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Increased MR-guided high intensity focused ultrasound (MR-HIFU) sonication efficiency of uterine fibroids after carbetocin administration☆

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HIGHLIGHTS

- Carbetocin administration resulted in more efficient MR-HIFU fibroid sonications.
- 16.7% of the women experienced mild side effects of carbetocin administration.
- Carbetocin may lead to a broader patient eligibility and reduced treatment times.

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ABSTRACT

Purpose: We investigated whether administration of the long-acting uterus stimulant carbetocin increased intra-subject sonication efficiency during Magnetic Resonance image guided High Intensity Focused Ultrasound (MR-HIFU) treatment of uterine fibroids.

Method: In this prospective cohort study, thirty women with symptomatic uterine fibroids undergoing MR-HIFU treatment were included between January 2018 and January 2019. Treatment started with three sonications on one side of the uterine fibroid. Subsequently, one ampoule of 1 mL carbetocin (100 μg/mL) was administered intravenously and treatment continued with three sonications on the other side of the uterine fibroid. We compared the intra-subject sonication efficiency, in terms of Energy Efficiency Factor (EEF), thermal dose volume and sonication time to ablate one cm^3 of fibroid tissue, before and after carbetocin administration. Adverse events that occurred within 30 min after carbetocin administration were recorded.

Results: Sonication efficiency improved after carbetocin administration as indicated by a significant decrease in EEF and sonication time ($p = 0.006$ and $p = 0.001$ respectively), and a significant increase in thermal dose

Abbreviations: EEF, Energy Efficiency Factor; EM, Equivalent Minutes; MaSS, Myoma Screening Study; MR-HIFU, Magnetic Resonance image guided High Intensity Focused Ultrasound; NPV, Non-Perfused Volume; SI, Signal Intensity; SSI, Scaled Signal Intensity; T1w-CE, Contrast-enhanced T1-weighted imaging; T2w, T2-weighted imaging.

☆ Trial registration: The conducted study was part of the Myoma Screening Study II (MaSSII) study which was approved by our IBR with protocol ID NL56182.075.16 and the MaSSII was retrospectively registered at ISRCTN as ISRCTN14634593.

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volume reached (p = <0.001). Five women (16.7%) experienced temporary tachycardia, one women in combination with headache, within 30 min after carbetocin administration.
Conclusion: Administration of the long-acting uterus stimulant carbetocin improved the MR-HIFU treatment intra-subject sonication efficiency in women with symptomatic uterine fibroids.

1. Introduction

For women suffering from symptomatic uterine fibroids, Magnetic Resonance image guided High Intensity Focused Ultrasound (MR-HIFU) is currently the only non-invasive treatment option when medication is not effective and/or undesirable. MR-HIFU has several advantages over (minimally) invasive treatments like hysterectomy or uterine artery embolization, including a low number of complications, short recovery time and no need for general or epidural anesthesia [1]. During MR-HIFU thermal ablation, an ultrasound transducer produces a focused beam of high-intensity ultrasound waves. Inside the focal area, the targeted tissue absorbs the acoustic energy leading to a temperature rise, which causes coagulative necrosis [1]. Thermal ablation is performed by multiple sonications of which the number and duration depend on the size and tissue characteristics of the fibroid. Directly post MR-HIFU, a contrast enhanced T1 weighted imaging (T1w-CE) MRI-scan is used to visualize the ablated tissue, which can be observed on such scans as a non-perfused volume (NPV). A high NPV to total fibroid volume (NPV%) is a technical predictor for good clinical outcomes and low re-intervention rates [2].

Not all women suffering from symptomatic uterine fibroids are eligible for MR-HIFU treatment, either due to patient characteristics, e.g. too high BMI, or fibroids characteristics such as high tissue perfusion [3,4]. Patient eligibility is based on a screening MRI-scan classification. The Funaki classification and Scaled Signal Intensity (SSI) score are the two most commonly used classifications and roughly distinguish fibroids that are expected to be easily ablated and those that will likely result in inefficient sonications [5,6]. Besides limited patient eligibility, another hurdle for clinical implementation of MR-HIFU is the treatment duration. Complete ablation takes on average two to three hours of costly MRI-scanner time per patient and light sedation is necessary during treatment for patient comfort [1]. This urges the need for a more efficient treatment, i.e. reaching a high NPV% in a shorter period of time without jeopardizing treatment safety. Broadening eligibility and reducing treatment time are essential factors for faster adoption of MR-HIFU treatment for uterine fibroids in clinical practice [7].

Previous studies showed that the use of the short-acting uterus stimulant oxytocin during ultrasound- or MR-guided HIFU treatment positively influences clinical outcomes on a treatment level [4,8]. Since oxytocin receptors could not be detected in the myometrium, it was initially believed that uterotonics did not have an effect on the non-pregnant uterus [9]. However, oxytocin infusion during myomectomy decreases blood loss [10]. Due to the contracting effect of the uterus stimulant, less blood flow in the uterine fibroid tissue is expected. This lower blood flow will result in less blood volume that needs to be heated and this is expected to result to more effective heating of fibroid tissue during MR-HIFU treatment, and less of the so called "cooling effect" [4,9]. Carbetocin is a synthetic octapeptide analogue of oxytocin with agonist properties at the oxytocin receptor [11–13]. Due to molecular changes, carbetocin is more stable and has a gradual breakdown, resulting in an up to ten times longer half-life time of carbetocin compared to oxytocin [11]. It was hypothesized before that sonication efficiency would benefit more from the use of the long-acting uterus stimulant carbetocin, instead of the short-acting oxytocin, because the MR-HIFU treatment can take up to three hours [14]. In previous studies, the effect of uterus stimulant administration on MR-HIFU treatment outcomes was determined on a treatment level by comparing women who had or had not received a uterus stimulant during the MR-HIFU treatment [9,14]. It could, however, not be excluded that several inter-subject differences like tissue characteristics, location of fibroid or radiologist's treatment experience also influenced treatment outcome. To circumvent the influence of inter-subject differences on the effect of uterus stimulants on sonication efficiency, we performed an intra-subject analysis in which we compared technical outcomes on a sonication level before and after uterus stimulant administration. The primary objective of this study was to investigate whether sonication efficiency in terms of the Energy Efficiency Factor (EEF), thermal dose volume and sonication time to ablate one cm^3 of fibroid tissue, would improve after administration of uterus stimulant carbetocin during MR-HIFU treatment.

