In vivo Assessment of Cold Stimulation Effects on the Fat Fraction of Brown Adipose Tissue using Dixon MRI

Vanessa Stahl[1], Florian Maier[1], Ralf O. Floca[2], Moritz C. Berger[1], Mauricio Berriel Diaz[3], Martin T. Freitag[2], Marc-André Weber[4], Antonia Dimitrakopoulou-Strauss[5], and Armin M. Nagel[1]

[1]*Medical Physics in Radiology, German Cancer Research Center, Heidelberg, Germany,* [2]*Department of Radiology, German Cancer Research Center, Heidelberg, Germany,* [3]*Molecular Metabolic Control, German Cancer Research Center, Heidelberg, Germany,* [4]*Diagnostic and Interventional Radiology, University Hospital of Heidelberg, Heidelberg, Germany,* [5]*Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center, Heidelberg, Germany*

Target Audience: Scientists and physicians interested in the research on brown adipose tissue, as well as in applications of water-fat-separated MRI.

Purpose: Brown adipose tissue (BAT) has the ability to dissipate energy through non-shivering thermogenesis, implicating a therapeutic potential for the treatment of obesity and metabolic diseases in humans[1]. BAT activity can be induced by cold-stimulation, which has been confirmed by *in vitro* measurements of adipose tissue samples from mice[2,3] and via blood-oxygenation level dependent functional MRI (BOLD fMRI) in humans. Based on its high water content compared to white adipose tissue (WAT), BAT was noninvasively detected by assessing fat fractions (FF) using MRI[4]. In the present work, the acute activation of BAT by induced cooling of the skin was evaluated *in vivo* using Dixon[5] water-fat-separated MRI. The FF decrease of human BAT under cold stimulation was monitored and quantified over time in interscapular BAT depots.

Materials and Methods: Five healthy volunteers (2 males, 3 females, age 22-29 years, BMI 19-26) were examined with informed consent on a 3T hybrid PET/MR system (*Biograph mMR 3.0T, Siemens, Erlangen, Germany*), using a spine-array coil, a flexible 3 × 3-body-matrix array coil, and a 32-channel head/neck coil. The clavicular region was imaged with a 2-point Dixon pulse sequence (VIBE; TR = 5.85 ms, TE_{in}/TE_{opp} = 2.46/3.69 ms, α = 10°, slices = 64, slice thickness = 1.2 mm, FOV = 500 × 312 mm², matrix = 416 × 260, BW = 710 Hz / px, GRAPPA R = 2) for 30 seconds under breath hold, applied every five minutes over a total time of 135 minutes. All volunteers wore a cooling vest (*Polar Products Inc., OH, USA*), circulated with temperature-controlled water from a water circulator (*Haake F6 Circulator, Artisan Scientific, IL, USA*). For baseline measurements, the water temperature was maintained at 23 °C (room temperature) for 20 min, followed by cooling to 12 °C for 90 min, and warming to 37 °C body temperature for 30 min. During the experiments, temperature was monitored with a four-channel fiber optic thermometer (*LumaSense Technologies Inc., CA, USA*). Probes were positioned directly in the water circuit at the inlet and outlet of the cooling vest, on the skin at the back of the volunteers and in the armpit as approximation for the body temperature. Data evaluation was done with MATLAB (*The MathWorks, Natick, AM, USA*) and MITK (*Medical Imaging Interaction Toolkit, German Cancer Research Center, Heidelberg, Germany*)[6]. To compensate for different breath hold positions, all Dixon water images (W) were registered to the first acquired image and the resulting transformations were applied to the corresponding fat images (F). Fat fractions were determined as *FF = F / (F+W)*. FF maps were 2D-median filtered in a 3-by-3 neighborhood and a linear fit was applied pixel-wise to estimate the FF change rate during the cooling period. To exclude non-fatty tissues and partial-volume effects, the following criteria were considered: a) $0.6 \leq FF_{base} \leq 0.8$, b) $FF_{cold} \geq 0.3$, c) negative gradient, d) minimum region-of-interest (ROI) size $N \geq 15$ px, (FF_{base}: FF before cooling, FF_{cold}: FF at the end of cooling). The results were overlaid on the corresponding fat images for verification of the expected BAT depots with the assistance of a radiologist. BAT ROIs were manually identified and subsequently compared to subcutaneous adipose (SAT) and muscle tissue. The mean SAT and muscle tissue ROI-size was 5 ml.

