Evidence-based cross validation for acoustic power transmission for a novel treatment system

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1) Title Page

Evidence Based Cross Validation for Acoustic Power Transmission via Trans-Fusimo Treatment System Software for MR Guided Focused Ultrasound

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Evidence Based Cross Validation for Acoustic Power Transmission via Trans-Fusimo Treatment System Software for MR Guided Focused Ultrasound

2) Abstract

Introduction The novel Trans-Fusimo Treatment System (TTS) is designed to control Magnetic Resonance guided Focused Ultrasound (MRgFUS) therapy to ablate liver tumours under respiratory motion. It is crucial to deliver the acoustic power within tolerance limits for effective liver tumour treatment via MRgFUS. Before application in a clinical setting; evidence of reproducibility and reliability is a must for safe practice. **Materials and methods** The TTS software delivers the acoustic power via ExAblate-2100 Conformal Bone System (CBS) transducer. A built-in quality assurance application was developed to measure the force values, using a novel protocol to measure the efficiency for the electrical power values of 100 and 150W for 6s of sonication. This procedure was repeated thirty times by two independent users against the clinically approved ExAblate-2100 CBS for cross-validation. **Results** Both systems proved to deliver the power within the accepted efficiency levels (70-90%). Two sample t-tests were used to assess the differences in force values between the ExAblate-2100 CBS and the TTS ($p>0.05$). Bland-Altman plots were used to demonstrate the limits of agreement between the two systems falling within the 10% limits of agreement. Two sample t-tests indicated that TTS does not have user dependency ($p>0.05$). **Conclusions** The TTS software proved to deliver the acoustic power without exceeding the safety levels. Results provide evidence as a part of ISO13485 regulations for CE marking purposes. The developed methodology could be utilised as a part of quality assurance system in clinical settings; when the TTS is used in clinical practice.

3) Keywords: acoustic power measurement for reliability; Blant-Altman; cross-validation; quality assurance; legislation; pre-clinical MRgFUS, two-sample t-test.

4) Main text

a) Introduction

Magnetic Resonance guided Focused Ultrasound (MRgFUS) has been CE **C**onformité **E**uropéene), and Food & Drug Administration (FDA) approved for the treatment of uterine fibroids and the treatment of pain for bone metastasis [1-4]. ExAblate 2000 and 2100 (InSightec, Israel) are systems for treatment of these diseases, to apply the static MRgFUS technique. However, the targeting of Focused Ultrasound (FUS) in upper abdominal organs, such as in liver remains particularly challenging due to the complexity of the displacement and the deformation due to the respiratory motion; adjacent risk structures and the possible interference by the rib cage [5]. Trans-Fusimo Treatment System (TTS) software (FP7 Project Trans-Fusimo, Fraunhofer, Mevis, Germany) is a recently developed software aiming at treatment of liver by using MRgFUS methodology. This novel software makes use of the mathematical models describing the motion due to breathing, the propagation of the ultrasound waves through the rib cage, and into the targeted tumour destination and the multi-base line algorithm to read the temperature during ablation [5]. Virtual reality simulations prove to be promising in achieving an accurate prediction of a real patient scenario [5]. However, safe and efficient application of this procedure requires and depends on successful configuration of the hardware and the efficient transmission of electrical power being converted into acoustical power.

The TTS system drives the transducer of the Conformal Bone System (CBS) (InSightec, Ltd, Tirat Carmel, Israel). To achieve this task, TTS software has a Graphical User Interface (GUI) where an operator activates a command to drive the transducer. GUI requires an operator to provide the information for the planned sonication coordinates,

sonication power, and the duration. An electronically steerable FUS transducer receiving this sonication command has a grid of small transducer elements. Focusing the transducer to a position is achieved by altering the phase differences between the elements such that the single element waves superpose constructively in the intended focal spot. During sonication in MR imaging, the phase values of the sonicated spot change. Based on this change, the colour mapped thermometry data reflecting the temperature increase caused by the FUS ablation, is visualized in the user interface of the TTS software. These images are collected by using the 1.5 T MR Scanner (GE Healthcare, UK) and sent to the TTS software in real time. The system configuration is shown in detail on Figure1. The treatment system requires real time interaction of sub-systems (Figure1) such as TTS workstation; TTS software; InSightec Control PC and CBS transducer; MR work station and Scanner. A Transistor-Transistor-Logic (TTL) pulse generator provides synchronization with TTS software and the MR Scanner.

[Insert Fig1]

The TTS software is classified as class 3/C high risk software, where serious injury or death is possible according to the international standard IEC 62304. It requires deep design documentation and testing before clinical trials. The TTS software controls the FUS transducer by sending the newly computed phase information to the FUS transducer to ablate human tissue; therefore, the major risk is that the TTS software might send the wrong command to the FUS transducer which may produce unexpected levels of power. Having this complex infrastructure, it is crucial to develop reliable protocols following the requirements of **I**nternational **O**rganisation for **S**tandardization ISO 13485 Quality Management System (QMS). This is a mandatory step for CE mark approval for clinical use. The CE mark is a legal designation that a medical product has met the requirements of all relevant Medical Device Directives in the EU. In this study, the power protocol,