2. Material and methods

2.1. Study design

We included women who took part in a prospective cohort study performed in our hospital (the Myoma Screening Study; MaSS registry ID ISRCTN14634593). Eligibility for MR-HIFU treatment was determined by a screening MRI-scan (performed on a 1.5 T MRI-scanner, Achieva, Philips Healthcare, Eindhoven, The Netherlands). All women who underwent the MR-HIFU treatment between January 2018 and January 2019, received carbetocin during treatment, unless a contra-indication for the use of a uterotonic was known. Women receiving a second MR-HIFU treatment for the same fibroid were excluded from our intra-subject analyses, as were the data of cases with technical and treatment failures (Fig. 1). When adequate heating could not be achieved, or when bowels were located within the beam pathway and could not be manipulated out of it, cases were considered as treatment failures.

2.2. MR-HIFU treatment

Each MR-HIFU treatment was performed by one of our radiologists trained on the Sonalleve V1 device (Profound Medical Inc. Mississauga, Canada), integrated into a 1.5 T MRI-scanner (Achieva, Philips Healthcare, Eindhoven, The Netherlands). Four differently sized ellipsoidal treatment cells of 4, 8, 12 or 16 mm in the axial dimension with volumes of 0.08, 0.67, 2.26 and 5.36 mL respectively, were available for volumetric ablation on the V1 device [7] and for every sonication the level of acoustic power (80–200 W) was determined based on the results of an initial test sonication using low power (40–60 W). Each treatment started with one or two test sonications and continued with at least three sonications on one side of the uterine fibroid (Fig. 2). Next, one ampoule of 1 mL carbetocin (100 μg/mL) was administered intravenously. Five minutes after the carbetocin administration was completed, treatment continued with at least three sonications on the other side of the same uterine fibroid. These sonications were part of the same treatment cell cluster, i.e. the distance between the transducer and the sonication target was comparable. After each sonication, the advised cooling time of the HIFU device was adhered to. During treatment, patients received light sedation including propofol infusion and administration of fentanyl bolus. A sedation professional continuously monitored patients' vital signs with a three-lead electrocardiogram, pulse oximetry, non-invasive blood pressure measurement, and continuous capnography. After collecting all necessary data of the six sonications to be analyzed, the treatment continued as usual [15]. Immediately after completion of the MR-HIFU treatment, the NPV% was determined on a T1w-CE MRI-scan (DOTAREM®, 0.2 mL/kg; Gadoterate Meglumine, 0.1 mmol/kg; Guerbet, France). Fibroid and NPV volume were measured using IntelliSpace

Portal software (Philips Healthcare) by semiautomatic segmentation in the tumor tracking function with review and manual correction of the segmentation [16].

2.3. Data collection

Three sonications before and three sonications after completion of carbetocin admission, were selected for analyses by IV and the performing radiologist (EB, RH or MV) during treatment. These sonications had to meet the following criteria: no technically failed sonication (due to either abortion by patient or software), sonication within the same treatment cluster (i.e. comparable distance from abdominal wall), optimal heating pattern (e.g. not gradually increasing, not reaching the plateau phase, prolonged time to reach the plateau phase or irregular temperature upslope) and comparable appearance on the T2 weighted imaging (T2w) MRI planning images, without visible heterogeneity of the fibroid tissue. When these criteria were not met, data of that sonication was excluded and the subsequent sonication that complied was included. Since uterine fibroids are not perfectly oval shaped, it was not always possible to obtain treatment cells of the same size within the same treatment cluster. In those cases, we needed to select a smaller or larger sized treatment cell. When selecting the sonications for post carbetocin administration analyses, overlap with previously treated cells was avoided to prevent treatment of preheated tissue. In exceptional cases, almost none of the performed sonications could be finished successfully. In these cases, IV and the performing radiologist chose sonications that were comparable in size and visually comparable in signal intensity (SI) or heating pattern until abortion. Analysis were performed by KA, HO and IN, who did not take part in these treatments.

Data on the size, location and number of fibroids per patient were retrieved from the screening T2w MRI-scans. These scans were also used to determine the Funaki classification and SSI score [16]. Possible adverse events occurring within 30 min after carbetocin administration were collected by the performing radiologist.

