Roessel Messtechnik, Dresden, Germany) with a diameter of 0.25 mm were inserted through these holes into the liver tissue up to a

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depth of 3 cm. The temperatures were recorded in a computer using a data logger (TopMessage, Delphin Technology AG, Gladbach, Germany) and its software. Thermocouple 1 was taken as a reference temperature in order to assess the temperature during heating. However, for the calculation, the readings from all thermocouples and respective variation in CT numbers were used.

The liver tissue was scanned using a multidetector CT scanner (Somatom Definition; Siemens Healthcare, Erlangen, Germany) in sequential acquisition mode (pitch=1) with 120 kVp, 200 mAs, 24×1.2 mm collimation and 500 ms rotation time. CT images were reconstructed at a slice thickness of 1.2 mm using a B31s kernel on a dedicated workstation (Syngo; Siemens Healthcare). At least one scan before heating and five scans during heating in each examination were performed. The radiation dose (CTDIvol) and dose-length product (DLP) during each examination were read from the workstation of the CT system. The effective dose per CT examination was calculated using a DLP to effective dose conversion factor for the liver of 0.015 [23].

In the reconstructed CT images, a circular region of interest (ROI) of approximately 21 mm² was manually drawn covering the tip of the thermocouples in one experiment. The CT number histogram was calculated for each ROI. From each histogram, lower and upper Hounsfield unit thresholds were determined to include only pixels belonging to tissue (Figure 2) for further calculations. The ROI was drawn at the tip of the thermocouples in all experiments. Using average upper and lower thresholds, the mean CT number and standard deviation were calculated in all ROIs for all 40 measurements. The standard deviation in the average CT number in the ROI in each examination was used to quantify noise. The measured data were analysed using statistical software (SPSS v. 16.0; IBM Corporation, Armonk, NY). The accuracy of the fit was determined by calculating the Pearson's correlation coefficient (r^2).

Results

The temperature in the tissue rose from room temperature (17°C) to 90°C as recorded by thermocouple 1 (Figure 1); at the same time, the temperature recorded by the other four thermocouples declined with increasing distance from the heat source. Figure 3 shows the CT images of liver tissue at room temperature (20°C) (Figure 3a) to 80°C (Figure 3d) measured by thermocouple 1 (Figure 1). A decrease in CT numbers as a hypodense area due to an increase in heating was observed (Figure 3). In addition, the extent of the hypodense area increased during heating. Gas pockets were formed nearer to the hot tube at the beginning of the heating process and continued to develop at larger distances from the hot tube at increased temperatures.

From the histogram analysis, we derived the lower and upper thresholds at 0 ± 4.9 HU and 70 ± 6.8 HU, respectively (Figure 2). The noise increased with temperature from 2 HU at 17°C to 14 HU at 90°C. The CTDIvol was 277 mGy, corresponding to a DLP of 798 mGy cm. Using the DLP-to-effective dose conversion factor, this corresponds to an effective dose of approximately 12 mSv.

The linear decline of CT numbers as a function of temperature is shown in Figure 4. In this graph, 98% of the data fall within the 95% prediction interval. Only one set of data points as an outlier was observed at approximately 85°C. A CT thermal sensitivity of -0.54 ± 0.03 HU °C⁻¹ ($r^2=0.91$) was determined for the range of 20–90°C.

Discussion

We have shown that CT numbers of *ex vivo* pig liver are linearly dependent on temperature with a thermal sensitivity of -0.54 ± 0.03 HU °C⁻¹ ($r^2=0.91$).

The need for accurate temperature assessment of the ablation zone arises from recurrence of tumours in the liver after thermal ablation therapy. These recurrences are thought to arise from inadequate temperature

Figure 1. Schematic drawing of experimental set-up of the liver tissue in the perspex cylinder (left) and placement of five thermocouples. An example of reconstructed CT image at room temperature showed the positions of thermal sensors from heating tube (right).

Figure 2. Example of histogram used to compute the upper and lower threshold to mask voxels of non-tissue structure from the measurements. The lower and upper thresholds were shown by arrows at 0 and 70 HU.

information of the ablation zone. Therefore, real-time information on the spatial distribution of temperature in the ablation zone would provide valuable information for more efficient ablation. Several studies have shown the influence of temperature on CT number [16–22].

The thermal sensitivity we found was significantly higher than the values reported for muscle tissue ($-0.45 \pm 0.01 \text{ HU } ^\circ\text{C}^{-1}$ and $-0.43 \pm 0.03 \text{ HU } ^\circ\text{C}^{-1}$), and involved an approximately 20% increase in CT numbers compared with two previous studies [16, 20]. These differences were mainly due to the types of tissues and CT systems used in the studies.