which was developed according to the requirements of ISO 13485, is explained in detail. ISO13485 provides the standards for evaluation of complex systems by taking precautions to prevent any errors and traps in the planning stage. An important part of the quality control is the detection of both random and systematic errors. This is achieved by critically looking at the performance, the analyses; the instruments and the operators taking part in the evaluation [6]. For this reason, design and development plans, risk assessment forms, risk assessment matrices and traceability matrices for the designed protocol is prepared according to the rules and regulations of ISO13485. To eliminate risk related to false positive and false negative test results, special attention was given to prepare easy to follow protocols; measuring one process parameter at a time only. The developed protocol enables the collection of results for the delivered acoustic power during a FUS application, and is utilised as a part of the required evidence for getting approvals for safe use in clinics. However, the TTS does not only require development of the power protocol but also the development of protocols for measuring the sonication duration; the position and thermometry to provide quantitative evidence in pre-clinical settings [7]. For this reason, initially, the system parameters were identified for the full system validation and the specs for these parameters were determined based on the current lab practices for static and moving case applications [7]. Based on the successful evaluation of the static and the moving case scenario validations of the TTS in pre-clinical settings, more clinical evidence via animal testing is intended to be collected [7]. Finally, the evidence of successful application of the treatment on volunteered patients, leads into the successful approval of CE marking procedure for MRgFUS in clinical settings.

The US Food and Drug Administration (FDA) has also reported requirements that the equipment should not be used for clinical application if it generates higher acoustic power

levels than similar equipment produced for the same application [6]. Power over a certain level might lead into skin burns of the patients and self-heating of the transducer [6]. In analytical work, data and its comparison against established standard is very important. In this study, the acoustic power data is used as an indication of performance so that it can provide guidance on safety. Knowledge of the output allows relative risk assessments of different values of power. Knowing the output of the acoustic power can help provide evidence for safe usage.

Measurement traceability is an important concept. To ensure that the comparisons between measurements made by different laboratories are valid, there is a need for common standard and concept [8]. For this reason, in this paper the FDA approved ExAblate 2100 CBS is treated as a gold standard when validating the recently developed TTS. Qualitative methods play an important role in performance assessment of the acoustic power. One of the reasons for using the qualitative methodology is to ensure that the most effective exposure levels are used during patient treatment. Another reason is to ensure that the exposure does not take place at levels which can be harmful to the human tissue [7]. It is also useful to know if the equipment is performing satisfactorily. Power is a useful and simple parameter for periodic performance evaluation [8]. In this study, the acceptable level for efficiency for converting electrical power to acoustic power is defined as 70-90%.

There have been several measurement methodologies in the literature for measuring the acoustic power output [6, 8-15]. One of them is the large target radiation force methodology [6], where the target intercepts the whole ultrasonic beam to indicate a value of the total acoustic power. The principle in the radiation force methodology is that

propagation of ultrasound through a medium is related to the transfer of momentum. This transfer shows itself as a force acting on the targeted area. Measurement of this force provides the base value for power. The force actually depends on the time-averaged intensity in the ultrasonic beam. In this study, large target methodology is used where the target intercepts the whole of the ultrasonic beam to yield the total value of the acoustic power. The force is related to the acoustic power, W, as described by the following expression:

$$F=h.W/c \quad (1)$$

Where c is the speed of ultrasound in the propagating medium (in our case water), h is a parameter that depends on the geometry of the target and is equal to 1 for plane or totally absorbing target [6]. Large target radiation force balance is classified as ideal for low cost and ease of use [6] and preferred in this study due to these advantages. Acoustic power measurements were completed by following the described protocol in this study. To cross validate the TTS software, against the clinical MRgFUS system, ExAblate 2100 CBS, by two independent operators on the same set up; to observe the limits of agreement and the differences between the means of the measured power values, and the user dependency of both systems to provide evidence to fulfil the requirements of implementation of ISO 13845.

b) Methodology

The protocol developed to test the ExAblate 2100 CBS system for obtaining FDA approval, was used with TTS software. A feasibility study was performed initially to verify the usage of the same protocol for applying electric power values of 100 W and 150 W for 6 seconds of sonication. These values are chosen to evaluate proper dosimetry

of the system with the actual acoustic power output by applying the protocol conforming to the requirements of ISO 13485 at our laboratory.

Preparation

Radiation force is measured by the weight scale holder assembly (InSightec Ltd, Tirat Carmel, Israel) (Figure2a). Radiation force is detected by CM 150-1 Weight Scale. This scale is placed on the target in the FUS beam direction of the CBS transducer, parallel to the transducer. Prior to the experiment, the initial force reading was completed by using a known weight on CM 150-1 Weight Scale for calibration purposes with an accuracy of 0.1 g.

[Insert Fig2a-f]

The force detected by the weight scale is directly proportional to the ultrasonic power providing the whole beam is intercepted (Eq1) [7]. Eq1 assumes that plane waves are incident on the target for fields generated by plane transducers. The main equipment used in this stage is a fixed transducer (CBS, 1024 elements) and as a non-fixed target; the force balance platform, is used in this study (Figure2a). To determine the total acoustic power output of a transducer, it is essential that the target is of sufficient size to intercept the whole of the ultrasonic beam. In this study, both the CBS transducer and the target have equal diameters. The algorithm used by the TTS for calculating the phases is shown below (pseudo code), with the assumption of homogeneous medium.

```
K = 2.0 * pi * Frequency / SpeedOfSound;
for (elementIndex = 0 .. numberOfElements) {
   Phase[elementIndex] = K * DistanceToElement(elementIndex, focusPosition);

}
```

The power value entered in the graphical user interface during planning is used for the "Regular Sonication Electric Power" parameter.