2.4. Sonication efficiency

Sonication efficiency was determined in terms of EEF, thermal dose volume and time needed to ablate one cm^3 of fibroid tissue on a sonication level. The EEF is the energy required to ablate one mm^3 of fibroid tissue [7,17]. To calculate the EEF the following formulas were used [17]:

$$Energy\ (J) = Power\ (W) \times Heating\ duration\ (s)$$

$$EEF\ (J/mm^3) = Energy\ (J)/Thermal\ dose\ volume\ (mm^3)$$

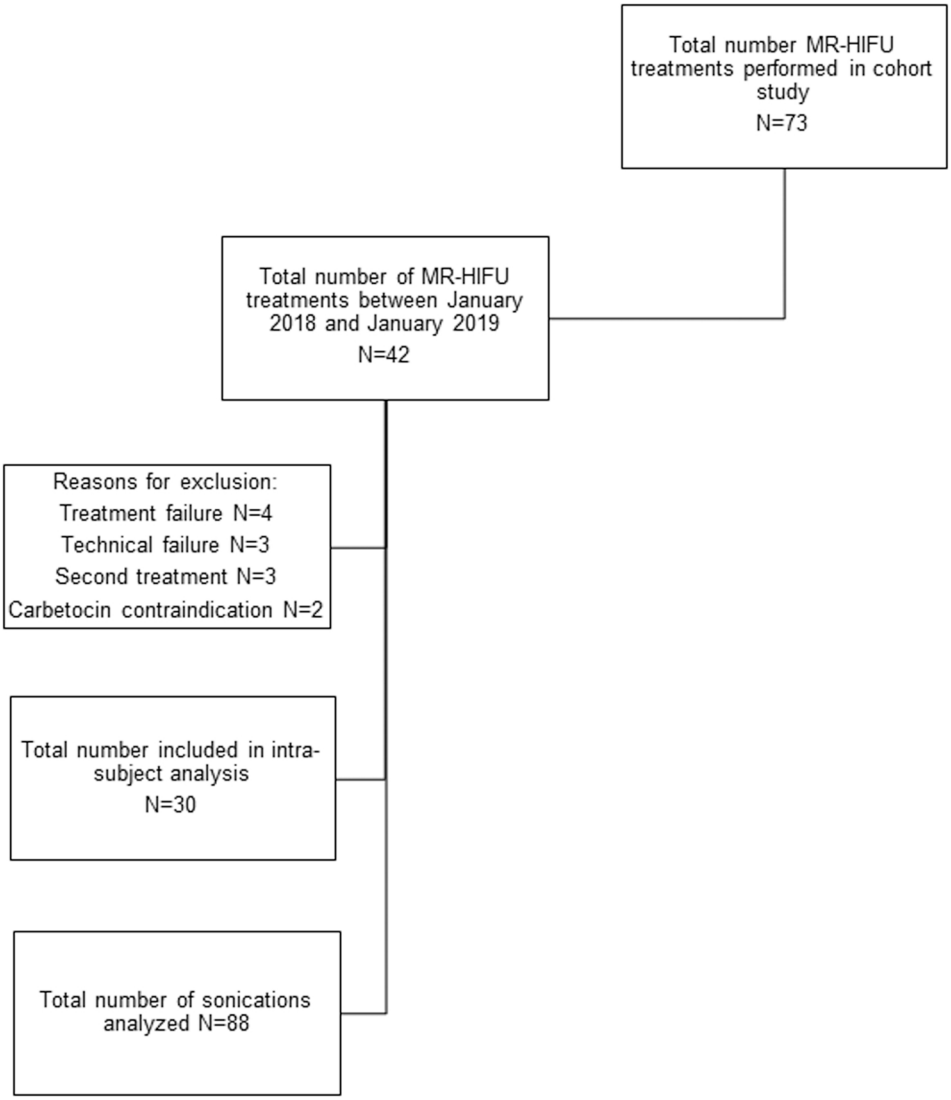

Fig. 1. Flowdiagram of women included in the intra-subject analysis.

The thermal dose is a measure of the effect of heating of tissue for a certain amount of time [7,18]. Whether this dose is lethal, depends on the biological characteristics of the heated tissue. A commonly accepted thermal dose threshold for cell death to occur is 240 equivalent minutes (EM) at 43 °C [18]. The HIFU device automatically calculated thermal dose maps with a unit of EM at 43 °C, and displayed the volume where a thermal dose > 240 EM at 43 °C was reached [7]. We refer to this volume as the thermal dose volume.

Time needed to ablate one cm^3 of fibroid tissue is referred to as the sonication time/cm^3 and was calculated as follows [17]:

$$Sonication\ \ time/cm^3\ \ (s/cm^3)\ \ =\ \ Heating\ \ duration\ \ (s)/Thermal\ \ dose\ \ volume\ \ (cm^3)$$

The selected acoustic power *(W)* transmitted by the transducer, the heating duration *(s)*, the reached temperature *(°C)* and thermal dose volume *(volume (cm^3) of 240 EM at 43 °C reached)* of all three sonications before and after carbetocin administration were collected from the HIFU device report. In case multiple fibroids were treated, only the efficiency data of the first treated fibroid was collected.