Results: Data is delineated as mean ± standard deviation. Results from all individual subjects are documented in Tab. 1. Fig. 1 shows a FF map of volunteer S01, marked with the evaluated ROIs of BAT, SAT and muscle. Fig. 2(a) shows the temperature measurements for S01. The water temperature at the inlet and outlet of the cooling vest followed the set circulator temperature. The mean outlet temperature was (1.3 ± 0.3) °C higher than the inlet temperature, indicating a heat transfer of (63 ± 3) W into the water circuit. While skin temperature at the back decreased during cold stimulation, body temperature stayed at (37.5 ± 0.3) °C. Focusing on the two interscapular BAT depots, a mean FF decrease of (-4.0 ± 1.7) % / h was detected during cold stimulation in a mean volume of (0.42 ± 0.28) ml. In S02 and S05 a slightly FF decrease during the baseline period was observed, whereas during the warming period no immediate recovery of the initial BAT FF was found within 30 min in all subjects. In SAT (mean FF_{SAT} = (77 ± 7) %) and muscle (mean FF_{muscle} = (8 ± 2) %) no change in FF was observed (cf. Fig. 2(b)). S05 stopped the measurement after 100 minutes.

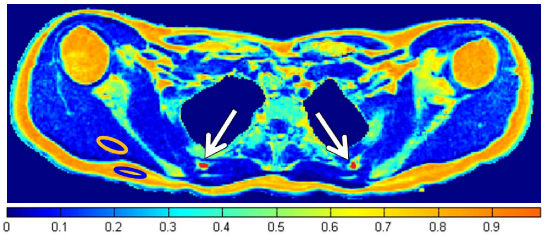

Fig. 1: Axial FF map of the first time point with marked ROIs of BAT (red, additionally indicated by white arrows), SAT (blue circle) and muscle (yellow circle). BAT-ROI is illustrated as projection over axial slices. ROIs were evaluated over time (cf. Fig. 2b).

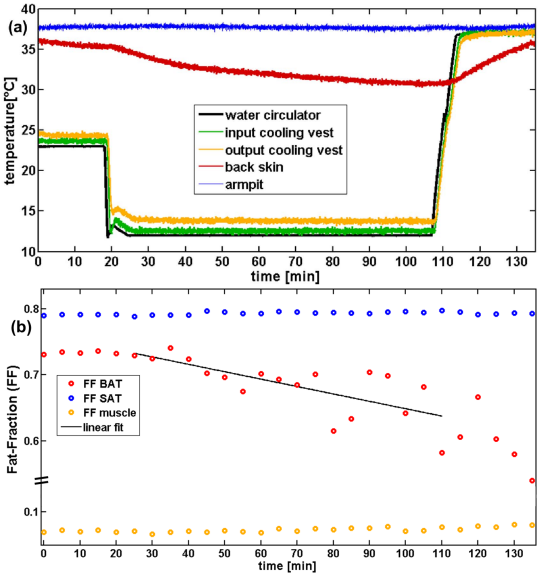

Fig. 2: Temperatures **(a)** acquired with 1 Hz. Water circulator temperature (black) and four thermal probes. FF values **(b)**, acquired every five minutes, of the right interscapular BAT depot (red) with applied linear fit (black), SAT (blue) and muscle (yellow) of S01. ROI positions are marked in Fig.1.

Tab. 1: Mean FF decrease from FF_{base} to FF_{cold} of detected BAT-ROI during cold stimulation by active cooling.

	FF_{base} [%]	FF_{cold} [%]	Slope [%/h]	Volume [ml]	Cooling [W]
S01	72 ± 6	59 ± 6	-5.5 ± 2.2	0.28	63 ± 3
S02	69 ± 3	67 ± 5	-3.3 ± 1.3	0.12	64 ± 3
S03	70 ± 6	66 ± 8	-3.4 ± 0.9	0.78	67 ± 3
S04	69 ± 5	68 ± 6	-1.9 ± 0.6	0.62	61 ± 3
S05	68 ± 6	59 ± 8	-6.1 ± 1.4	0.28	58 ± 2

Discussion and Conclusion: A FF decrease over time during cooling in evaluated BAT depots could be observed as well as a partly slight FF decrease during the baseline period indicating that BAT was already mildly stimulated by room temperature warm water. The acute change in FF during cooling might be caused by increased water content due to increased perfusion of BAT upon activation rather than by direct tissue re-modelling due to reduction of fat stores or changes in cellular morphology to increase thermogenic capacity. In the next step, we will investigate the link between acute FF changes and BAT activation and develop an algorithm for fully automatic detection of BAT activation. Therefore, a more robust registration algorithm is required. In conclusion, our approach detected FF changes at the expected position of the interscapular BAT depots in all volunteers during cold stimulation using time series of FF data.

References: **[1]** Berriel Diaz et al, Metabolism 63: 1238-49 (2014) **[2]** Hu et al., Magn. Reson. Imaging 31: 1195-1202 (2010) **[3]** Brunner et al., ISMRM 2014, 1674 **[4]** Chen et al., JNM, 54: 1584-1587 (2013) **[5]** Dixon et al., Radiology 153: 189-194 (1984) **[6]** Nolden et al., Int J Comput Assist Radiol Surg, 8: 607-20 (2013)

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