With C=1500 [m/sec] and the equivalence of 102 gram/N, to calculate power the equation below is used (Eq2).

$$P\,[\text{Watt}] = 14.7 * F[\text{gram}] \qquad (2)$$

Where P was the absorbed power in target (Watt), and F was the exerted force on target [N].

Trans-Fusimo Execute Sonication Application

For regular quality assurance (QA) purposes, the TTS software has a Trans-Fusimo Execute Sonication Application (TESA). The main TTS software requires time consuming treatment planning imaging, and monitoring of the sonication procedure for thermometry data and tracking of land marks. However, TESA does not require MR monitoring and imaging. This protocol enables the power measurement procedure in a realistic time frame for the planned number of sonications to take place by two independent operators without providing any imaging or thermometry information but power information only.

To use TESA, the information for the magnitude of electrical power, the focal position, and the duration of sonication is entered manually by the operator into the graphical user interface (GUI), as shown in Figure3a. Pressing the "Arm HIFU Transducer" button initializes the transducer and makes it ready for instant sonication i.e. the transducer is powered up and the elements are configured to random phases and almost-zero output

power. Once arming is complete, the sonication can be executed. Pressing the "Execute Sonication" button configures the transducer to focus on the specified position with the specified power. The sonication duration is completed by running a loop of 250-ms sonication intervals (due to safety reasons) until the planned duration time is reached. Once this loop is complete, sonication is stopped automatically. The "Stop Sonication" button is not activated in this protocol by the operator it is used only when there is an emergency.

[Insert Fig3 a b]

Test Protocol

A qualified operator secures cable connections for the TTS software to control the transducer (Figure 1). The Control PC rack of ExAblate 2100 (InSightec, Israel) is put on power for CBS transducer. A phantom holder is placed over the transducer (Figure 2b). To provide good acoustic coupling, the membrane is supposed to be kept wet. For this reason, wet tissue is placed between the membrane and the phantom holder. The phantom holder is filled with degassed water 3 cm below of the top of the cylinder. Wet tissue is removed (Figure 2c). The cooling system of the CBS transducer is put in circulation mode at least for 10 minutes. Verification is then performed to check if there are any air bubbles between the membrane and phantom holder by visual inspection and MR scanning in sagittal, coronal and axial views. If any air bubbles are present; the operator will remove them for safe usage of the system. After corrective actions are taken, another MR scan is completed to double check if there are any remaining air bubbles. The distance from the setup base to the phantom holder bottom is measured and recorded. This ensures the same membrane inflation each time for reproducibility purposes.

The weight scale holder assembly is shown in a sketch (Figure 2g). This assembly is placed in the cylinder and inserted diagonally to prevent trapping of air bubbles (Figure 2c); the holder is then checked for levelness. There is a tolerance between holder legs and holes in the disk to rest on the water bath (Figure 2d). The scales are placed between the absorbing target and the freely moving legs to measure the force as shown in Figure 2e. The triangular platform is free to move along the beam direction so that force values can be read from the scales and recorded (Figure 2f).

Test Parameters

To measure the acoustic power, a sonication is performed with the parameters described below by using the TESA graphical user interface, with the parameters in Table 1a.

When sonication is applied, the weight is viewed on the weight scale screen. When the reading on the balance stabilizes, the weight difference between the maximum value during the sonication and the value after the sonication ended is calculated in grams. The collected force data is recorded for each sonication. Using Eq.2, the power is calculated. The efficiency is calculated by dividing the calculated power by input power. The result is checked, if it is within the acceptable tolerance range (70 to 90%). The sonication is repeated for 30 times by two independent operators. The null hypothesis is that system is indifferent to different operators.

Validation against Gold Standards

CGA stands for **C**entral **G**UI **A**pplication, installed on the Control PC (CPC) of the CBS ExAblate2100. Using the same setup, the CGA software of the ExAblate 2100 System was activated (Figure 3b). The GUI of the CGA allows to define the magnitude of electrical power, the focal position and the sonication duration. The same test parameters were applied by two independent users for sonication for 30 times. These features are

shown in Figure3b. Both TESA and CGA have this manual input interface for the operators to provide input.

Post Processing of the Data

From the calculated power data for each system and operator, the average power was calculated. Average efficiency was calculated by dividing average power by planned input power. Mean values and standard deviations (SD) for each operator and each system were provided as indication of performance of the system. The graphs showing the number of trials and calculated power value were plotted. A trend line was fitted in to each plot to calculate the Normalized Root Mean Square Error (NRMSE). NRMSE was calculated by dividing the RSME with the average magnitude of the measured data, to eliminate dependency on measured magnitude. NRMSE was used as a measure of accuracy.

To construct the B&A plot and to evaluate the agreement, each data set was measured by using the TTS and the ExAblate 2100 CBS and then sorted from smallest to largest and paired [15]. The difference for each paired data was calculated by simple subtraction (TTS data -ExAblate 2100 CBS data). The mean for each paired data was calculated by adding each paired data and dividing by 2 (TTS data + ExAblate 2100 CBS data)/2. B&A was plotted using the differences between two data sets against the mean of the two measurements. Plotting difference against mean allows us to investigate any possible relationship between the measurement error and the true value [15]. The mean of the two paired measurements was assumed as the true value. The percentile difference for each paired data was calculated by dividing the difference by the calculated mean Difference/Mean (%). The average of this percentile differences was calculated for the full data set to check against the previously set 10% difference criterion based on the current lab practices. The limits of agreements between two systems were calculated by

using the mean value ± 2s (standard deviation). It is recommended that 95% of the data points should lie within the ± 2s of the mean difference as demonstrated in B&A plots [15].