2.5. Statistics

Statistical analyses were performed using IBM SPSS version 26 and

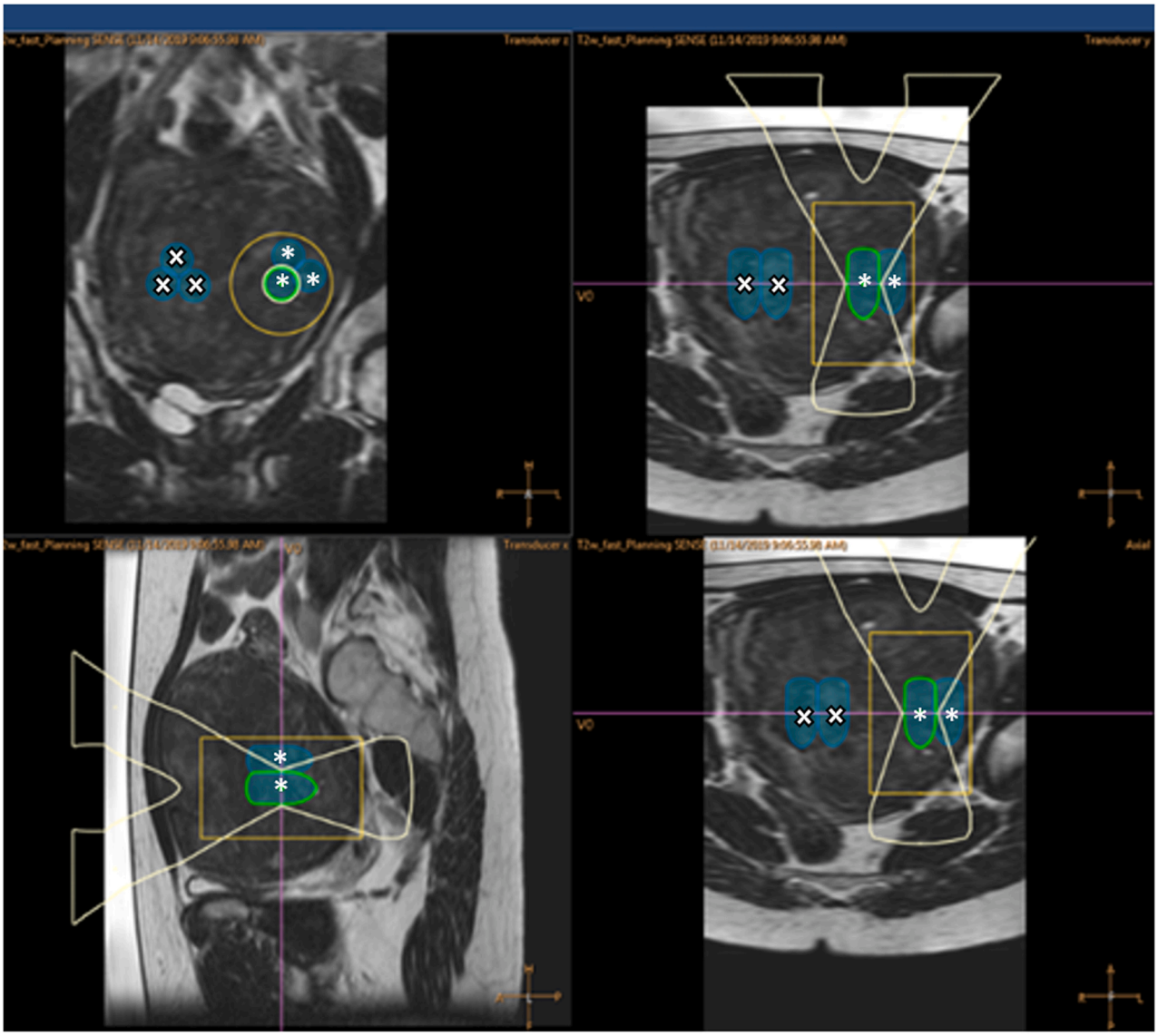

Fig. 2. Screenshot of the Sonalleve MR-HIFU therapy application-planning screen with sonications planned on T2w MRI-scan images. **description:** During treatment preparation, the uterine fibroid is displayed in three directions; top left coronal direction, top and bottom right axial direction and bottom left sagittal direction. The three sonications (blue shaped, sized 16 mm) before carbetocin administration are marked with white asterisks and placed on one side of the uterine fibroid. The three sonications (blue shaped, sized 16 mm) after carbetocin administration are marked with white crosses and placed on the other side of the uterine fibroid. The selected sonication is illuminating in green and the borders of the ultrasound beam are displayed in yellow in all three directions.

STATA version 15. Categorical data were presented as n (%), continuous variables were presented as mean (± SD) in case of a normal distribution, or median (range) in case of a skewed distribution. Distribution was assessed by normal probability plots and eyeball testing.

We tested for differences between efficiency determinants before and after carbetocin administration on a sonication level using linear multilevel analysis with correction for potential individual differences. For this, a two-level structure was used; efficiency determinants before and after carbetocin were clustered per patient. We analyzed the difference between efficiency determinants pre and post administration with and without addition of the possible confounder treatment cell size, classified as a categorical variable. Furthermore, a sensitivity analyses was performed, excluding the cases with a difference in treatment cell size before and after administration.

3. Results

3.1. Study population

Median age of the 30 included women was 43.5 years (range 26–54, Table 1) and most fibroids were classified as Funaki 2 fibroids (86.7%).

3.2. Sonication efficiency

The overall mean selected treatment cells size *(mm)* pre and post carbetocin administration differed. In 18 of 30 cases (60.0%), treatment cell size *(mm)* before and after carbetocin administration was the same, in 10 cases the treatment cell size was larger pre carbetocin administration, in the remaining two cases, the cell size was larger post carbetocin administration. In two cases, the uterine fibroid was too small to collect data of three sonications without overlap with three previous sonications. In these two cases, only two sonications before and after carbetocin administration were selected for analysis. Before and after correction for treatment cell size, the selected acoustic power *(W)* was significantly higher (respectively $p < 0.001$ and $p = 0.001$) after carbetocin administration (Table 2). The transmitted energy *(J)* and the heating duration *(s)* did both not differ significantly (Table 2). The thermal dose volume *(cm^3)* of the three sonications after carbetocin administration, and after treatment cell size correction, was significantly higher ($p < 0.001$) than the three sonications before carbetocin administration (Table 2). The EEF *(J/mm^3)* and sonication time to ablate one cm^3 *(s/cm^3)* decreased significantly after carbetocin administration ($p = 0.006$ and $p = 0.001$ respectively, Table 2). Comparable results were seen when performing sensitivity analysis, as shown in the supplement. There were relatively large inter-subject differences between the mean of the sonication efficiency parameters of the three sonications before and after carbetocin administration (Fig. 3). After all sonications were performed, a median NPV of 91.9% [14.5–100] was reached.

