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Main title: Continuous mode 448 kHz capacitive resistive monopolar radiofrequency induces greater deep blood flow changes compared to pulsed mode shortwave: A crossover study in healthy adults.

Authors: Binoy Kumaran; Anthony Herbland; Tim Watson

Running title: Physiological effects of radiofrequency-based therapy

Affiliation of authors: Department of Allied Health Professions and Midwifery, School of Health and Social Work, University of Hertfordshire, Hatfield, AL10 9AB, UK.

First author (corresponding author): Binoy Kumaran, Physiotherapy, Department of Allied Health Professions and Midwifery, School of Health and Social Work, University of Hertfordshire, Hatfield, AL10 9AB, UK.
Tel: 01707 282395; Email: b.r.kumaran@herts.ac.uk (email can be published)

Second author: Dr Anthony Herbland, Department of Allied Health Professions and Midwifery, School of Health and Social Work, University of Hertfordshire, Hatfield, AL10 9AB, UK.
Tel: 01707 286120; Email: a.j.m.herbland@herts.ac.uk

Last author: Professor Tim Watson, Physiotherapy, Department of Allied Health Professions and Midwifery, School of Health and Social Work, University of Hertfordshire, Hatfield, AL10 9AB, UK.
Tel: 01707 284970; Email: t.watson@herts.ac.uk

Abstract

Aims: Radiofrequency-based electrophysical agents (EPAs) have been used in therapy practice over several decades (e.g. shortwave therapies). Currently there is insufficient evidence supporting such EPAs operating below shortwave frequencies. This laboratory-based study investigated the deep physiological effects of 448 kHz capacitive resistive monopolar radiofrequency (CRMRF) and compared them to pulsed shortwave therapy (PSWT). *Methods:* In a randomised crossover study, seventeen healthy volunteers initially received four treatment conditions – High, Low and Placebo dose conditions receiving 15-minute CRMRF treatment and a Control condition receiving no intervention. Fifteen participants additionally received high dose PSWT as fifth condition, for comparison. Pre and post treatment measurements of deep blood flow and tissue extensibility were obtained using Doppler ultrasound and Sonoelastography. Group data were compared using ANOVA model. Statistical significance was set at $p \leq 0.05$, 0.8 power, and 95% CI. *Results:* Significant increases in volume and intensity of deep blood flow were obtained with CRMRF over placebo, control ($p=0.003$) and PSWT ($p<0.001$). No significant changes in blood flow velocity or tissue extensibility were noted for any condition. *Conclusions:* Deep blood flow changes with CRMRF were more pronounced than that with PSWT, placebo or control. Potential greater therapeutic benefits need to be confirmed with comparative clinical studies.

Key words

Introduction

The efficacy of electrophysical agents (EPAs) used in therapy practice is underpinned by their ability to influence the body's physiological mechanisms, thereby affecting the underlying pathological processes. Ultimately, this can lead to effects such as reduction in pain and inflammation, acceleration of tissue healing and overall improvements in function (1, 2). Several of these benefits relate to thermophysiological responses in the body such as changes to blood flow, muscle tone and tissue compliance achieved primarily through induced tissue hyperthermia (3-6).

The physical nature and metabolic state of tissues can be altered by changes in blood flow and tissue extensibility, and thereby provide the therapeutic benefits either directly or create a tissue environment that enables the clinician to deliver treatment more effectively in patients and in non-clinical situations (such as in an athlete recovering from muscle fatigue). For example, increasing the compliance of tight soft tissue structures will enable the therapist to stretch them more effectively and gain improved range of movement (7, 8). Increasing muscle blood flow may potentially aid faster recovery from post exercise fatigue. In physiotherapy, radiofrequency (RF)-based EPAs are among those that claim to increase blood flow as well as improve soft tissue compliance, mainly by inducing tissue hyperthermia (9-15). Measures relating to blood flow and tissue compliance closely reflect the body's response when tissues are exposed to heat, with the radiofrequency energy potentially capable of inducing a hyperthermic effect at depth (16-18).