Two sample t-tests were used to investigate the significance of difference between the mean values of the delivered power by using the TTS and ExAblate 2100 CBS. Two sample t-tests were also utilised to check the significance of difference based on two independent operators using the system.

c) Results

Descriptive statistics for calculated power and calculated average efficiency are listed for applied power of 100 W and 150 W for both TTS software and ExAblate 2100 systems in Table1b and Table 1c respectively for both operators. The acoustic efficiency is calculated for each system. Results show that both systems produce efficiency values within the accepted tolerance limits (70-90%). There is no single data falling out of this efficiency range during the experiments for each system.

The calculated acoustic power versus number of trials graphs are provided for each operator (Figure Appendix). By using the fitted line as a model and computed acoustic power as the data, the NRMSE was calculated for each data set. For the first operator with TTS software NRMSE for 100 W and 150W was calculated as 0.02 and 0.04 respectively. For the second operator, NRMSE was 0.02 and 0.01 respectively and for ExAblate2100, NRMSE was calculated as 0.02 and 0.01 for the first operator and 0.02 and 0.01 respectively. Overall, NRMSE being less than 0.1 for both systems indicated good accuracy levels.

The calculated mean difference (%) between the TTS and the ExAblate 2100 was 0,13 % for 100 W and 3.8 % for 150 W, meeting the pre-defined spec based on current lab practices, which was set as 10 %. Bland-Altman plots were used to interpret the limits of agreement. Any other new set of tests by using the TTS software and ExAblate 2100 would be expected to fall in the limits of agreement shown in the graphs (Figure 4 a-d) with 95% level of confidence. Two-sample t-tests were used to assess the differences in force values between the ExAblate-2100 CBS and the TTS ($p>0.05$), indicating the difference between the means is insignificant.

Two-sample t-tests were also used to assess the dependency of the system to the operators. P values were calculated for 100W and 150W between the operators for using TTS. P being >0.05, the null hypothesis is not rejected. Also for ExAblate 2100, P values for delivered acoustic power values of 100 W and 150 W between the operators were calculated as ($p>0.05$). The results show that there is no significant difference in delivered power, due to different operators for both systems.

[Insert Table1a-c]

[Insert Fig 4 a- d]

d) Discussions

The Trans-Fusimo Treatment System software aims at sonicating to a moving target (i.e. liver tumour) by delivering high levels of power. The radiation force technique is the most widely used and accepted fundamental technique due to its practicality [16]. For safe delivery of the power, it is crucial that the system is deemed to be reliable and to be producing acoustic power outputs [16] within the established safety margins in in a reproducible way.

To evaluate this, the developed protocol was used to compare against the approved systems standards. Feasibility tests were run before the independent operators ran their sessions. Prior to the experiments, risk assessment forms were filled in. Risk assessment matrices were evaluated based on the severity of risk involved and probability of the risk occurring during the experiments. Risk mitigation procedures were completed and traceability matrices were evaluated for each risk mitigation point. Risk mitigation points involved secure cabling between subsystems such as TTL cable from the TTS workstation, to MR scanner and ExAblate 2100 CBS, to avoid any power transmission problems, calibration of the scales, and training of the operators to understand the protocol steps in application. Instructions were printed before the repeatability experiments and operators followed the steps accordingly, so that the dependency of the system to operator's usage was minimized. T-test evaluations showed that the difference in acoustic power between the independent operators using the same system is insignificant with $p>0.05$. One of the limitations of this study was that independent operators were not randomized and only two qualified operators tested the system. Although as an improvement point; it could be argued that the number of operators should be increased, with a p value being greater than 0.05, this would only lead into more testing time and results might not have been affected. The results imply that the designed protocols were effective in guiding the operators to apply the protocols correctly. Ideally, the system is not expected to produce different power values when different operators employ it. The results are also in support of this expectation.

Statistical methods used to test for agreement of medical instruments, play a crucial role to draw correct conclusions from the data gathered to compare the devices. Bland-Altman (B&A) plots are reported to be the most popular statistical method when testing for

agreement of medical instruments [18]. This method provides the means to check how close the pairs of values are from two different systems. It also relaxes the expectation that two different instruments with different methodologies should give identical paired measurements. The other option to evaluate consistency between the two systems would be the correlation coefficient (r). However, the correlation coefficient is more suitable for investigating the linear relationship. It is not our expectation that two systems should produce paired linearly increasing or decreasing values in this protocol. The B&A plot analysis is a simple way to evaluate a bias between the mean differences, and to estimate an agreement interval, within which 95% of the differences of the second method, compared to the first one, fall [15]. The B&A plots define the intervals of agreements as shown in Figure 4 a-d. The limits of agreement between the means were set as 10 % prior to the design of the experiments for checking the acceptable limits of agreement with B&A plots. The plots show that all the measured data using TTS software and the gold standard used in this study, fall into the ±1.96+ mean difference interval, meeting the specifications set prior to the current experiments. B&A methodology was considered as a suitable statistical method to draw conclusions based on the designed protocol. To evaluate the significance of difference between the ExAblate 2100 CBS and the TTS, two sample t-tests showed that the difference between the means by ExAblate 2100 CBS and TTS is insignificant; $p>0.05$.