Table 1
Patient characteristics.

Patient characteristics	N = 30 Mean ± SD or median [range]
Age (years)	43.5 [26–54]
BMI (kg/m^2)	25.1 ± 3.0
Number of fibroids:	
1	14 (46.7%)
2	5 (16.7%)
3	4 (13.3%)
4	1 (3.3%)
5	3 (10.0%)
> 5	3 (10.0%)
Location of fibroids[a]	
Submucosal	12 (40.0%)
Intramural	6 (20.0%)
Subserosal	6 (20.0%)
Hybrid	6 (20.0%)
Fibroid diameter (cm)[a]	5.6 [1.6–16.9]
Fibroid volume (mL)[a]	66.3 [2.7–1094.5]
Funaki type:[a]	
1	2 (6.7%)
2	26 (86.7%)
3	2 (6.7%)
SSI score[a]	9.3 [− 3.0–90.0]

[a] Only measured on largest fibroid in case of multiple fibroids. SSI: Scaled Signal Intensity.

3.3. Adverse events

Tachycardia within 30 min after administration of carbetocin occurred in 16.7% of patients (5/30). One patient reported a headache in combination with the tachycardia. All of these side effects were temporary and resolved spontaneously.

4. Discussion

In this study, we showed on a sonication level that the administration of the long-acting uterus stimulant carbetocin led to a significant decrease in EEF and sonication time needed to ablate one cm^3 of fibroid tissue, and a significant increase in thermal dose volume. An increase in thermal dose after carbetocin administration reduces the time needed to sonicate one cm3 of fibroid tissue whereas it does not affect the duration of a sonication i.e. heating duration. Thus, the same duration of a sonication can be applied to heat a larger volume of fibroid tissue, leading to more efficient MR-HIFU sonications. It is expected that the use of carbetocine during a complete MR-HIFU treatment, will result in a more efficient overall uterine fibroid treatment as well.

Our findings are a quantitative analysis of the effect of a uterus stimulant on fibroid tissue during a sonication, and are line with the previously described significant reduction in sonication power and treatment time needed on a treatment level as reported by Jeong et al. They compared women treated with carbetocin during MR-HIFU, to women in a control group who did not receive carbetocin [14]. Zhang et al. analyzed EEF and time needed to ablate one cm^3 of adenomyose tissue after administration of oxytocin during ultrasound guided HIFU [17]. In their study, a significant decrease in EEF on a treatment level was seen in women who had received oxytocin compared to women who had received normal saline. Furthermore, a significant decrease in sonication time on a treatment level was seen in the oxytocin group. It is important to note that external factors as intermediate cooling time, planning difficulties or patient check-ups can prolong the total procedure time. Therefore, total procedure time might not be an appropriate measure to analyze the effect of a uterus stimulant on MR-HIFU treatment efficiency.

A related problem occurs when comparing NPV% reached after the treatment with and without uterus stimulant administration. The studies of Zhang et al., Jeong et al. and Lozinski et al., all reported a significant improvement in NPV% on treatment level, as a result of introducing oxytocin or carbetocin administration in their treatment protocol [9,14,17]. NPV% is an important predictor of clinical symptom improvement, and a high NPV% should be aimed for [1,19]. Final NPV% reached is, however, dependent on external factors as well. These include possible technical difficulties, impossibilities in manipulation, treatment site or radiologist learning-curve stage and treatment time left. Our study design allowed for an intra-subject analysis, which was independent of these external factors and therefore added valuable information on the effect of carbetocin. The more effective heating of the fibroid tissue on a sonication level in our study might, on a treatment level, have led to more sonications within the same time frame. This more effective heating may also have contributed to our post treatment average NPV% of 91%, which can be considered a very good result [1].

The sonication efficiency improvement of carbetocin is expected to be the result of uterus contractions reducing blood flow in fibroid tissue [9,20]. A high blood flow carries away the local heat generated and therefore the tissue around the blood vessel is not sufficiently heated and

Table 2
Intra-subject analyses technical parameters pre- and post carbetocin administration.

Variable N = 30	*Pre-carbetocin Mean ± SD*	*Post-carbetocin Mean ± SD*	*Mean difference [CI]*	*P-value*	Mean difference [CI] with TCS as covariate	P-value with TCS as covariate
Temperature reached (°C)	66.9 ± 4.0	67.9 ± 4.8	1.0 [− 0.1 – 2.1]	0.069	0.7 [− 0.4 – 1.8]	0.188
Power (W)	133.0 ± 27.6	140.6 ± 28.1	7.6 [4.0 – 11.2]	< 0.001*	5.9 [2.4– 9.5]	0.001*
Heating duration (s)	41.1 ± 14.6	38.7 ± 12.5	-2.4 [− 5 – 0.2]	0.073	0.9 [− 1.5 – 3.2]	0.468
Energy (J)	5347.7 ± 1837.4	5371.6 ± 1799.5	23.8 [− 302.9 – 350.6]	0.886	338.8 [29.5 – 648.0]	0.032*
Thermal dose volume (cm^3)	2.0 ± 1.6	2.5 ± 1.8	0.5 [0.2 – 0.8]	< 0.001*	0.7 [0.4 – 1.0]	< 0.001*
EEF (J/mm^3)	4.8 ± 10.7	2.8 ± 3.4	-2.1 [− 3.9 – (- 0.4)]	0.018*	-2.6 [− 4.5 – (−0.8)]	0.006*
Sonication time (s/cm^3)	46.0 ± 79.2	25.9 ± 26.0	-20.1 [− 33.5 – (- 6.7)]	0.003*	-23.0 [− 38.1 – (−9.9)]	0.001*