The criteria for non-invasive thermometry for the monitoring of thermal ablation are (1) a spatial resolution better than 2 mm, (2) an acquisition time $<30 \text{ s}$ and (3) a temperature accuracy in the order of $1\text{--}2^\circ\text{C}$ in the temperature range [24]. In the present study, criteria (1) and (2) were met, with a spatial resolution of 1.2 mm and an acquisition time of 500 ms. Although it has been shown that a temperature accuracy of approximately 5°C is feasible with submillimetre spatial resolution [19], criterion (3) was not met. The temperature accuracy can be increased by improving the CT image quality and using non-metallic thermal sensors.

Figure 3. Example of CT images at temperatures (a) 20°C , (b) 40°C , (c) 60°C and (d) 80°C as measured by thermocouple 1. The images showed a hypodense area around the heat source which was increased at increasing temperature.

Figure 4. CT number as a function of temperature in liver tissue during heating. The solid line represents a least-square linear fit with $R^2=0.91$. The dotted line represents the 95% prediction interval (PI). Most of the data (~98%) fell within the PI.

For CT temperature assessment, it is necessary to perform a baseline scan and at least six repeated scans to monitor the temperature-induced changes in CT numbers [19]. For the treatment of a single hepatic tumour measuring 30 mm, approximately 50 mm should be covered during the CT scan to include a safety margin. During the positioning of the heat source or radio-frequency needle in the liver, a low-dose CT protocol such as CT fluoroscopy can be used. However, this protocol cannot be used for monitoring of the temperature distribution, owing to poor image quality.

We derived an effective dose of approximately 12 mSv for the entire ablation procedure using CT temperature assessment. If the procedure had been done without CT temperature assessment, the effective dose would have been approximately 2–4 mSv depending on the specific CT technique used. This implies that CT temperature assessment technique adds an excess effective dose for the patient of 8–10 mSv. Using a tumour induction probability of 5% per sievert, this excess effective dose would yield 1 extra fatal tumour in 2000–2500 patients. However, this number should be compared with the number of patients who do not suffer from local recurrences or distant metastasis because of incomplete tumour ablation without CT temperature assessment. Although we have no information about the actual skin dose, it is highly unlikely that this effective dose of 12 mSv would yield a skin dose which lies in the range of skin erythema (*i.e.* 200 cGy). During *in vivo* implementation of this method, one may need additional scans in order to follow the heating pattern accurately and to assess the cooling effects due to blood perfusion. The excess effective dose delivered to the patient can be further reduced by limiting the number of scans and by optimising imaging techniques to monitor the heating pattern.

This study was performed in *ex-vivo* liver tissue and further animal studies are essential to understand the vascular and perfusion response to heating. The interpretation of vascular and perfusion response during heating is very difficult, owing to the complex morphology of living tissue [25]. Heating causes initial vasodilatation; however, at higher temperatures, vasoconstriction

occurs. As a consequence, the tissue blood volume and, additionally, the heat distribution changes. Highly perfused tissue with large vessels may act as a heat sink by transporting heat from the local to the peripheral tissue [26–28]. The effect of perfusion makes native liver parenchyma relatively more resilient to thermal damage than tumour tissue. This effect can cause a more asymmetrical temperature distribution and a more irregular necrosis zone [29] than the approximately radial symmetric temperature distribution shown in the present study. To implement this method in further animal studies, the role of vascular and perfusion should be correctly interpreted.

With the use of temperature sensitivity derived in this study, the CT images can be used to transform temperature distribution into a colour-coded map. Furthermore, temperature information could be used in low heating therapy such as hyperthermia to calculate CEM or thermal dose.

There are certain limitations in this study. Firstly, the lack of surrounding saline or agar to mimic a body could have influenced CT numbers and image noise, particularly at the border of the liver tissue. However, this had a minor influence in the local heated area. Secondly, it was supposed that thermally ablated tissue may actually increase in CT number, owing to phase transitions in tissue, especially at coagulation by changing tissue density. Such tissue characteristics due to desiccation were not observed during heating, but could be seen tissue cooled down. Although the main aim of this study was to determine the area of necrosis by detecting the regions with temperature $>60^{\circ}\text{C}$ [30] during heating, further study may be necessary to investigate the increase in CT numbers during cooling. Finally, this study did not resemble an *in-vivo* situation in which additional physiological processes and inhomogeneous structures increase the CT noise [31]. Therefore, further studies using CT for non-invasive temperature assessment are needed to verify the current results in an *in-vivo* situation.

In this study, the non-invasive approach of current CT systems was assessed for temperature discrimination during tissue heating. The method presented here could

be used to assess non-invasive CT temperature mapping in an *in vivo* study.

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