Quantitative analysis of the results shows that the efficiency is relatively low (73%) for 100 W, when compared to 150 W (80-83%). This could be explained by the fact that h value in Eq1, is actually higher than unity for higher powers as it is difficult to produce a material that will completely absorb incident ultrasound with no reflections. Also, for higher powers, the absorbed power might lead into heating up of the absorbing material

causing thermal expansion and thereby change in bouncy forces [12-15]. This might explain the difference of efficiency between low (100W) and high (150W) power application. In fact, the speed of sound in Eq1 is also temperature dependent. It could have been ideal to observe the water temperature at the same time during the experiment. However, this could have interfered with the force readings and complicate the experiment design. For this reason, the c value during these experiments was assumed to be constant. To minimize the thermal heating effect, a five-minute time break between the measurements was given. It should also be noted that the calculated efficiency levels were not higher than pre-established limits i.e. (70-90%) eliminating the need for further investigation. In this protocol, due to the design geometry of the force balance platform, the sonication coordinate was chosen as 170mm for limiting the energy density on the absorber in a way that compromises between the need to have the entire beam in the absorber and the damage that the focused ultrasound beam can do to the absorber. The applied methodology has strengths for simplicity for conducting repeatability experiments in MR unit for MRgFUS application, and cost effectiveness. With radiation force methodology uncertainty in the measurements is also known to be lower when compared to hydrophone measurements where uncertainties could be up to 20% [9].

The results showed that the TTS software was less efficient than the ExAblate 2100 system by 3% for power values of 150 W. However, the system did not exceed the established tolerance levels, and actually did not cause any excessive energy levels. Thus, in terms of safety, the TTS software proved to be safe. This result might also imply that the TTS software might not be as efficient as the ExAblate 2100 CBS system in reaching high temperature values. For this reason, it is very important to develop protocols for

measuring thermometry to observe if an efficient temperature increase for tumor ablation could be achieved by using TTS software as a next step.

In the developed protocol, power values were only applied for 6 seconds, however, in practice longer sonication durations are used. The force was calculated as time averaged value over a short-duration of time as 6 s, however, the main focus in the applied protocol was not the duration of the planned sonication but the power. In fact, another protocol has been designed to test the deviation of sonication duration and any delay after sonication is stopped in case of emergency as a next step

The developed protocol showed the importance of following the requirements of the quality management system ISO 13485 to improve the quality of the tests results in generating evidence when testing agreement of medical system before use in clinics. Results were convincing that the TTS software can deliver the power in a controlled way within expected efficiency limits. Based on this evidence, novel protocols are designed for testing of remaining system parameters again following the requirements of ISO 13485.

e) Conclusions

This study demonstrated the steps in evaluating the high risk TTS software; according to the international standard IEC 62304. Acoustic power measurements proved to be consistent with the defined clinical standard. However, the application of MRgFUS in the liver has some other important system parameters such as; sonication duration deviation, emergency stop delay, thermometry, and sonication position deviation that need to be quantified by applying reproducible protocols. The next step in our work is to design novel protocols, check their feasibility, and improve these protocols for each of

these crucial system parameters. The efficiency of power delivery is set as the first milestone, affecting all the other parameters. For this reason, priority was given to measuring the efficiency of acoustic power delivery. Based on this evidence, following the procedures of ISO13485, full validation of the system is planned. This study is the first, but most crucial step in system validation as it paves the way to the next system parameters to be tested.

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Appendix

[Insert Figure Appendix here]

6) References

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7) Legend of Figures and Tables

Figure 1. Detailed description of hard- and software interfaces

Figure 2 a. Weight scale and holder assembly as a moving target to place the weight scale on. 2b. Experimental Setup with membrane (ExAblate 2100 CBS, InSightec, Tirat Carmel, Israel.), wet tissue in between the membrane and the cylinder where degassed water is filled in. 2c. Weight scale holder assembly insertion. 2d. Positioning of weight scale and moving target using the tolerance between holder legs and the disk 2e. Positioning of the scale during experiment to read the values 2f. Screen of the scale to read the values g) schematic view of the weight scale assembly, and side view with weight scale assembly inserted in degassed water in cylindrical water bath.