* Significant difference between pre- and post-carbetocin administration. CI: Confidence interval; TCS: Treatment cell size; EEF: Energy Efficiency Factor

ultimately not completely ablated [20]. This is referred to as the "cooling" or "heat-sink" effect [9,20]. A study by Otonkoski et al., showed that oxytocin administration resulted in a strong decrease in blood flow of the fibroid tissue, while having minor or no effect on the blood flow of normal myometrium. Therefore, not the increased contractility of the uterus, but the fibroid itself or the supplying circulation might be related to this effect [21]. Furthermore, they stated that routine use of oxytocin during HIFU treatment might make the treatment suitable to a larger group of women.

At this point, not all women are suitable for MR-HIFU treatment. Funaki classifies fibroids in fibroids with a higher SI compared to myometrium (Funaki type 3) or lower SI compared to myometrium (Funaki type 1 and 2) and in general, ablating Funaki type 3 fibroids leads to a low NPV% [5]. This is due to the fact that Funaki 3 fibroids are more heterogeneous, resulting in less effective heating due to scattering of ultrasound waves, and contain higher blood flow and vascularization, making it difficult to obtain adequate temperature elevation (due to heat-sink effect) [20]. Park et al. developed the SSI score as an alternative for the Funaki classification. Fibroids reaching a SSI score above 16, on a 0–100 scale, often result in a NPV of 45% or below [6]. Funaki type 3 fibroids or fibroids with a high SSI score may particularly benefit from the reduced blood flow through the fibroid by the administration of a uterus stimulant. Maybe a blood flow cutoff point should be identified as eligibility tool, as was suggested by Otonkoski et al. [21]. Because most fibroids of the patients in our study were classified as Funaki 2, we could not analyze the effect of carbetocin administration per Funaki subtype.

As far as we know, no data is at this point available on the effect of heating of carbetocin. However, no effects are expected due to the limited dosage and no adverse events reported in previous studies om the use of uterus stimulants during HIFU treatment [14,17]. In our study, we observed possible carbetocin administration related adverse events in five of 30 women, but all adverse events were temporary, relieved spontaneously and are known side effects of carbetocin. Furthermore, Holleboom et al. suggested that the administration of a single injection of carbetocin is more convenient compared to continuous bolus injections of oxytocin, which requires preparation of a dosing pump and is therefore more prone to dosing errors [13].

4.1. Limitations

Ideally, we would have performed three sonications with the same size before and after carbetocin administration and compared their efficiency parameters. However, in reality, additional sonications needed to be performed since they did not meet the selection criteria and additional sonications were performed while the effect of carbetocin was awaited, to minimize wasting valuable treatment time. Sonications were selected based on visually comparable heating patterns. Not optimal heating patterns are often seen during MR-HIFU treatment, and by excluding this data, both before and after carbetocin administration, risk of eliminating effect of carbetocin on the heating pattern is not expected. Since fibroid tissue is heterogeneous, another limitation of our method is the possibility that the SI of the pre carbetocin sonication location differed from the post-carbetocine location. Fibroid tissue with a low SI on T2w MRI-scans is easier to heat compared to high SI fibroid tissue, and selection of different tissue before and after carbetocin administration, could therefore lead to incorrect assumptions. Furthermore, it might be possible that post carbetocin locations were preheated by pre carbetocin sonications due to thermal conductivity, resulting in beneficial results for the post-carbetocin sonications [22]. However, we believe this impact is negligible since we awaited the advised cooling time. To minimize selection bias, analyses were performed by KA, HO and IN, who were not involved in the treatment procedure and therefore sonication selection. However, they were not blinded for the fact if a sonication was performed before or after carbetocin administration.

By analyzing different sized treatment cells before and after carbetocin, another bias could have been introduced. Therefore, treatment cell size was included as possible confounder in the intra-subject analyses and a separate sensitivity analyses was performed as well, excluding all unequal treatment cells (Supplementary).

Despite the long-acting activity of carbetocin in comparison to the short-acting oxytocin, the effect of this long-acting uterus stimulant might still decline over time. Little is known about the effect of carbetocin on fibroid tissue after half time has passed. Since the half time of carbetocin' is 40 min, and average treatment time between 120 and 180 min, a second dosage might be necessary to achieve an optimal effect of carbetocin during the complete procedure.

4.2. Future perspectives

Our intra-subject analysis showed that carbetocin has a beneficial effect on the sonication efficiency on a sonication level and is therefore implemented in our clinical practice. However, not enough is known about the effect of carbetocin on fibroids with different SI's and on the most important outcome from a patient perspective, the improvement of symptoms and quality of life. Future studies should therefore include a larger study population with a better distribution over the Funaki classification and/or SSI scores and perform preplanning of the three sonications on each side, in order to determine whether carbetocin administration is especially beneficial for the treatment of more fluid

