In vivo ultra short TE (UTE) MRI detects diffuse fibrosis in hypertrophic mouse hearts

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Target audience

(Pre)clinical scientists interested in novel contrast mechanisms to improve diagnosis and risk stratification of heart failure patients.

Purpose

Diffuse myocardial fibrosis is an important hallmark of various cardiac pathologies. The excessive accumulation of extracellular matrix (ECM) proteins, particularly collagen, plays a pivotal role in the transition towards heart failure (HF)[1]. Late gadolinium enhancement MRI can be used to detect diffuse myocardial fibrosis, however this technique is highly depended on the Gd-chelate accumulation kinetics and timing of the MRI examination. Ultra short TE (UTE) MRI can detect protons with very high transverse relaxation rates (low T_2 relaxation time) directly, including those associated with fibrotic tissue and especially collagen. Previously, *ex vivo* UTE MRI was used to visualize replacement fibrosis in rat myocardial infarcts[2]. *In vivo* imaging of diffuse fibrosis by UTE cardiovascular MRI has not been demonstrated thus far.

Methods

Mouse model: Pressure overload hypertrophy was induced by a severe transverse aortic constriction in C56BL/6 mice (♂, age 11 weeks, n = 18). MRI measurements were performed 11 weeks after surgery. Healthy littermates were used as control (n = 10).

In vivo MRI: MRI was performed at 9.4T with a 3D UTE sequence, consisting of a non slice-selective RF block-pulse followed by a radial readout, as previously described[3]. Sequence parameters were: TR=8.4 ms, NSA=1, FOV=3x3x3 cm^3, matrix size=128x128x128, minimum TE = 21 µs. Other TEs were 100, 300, 714 µs and 1.429 ms. Mice were anesthetized with isoflurane. *In vivo* UTE measurements were ECG triggered and respiratory gated to prevent motion artifacts. A blood-saturation slice in a short-axis orientation positioned above the left ventricle (LV) base provided improved contrast between blood and myocardium. To limit the acquisition time to about 14-16 min (depending on the mouse heart rate), 3 k-lines were measured after every R-wave and the acquisition matrix was undersampled by a factor 2.

Histology: Immediately after MRI, mice were euthanized and their hearts were excised for *ex vivo* UTE measurements. TE was varied between 21 µs and 4 ms. Finally, TAC (n=6) and control hearts (n=1) were embedded in paraffin, cut in 5-µm-thick sections and collagen was stained with Picrosirius Red. The collagen fractional area was determined from histology as a measure of the amount of diffuse fibrosis.

Data analysis: In vivo ΔUTE images were obtained by subtracting long-TE (1.429 ms) from short-TE (21 µs) images and the average ΔUTE signal change was quantified using a region-of-interest based approach. The *ex vivo* MR signal behavior as a function of TE was fitted to a 3-component model using a Levenberg-Marquardt least-squares algorithm[4]. All data analysis was done using Matlab (The Mathworks, Inc).

Results and Discussion

Fig. 1 shows representative examples of short-axis midventricular UTE images of control and TAC hearts with a short-TE, long-TE and the corresponding ΔUTE images. Due to time restrictions, only a limited number of TE values could be measured *in vivo*. (**Fig. 2**). Alternatively, the ΔUTE signal decrease from TE=21 µs to TE=1.429 ms was quantified. ΔUTE was larger for TAC hearts (0.21±0.07) as compared to control hearts (0.13±0.04) ($P < 0.001$), which we attribute to the presence of diffuse fibrosis in the TAC hearts. To prove this hypothesis, the *ex vivo* UTE signal behavior as a function of TE was studied in detail and related to the fractional collagen area from histology.

Three signal components were revealed, i.e. a fast and slow exponential decaying pool, and an oscillating pool, which likely resulted from the chemical shift resonance frequency difference of the lipid pool (**Fig. 3**). No change in $T2^*_{lipid}$ (average: $T2^* = 820 \pm 470$ µs) was detected. $T2^*_{fast}$ was slightly increased in TAC hearts (38 ± 3.9, $P < 0.05$) as compared to control hearts (34 ± 3.9) and $T2^*_{slow}$ showed a moderate decrease in TAC (23 ± 4.7 ms) as compared to control hearts (30 ± 11 ms) ($P = 0.09$). Surprisingly, the relative contributions of the different pools to the total signal remained essentially constant. Importantly, the amount of diffuse fibrosis linearly correlated with $T2^*_{slow}$ (r = 0.82, $P = 0.01$) (**Fig. 4**).

Conclusion

The *in vivo* ΔUTE signal change in TAC heart was larger as compared to control hearts. *Ex vivo* measurements revealed that this can be attributed to changes in T2* as a consequence of the presence of diffuse fibrosis. Thus, UTE cardiovascular MRI provides an unique opportunity for the noninvasive assessment of diffuse myocardial fibrosis, without the use of contrast agents. Clinical translation of this method could ultimately improve risk stratification of heart failure patients.

Acknowledgement

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References

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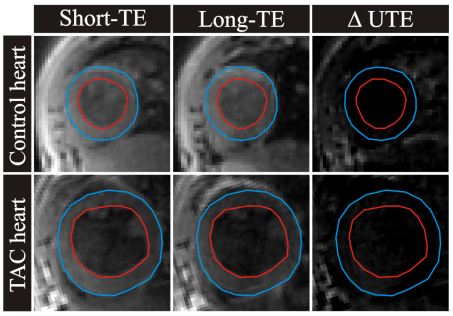

Fig. 1. *Short-axis UTE images of a control heart and a TAC heart with a short-TE (21µs), long-TE (1.429 ms) and the corresponding ΔUTE image, in which no regional hyperenhancement was observed visually.*

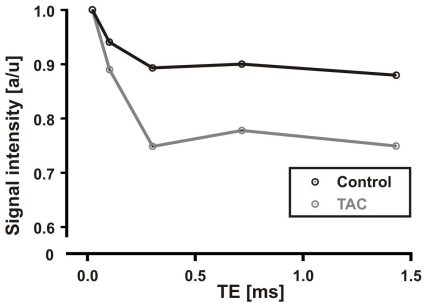

Fig 2. *In vivo* UTE signal behavior in a control and TAC heart.

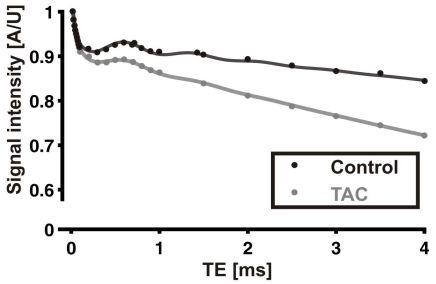

Fig. 3 *Ex vivo* UTE signal as a function of TE in a control and TAC heart.

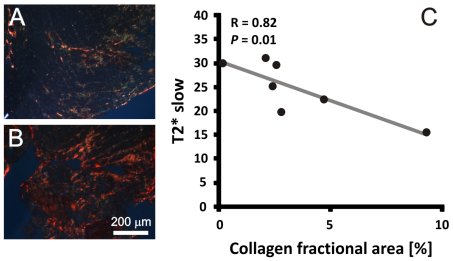

Fig. 4. *Picrosirius Red stained slices of a TAC heart with a small (**A**) and large amount of fibrosis (**B**). Relation between T2*slow and the collagen fractional area (**C**).The gray line is a linear fitting.*