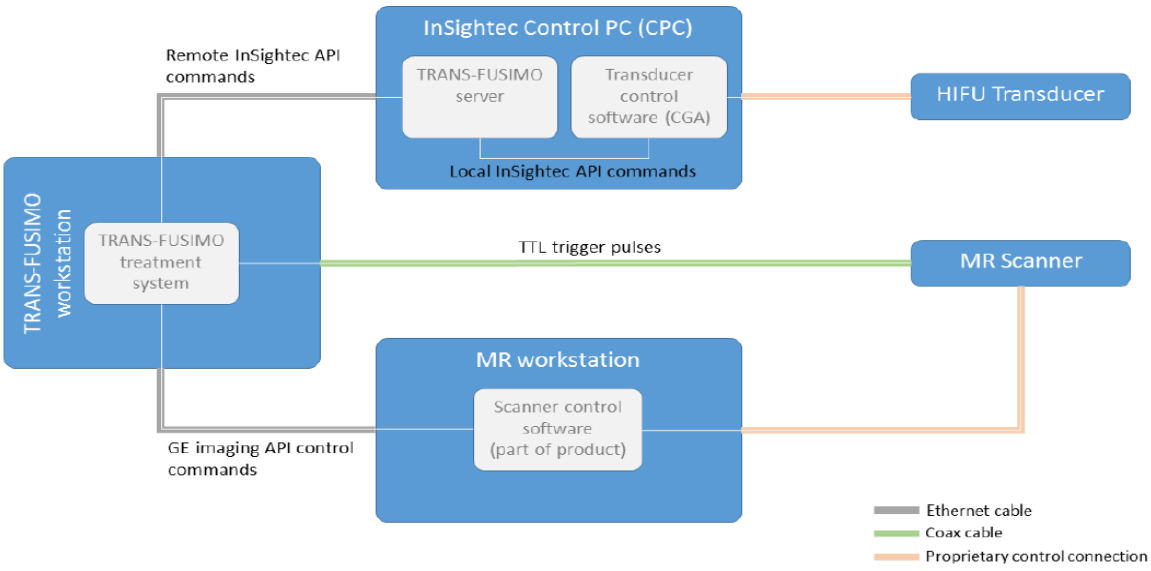
Figure 3a. Trans-Fusimo Execute Sonication Application showing the GUI for entering focus position, sonication duration and power for QA purposes, with buttons to start the transducer and execute the sonication b) CGA software of ExAblate 2100 (InSightec) system.

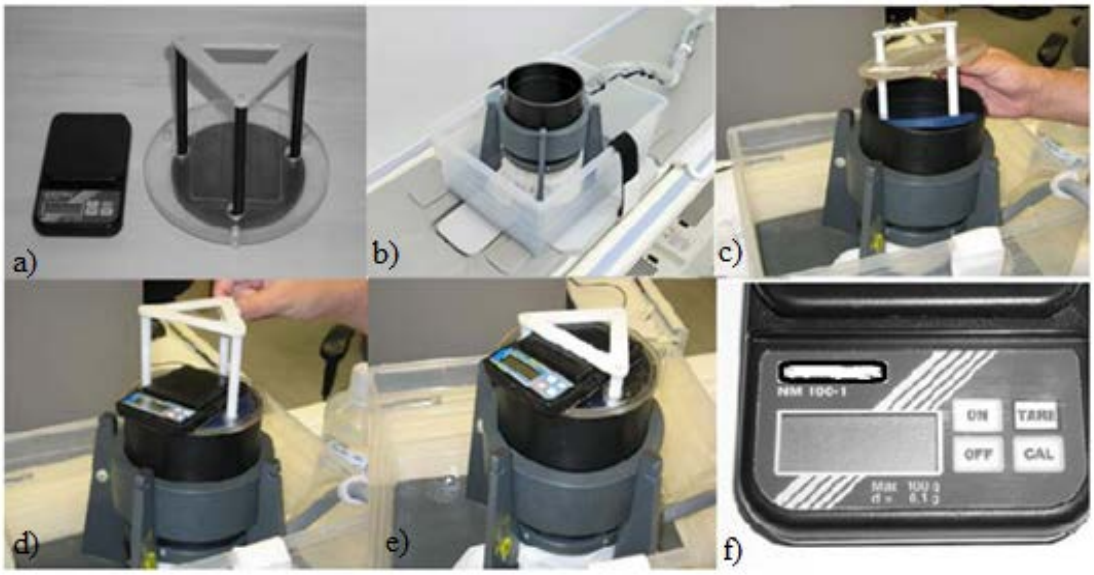
Figure 4. Bland-Altman plot of difference in measured delivered acoustic power for 100 W by TTS and ExAblate 2100 against the mean of the measured delivered acoustic power, by the first operator a) and second b), showing mean and mean±1.96SD as upper and lower limits of agreement, and for 150 W by TTS and ExAblate 2100 against the mean of the measured delivered acoustic power, by the first operator c) and second d), showing mean and mean±1.96SD as upper and lower limits of agreement

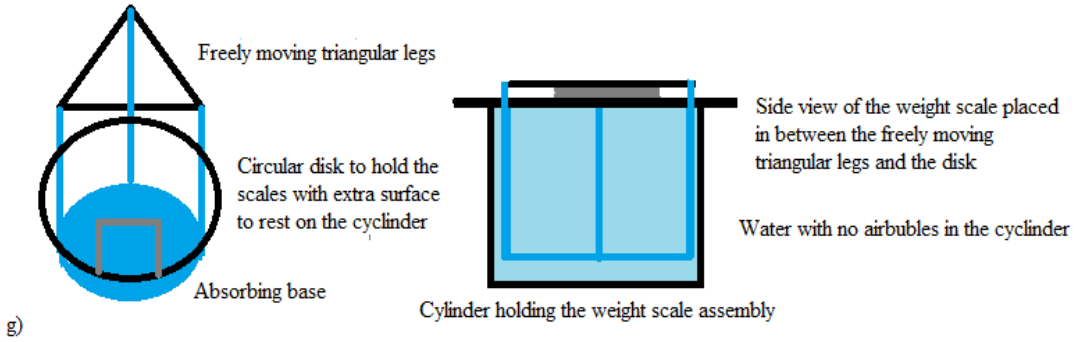
Figure Appendix. Measured acoustic power for 1^{st} (a,b) and 2^{nd} (c,d) operators by using TTS software and ExAblate 2100 software, with best fit trend line formula to calculate NRMSE.