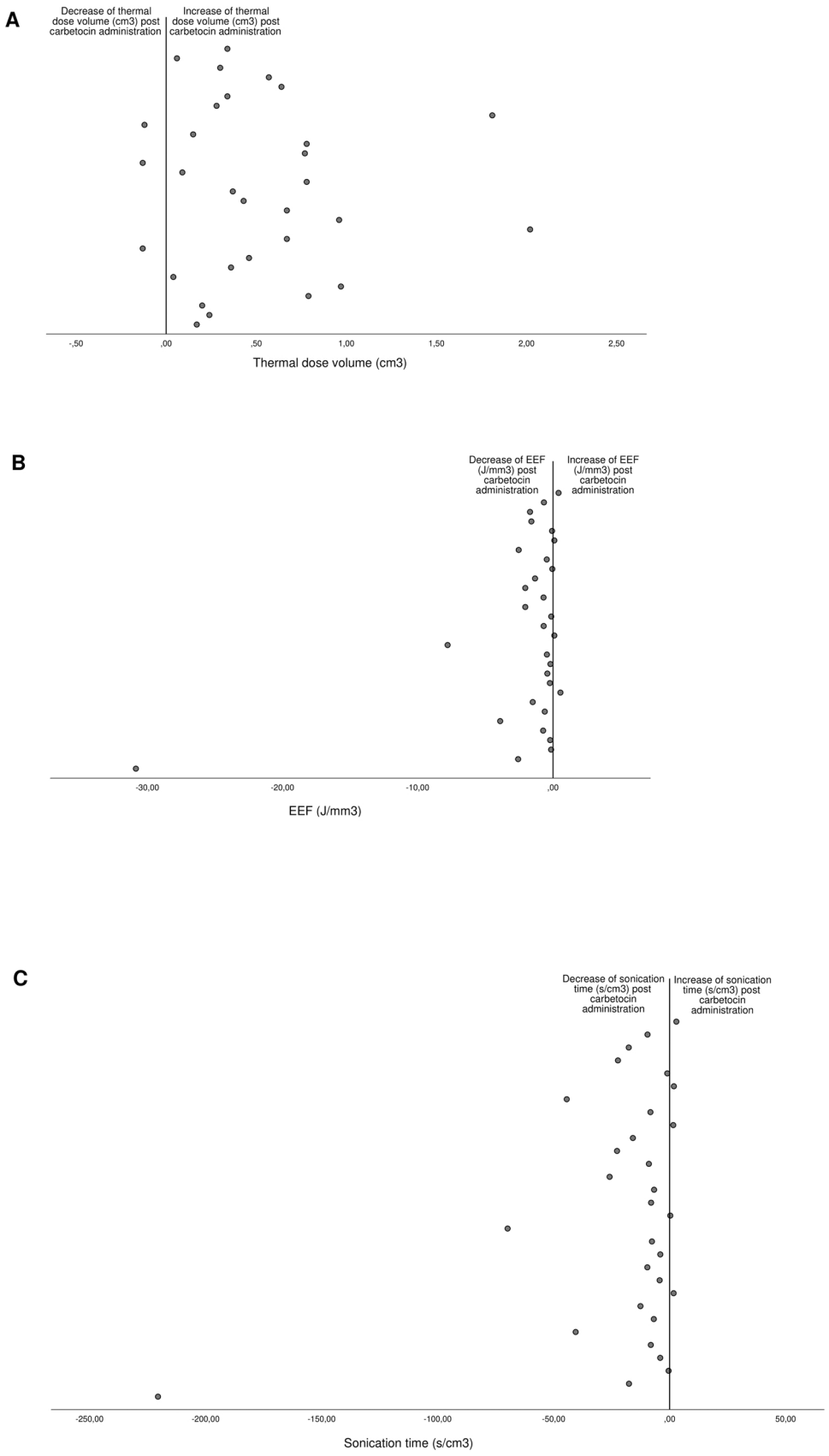

Fig. 3. Scatter plots of the difference of efficiency parameters pre and post carbetocin administration. **description**. Plots showing the difference in thermal dose volume (A), Energy Efficiency Factor (EEF) (B) and sonication time to ablate one cm3 of fibroid tissue (C) between post and pre carbetocin administration for each individual patient. Each patient is represented by a dot**.**

rich fibroids. This would aid prognostic models that can predict MR-HIFU treatment outcome. The optimal way to assess the effect of carbetocin on clinical outcomes may be by performing a large double blind randomized placebo-controlled trial.

5. Conclusion

Administration of carbetocin during MR-HIFU treatment of uterine fibroids leads to more efficient sonications when analyzed on an intra-subject level.

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Ethical statement

All authors state that this study complies with the Declaration of Helsinki. All participants signed informed consent as part of participation in the Myoma Screening Study II (MaSSII; protocol ID NL56182.075.16) which was approved by our local Research Ethics Committee (number 16.0479).

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Kimberley Anneveldt: Conceptualization, Methodology, Formal analysis, Validation, Writing – original draft, Visualization. **Heleen van 't Oever:** Formal analysis, Validation, Writing – original draft. **Inez Verpalen:** Conceptualization, Methodology, Data curation, Funding acquisition, Methodology, Validation, Writing – review & editing. **Ingrid Nijholt:** Formal analysis, Validation, Writing – review & editing. **Wilbert Bartels:** Conceptualization, Validation, Writing – review & editing. **Jeroen Dijkstra:** Conceptualization, Writing – review & editing. **Rolf van den Hoed:** Conceptualization, Data curation, Writing – review & editing. **Miranda van 't Veer:** Conceptualization, Data curation, Writing – review & editing. **Erwin de Boer:** Conceptualization, Data curation, Writing – review & editing. **Sebastiaan Veersema:** Supervision, Writing – review & editing. **Judith Huirne:** Supervision, Writing – review & editing. **Joke Schutte:** Conceptualization, Supervision, Writing – review & editing. **Martijn Boomsma:** Conceptualization, Resources, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejro.2022.100413.

References

[1] I.M. Verpalen, K.J. Anneveldt, I.M. Nijholt, et al., Magnetic resonance-high intensity focused ultrasound (MR-HIFU) therapy of symptomatic uterine fibroids with unrestrictive treatment protocols: a systematic review and meta-analysis, Eur. J. Radiol. (2019) 120.
[2] B. Keserci, N.M. Duc, Magnetic resonance imaging parameters in predicting the treatment outcome of high-intensity focused ultrasound ablation of uterine fibroids with an immediate nonperfused volume ratio of at least 90, Acad. Radiol. 25 (2018) 1257–1269.
[3] N.M. Duc, B. Keserci, Review of influential clinical factors in reducing the risk of unsuccessful MRI-guided HIFU treatment outcome of uterine fibroids, Diagn. Interv. Radiol. 24 (2018) 283–291.
[4] T. Łoziński, A. Ludwin, J. Filipowska, et al., Oxytocin and misoprostol with diclofenac in the preparation for magnetic resonance–guided high-intensity ultrasound treatment of symptomatic uterine fibroids: a prospective cohort study, Ultrasound Med. Biol. 47 (2021) 1573–1585.
[5] K. Funaki, H. Fukunishi, T. Funaki, K. Sawada, Y. Kaji, T. Maruo, Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images, Am. J. Obstet. Gynecol 196 (2007) 184.e1–184.e6.
[6] H. Park, S. Yoon, A. Sokolov, Scaled signal intensity of uterine fibroids based on T2-weighted MR images: a potential objective method to determine the suitability for magnetic resonance-guided focused ultrasound surgery of uterine fibroids, Eur Radiol 25 (2015) 3455–3458.
[7] Y. Kim, B. Keserci, A. Partanen, et al., Volumetric MR-HIFU ablation of uterine fibroids: Role of treatment cell size in the improvement of energy efficiency, Eur. J. Radiol. 81 (2011) 3652–3659.
[8] S.C.- Yu, E.C.- Cheung, V.Y.- Leung, L.W.- Fung, Oxytocin-augmented and non-sedating high-intensity–focused ultrasound (HIFU) for uterine fibroids showed promising outcome as compared to hifu alone or uterine artery embolization, Ultrasound Med. Biol. 45 (2019) 3207–3213.
[9] T. Lozinski, J. Filipowska, P. Krol, A. Kubaty, P. Wegrzyn, Oxytocin administration in high-intensity focused ultrasound treatment of myomata, BioMed. Res. Int. 2018 (2018) 1–5.
[10] S. Atashkhoei, S. Fakhari, H. Pourfathi, E. Bilehjani, P. Garabaghi, A. Asiaei, Effect of oxytocin infusion on reducing the blood loss during abdominal myomectomy: a double-blind randomised controlled trial, BJOG: Int. J. Obstetrics Gynaecol. 124 (2017) 292–298.
[11] L.S. Meshykhi, M.R. Nel, D.N. Lucas, The Role of Carbetocin in the Prevention and Management of Postpartum Haemorrhage, Obstetric Anesthesia Digest 37 (2017) 115–116.
[12] M. De Bonis, M. Torricelli, L. Leoni, et al., Carbetocin versus oxytocin after caesarean section: similar efficacy but reduced pain perception in women with high risk of postpartum haemorrhage, J. Maternal-Fetal Neonatal Med. 25 (2012) 732–735.
[13] C. Holleboom, J. van Eyck, S. Koenen, et al., Carbetocin in comparison with oxytocin in several dosing regimens for the prevention of uterine atony after elective caesarean section in the Netherlands, Arch. Gynecol. Obstet. 287 (2013) 1111–1117.
[14] J. Jeong, G.P. Hong, Y. Kim, J. Ha, K. Lee, Clinical consideration of treatment to ablate uterine fibroids with magnetic resonance imaging-guided high intensity focused ultrasound (MRgFUS): Sonalleve, J. Menopausal Med. 22 (2016) 94–107.
[15] K.J. Anneveldt, I.M. Verpalen, I.M. Nijholt, et al., Lessons learned during implementation of MR-guided High-Intensity Focused Ultrasound treatment of uterine fibroids, Insights Imaging 12 (2021) 188.
[16] I.M. Verpalen, K.J. Anneveldt, P.C. Vos, et al., Use of multiparametric MRI to characterize uterine fibroid tissue types, MAGMA (2020).
[17] X. Zhang, M. Zou, C. Zhang, et al., Effects of oxytocin on high intensity focused ultrasound (HIFU) ablation of adenomysis: a prospective study, Eur. J. Radiol. 83 (2014) 1607–1611.
[18] G.R. Harris, B.A. Herman, M.R. Myers, A comparison of the thermal-dose equation and the intensity-time product, Itm, for predicting tissue damage thresholds, Ultrasound Med. Biol. 37 (2011) 580–586.
[19] I. Mindjuk, C.G. Trumm, P. Herzog, R. Stahl, M. Matzko, MRI predictors of clinical success in MR-guided focused ultrasound (MRgFUS) treatments of uterine fibroids: results from a single centre, Eur. Radiol. (2014).
[20] Y. Fu, Q. Feng, S. Zhang, Y. Li, Application of oxytocin in ultrasound-guided percutaneous microwave ablation for treatment of hypervascular uterine fibroids: a preliminary report, Int. J. Hypertherm. 36 (2019) 760–766.
[21] S. Otonkoski, T. Sainio, G. Komar, et al., Oxytocin selectively reduces blood flow in uterine fibroids without an effect on myometrial blood flow: a dynamic contrast enhanced MRI evaluation, Int. J. Hypertherm. 37 (2020) 1293.
[22] Y. Kim, J. Kim, H. Rhim, et al., Volumetric mr-guided high-intensity focused ultrasound ablation with a one-layer strategy to treat large uterine fibroids: initial clinical outcomes, Radiology (2012) 263.