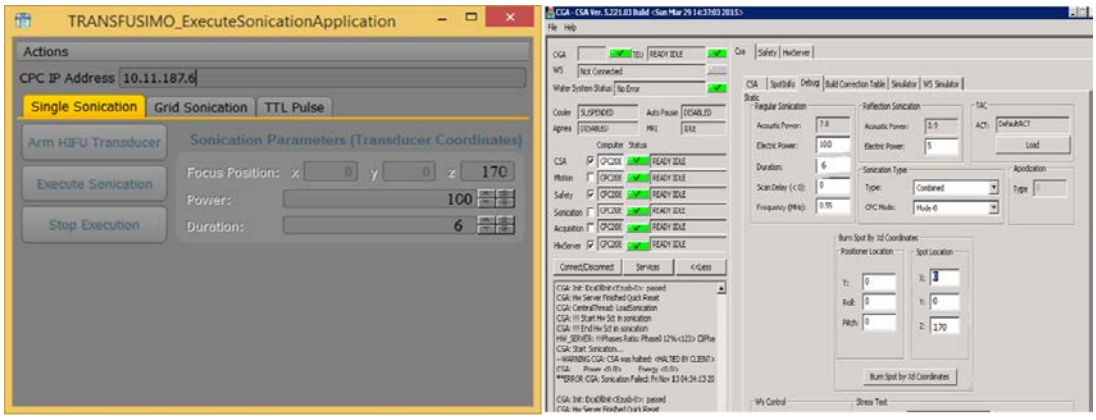
Table 1a) Test parameters which are logged into the GUI of TESA by the operators b) Descriptive statistics for electrical power values of 100W and calculated average efficiency c) Descriptive statistics for electrical power values of 150 W and calculated average efficiency.

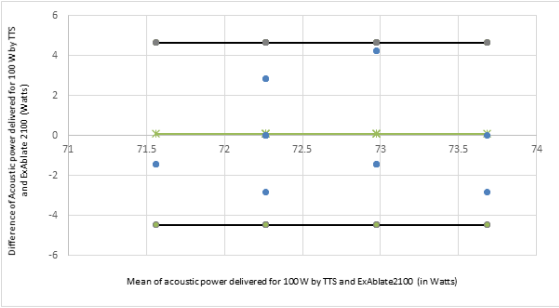
8) List of Table and Figures

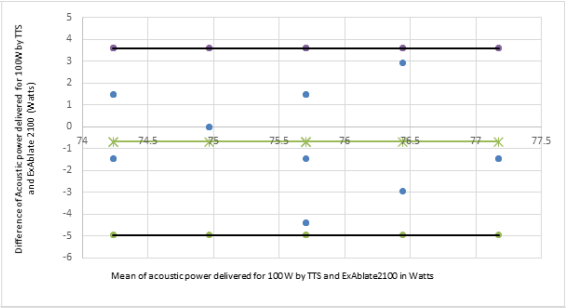


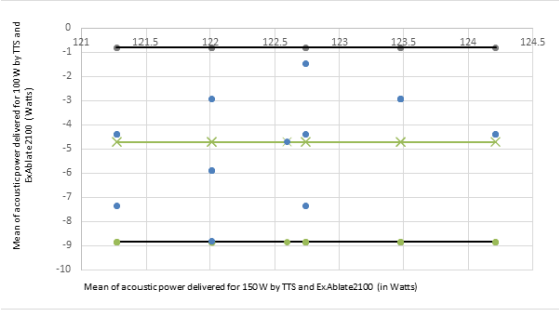

a)
b)
c)
d)
e)
f)
NM 100-1
ON
TARE
OFF
CAL

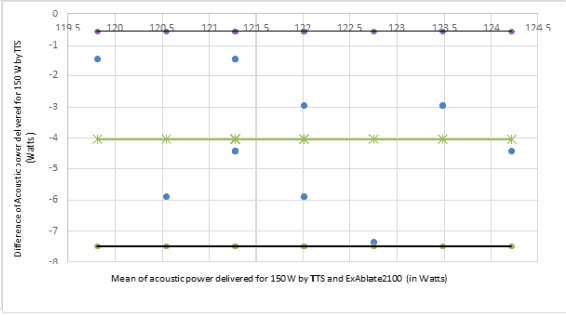

Freely moving triangular legs
Circular disk to hold the scales with extra surface to rest on the cyclinder
Absorbing base
Side view of the weight scale placed in between the freely moving triangular legs and the disk
Water with no airbubles in the cyclinder
Cylinder holding the weight scale assembly
g)

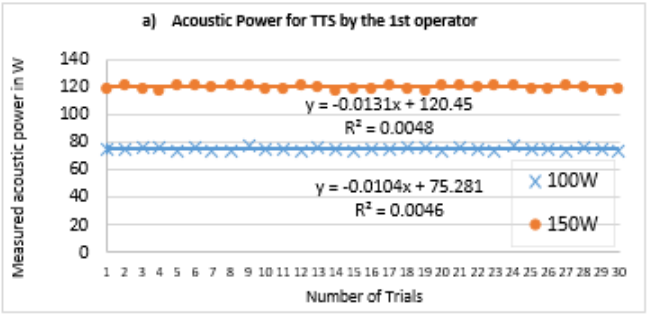

TRANSFUSIMO_ExecuteSonicationApplication
Actions
CPC IP Address 10.11.187.6
Single Sonication
Grid Sonication
TTL Pulse
Arm HIFU Transducer
Execute Sonication
Stop Execution
Sonication Parameters (Transducer Coordinates)
Focus Position: x 0 y 0 z 170
Power: 100
Duration: 6

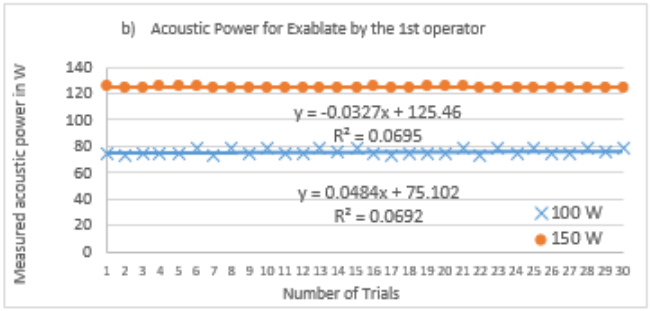

Difference of Acoustic power delivered for 100 W by TTS and ExAblate 2100 (Watts)
Mean of acoustic power delivered for 100 W by TTS and ExAblate2100 (in Watts)

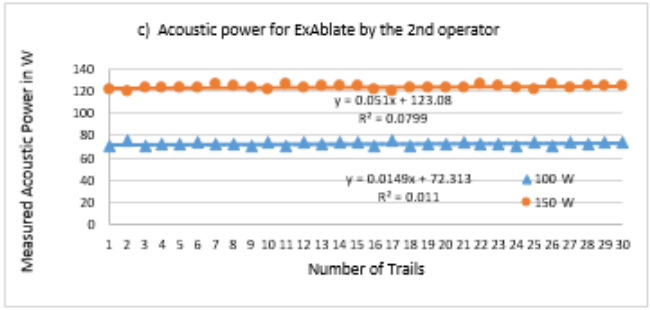

Difference of Acoustic power delivered for 100W by TTS and ExAblate 2100 (Watts)
Mean of acoustic power delivered for 100 W by TTS and ExAblate2100 in Watts


Mean of acoustic power delivered for 100 W by TTS and ExAblate2100 (Watts)
Mean of acoustic power delivered for 150 W by TTS and ExAblate2100 (in Watts)


Difference of Acoustic power delivered for 150 W by TTS (Watts)
Mean of acoustic power delivered for 150 W by TTS and ExAblate2100 (in Watts)


a) Acoustic Power for TTS by the 1st operator
Measured acoustic power in W
y = -0.0131x + 120.45
R² = 0.0048
y = -0.0104x + 75.281
R² = 0.0046
100W
150W
Number of Trials


b) Acoustic Power for Exablate by the 1st operator
Measured acoustic power in W
y = -0.0327x + 125.46
R² = 0.0695
y = 0.0484x + 75.102
R² = 0.0692
100 W
150 W
Number of Trials


c) Acoustic power for ExAblate by the 2nd operator
Measured Acoustic Power in W
y = 0.051x + 123.08
R² = 0.0799
y = 0.0149x + 72.313
R² = 0.011
100 W
150 W
Number of Trails

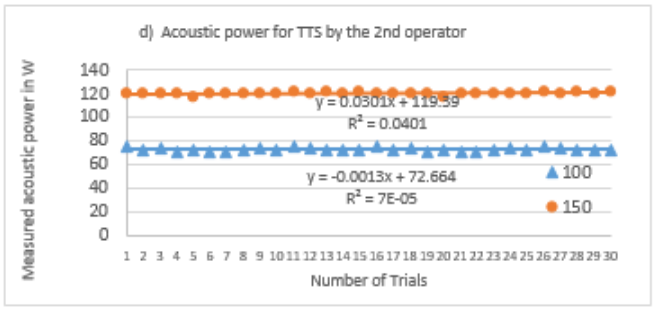

d) Acoustic power for TTS by the 2nd operator
Measured acoustic power in W
y = 0.0301x + 119.39
R² = 0.0401
y = -0.0013x + 72.664
R² = 7E-05
100
150
Number of Trials

TABLE I A)
Test parameters logged into the GUI of TESA by the operators.

Parameter	Value
Power	100 W, 150 W
Duration	6 seconds
Z distance	170 mm
Frequency	0.55 MHz

TABLE 1B
DESCRIPTIVE STATISTICS FOR ELECTRICAL POWER VALUES OF 100 W AND CALCULATED AVERAGE EFFICIENCY

1st operator	Power	Calculated Average Acoustic Power	Calculated Average Acoustic Efficiency
TTS	100	72.65 (Std 1.31)	0.73
ExAblate	100	72.55 (Std 1.29)	0.73
2nd operator	Power	Calculated Average Acoustic Power	Calculated Average Acoustic Efficiency.
TTS	100	72.65 (Std 1.31)	0.73
ExAblate	100	72.55 (Std 1.29)	0.73

TABLE 1C
DESCRIPTIVE STATISTICS FOR ELECTRICAL POWER VALUES OF 150 W AND CALCULATED AVERAGE EFFICIENCY

1st operator	Power	Calculated Average Acoustic Power	Calculated Average Acoustic Efficiency.
TTS	150	119.85(Std 1.31)	0.80
ExAblate	150	123.87 (Std 1.26)	0.83
2nd operator	Power	Calculated Average Acoustic Power	Calculated Average Acoustic Efficiency.
TTS	150	120.25 (Std 1.63)	0.80
ExAblate	150	124.95 (Std 1.07)	0.83