Abnormalities in blood flow have an overarching relationship to pathological states and their treatment; hence an accurate measurement of blood flow without interfering with the circulatory process itself is imperative. A relative change in the local blood flow can characterise a variety of physiological states, either normal or pathological. For example, an increase in local blood flow may be noticed when there is tissue inflammation (19, 20). When localised radiofrequency treatment is administered, monitoring of the blood flow can help in determining how much heating will occur in the tissues. Hence, it enables a protective regulatory mechanism ensuring that there is no undue tissue hyperthermia (21, 22).

The RF frequency ranges used in physiotherapy are largely limited to 30 kHz–30 MHz (23-26). Within this range the main EPA used is shortwave therapy (SWT), which commonly operates at 27.12 MHz, either in continuous (CSWT) or pulsed (PSWT) mode although it is

largely limited to PSWT in contemporary practice (25, 27). SWT is also the most widely researched radiofrequency-based EPA. Nonetheless, EPAs employing significantly lower frequency RFs (<1 MHz) have also been reported in therapy practice, despite their evidence base being minimal. An example for such an EPA is Capacitive Resistive Monopolar Radiofrequency (CRMRF) that employs radiofrequency at 448 kHz. This mode of therapy is relatively new, but is reported to be available and used by clinicians worldwide as a safe form of electrophysical therapy. Similar to SWT, the particular frequency employed relates to international guidelines rather than reported optimum efficacy.

The CRMRF differs from SWT mainly in two ways – firstly the operating frequency, which is significantly smaller than the shortwaves and secondly, unlike SWT it cannot be delivered to the target tissues through an air gap. Hence, a coupling medium similar to ultrasound gel that acts as a conductor is used to transmit the energy. The inability of CRMRF to transmit through air may act as a potential advantage over SWT since scattering of the CRMRF waves will be considerably lower. Without the need for a special conducting medium, shortwave devices are known to emit stray radiations in the air (1, 28). Therefore some of the shortwave energy will be lost through scattering, making it difficult to concentrate the delivery in the required area treated (29, 30).

In this study the authors aimed to investigate the deep blood flow and tissue extensibility responses to continuous-mode CRMRF therapy in asymptomatic adults and compare them to those obtained with PSWT. Similar studies involving only SWT that were conducted on either asymptomatic subjects (12, 14, 15, 31) or patient groups (10, 32, 33) have been reported previously. However, to our knowledge this will be the first *in vivo* study that investigated the deep physiological responses to RF exposure below the shortwave frequency band.

Although CRMRF is a continuous mode therapy unlike PSWT, comparison of these two EPAs was done on the basis that PSWT is the most relevant comparator to CRMRF in contemporary therapy environment. The clinical use of CSWT has decreased significantly in the western world over the recent decades (25, 27). Currently, no data is available from the literature comparing the two EPAs. Since CRMRF was shown to substantially increase and sustain skin temperature in our previously reported study (16), it was hypothesised that similar significant effects may be obtained on deep blood flow and tissue extensibility. The

results of this study are expected to provide important insight into the mode of action of low frequency RF-based EPAs such as CRMRF that has largely remained unexplored (23, 26).

Materials and Methods

Study design

The aims of the study were investigated in a crossover study conducted in the physiotherapy research laboratory of the University of Hertfordshire on 17 asymptomatic (self-reported) adults.

Sample and groups

The participants were randomly recruited via emails from the 27,000 members of the University of Hertfordshire. They all had normal skin thermal perception and no contra-indications to radiofrequency-based therapy. Each of the 17 participants attended four sessions using a randomised crossover design, representing four experimental conditions – CRMRF high (thermal), CRMRF low (sub/minimally thermal) and CRMRF placebo dose conditions, and a control condition with no intervention (Figure 1). The order of attendance was randomised using a computer generated randomisation chart (IBM SPSS Statistics, Version 20), and concealed blinded from the participants. Fifteen participants additionally attended a fifth session representing 'PSWT high dose' condition to enable a comparison between the two EPAs. Attendance to PSWT condition was not randomised, and hence not truly blinded although they were only informed that it was another type of RF. The study was approved by the Health and Human Sciences Ethics Committee with Delegated Authority (HHSECDA) of the University of Hertfordshire (Protocol number: cHSK/PG/UH/00143). All participants signed an informed consent prior to the study.

Insert Figure 1 here

Apparatus

CRMRF device

The CRMRF energy at 448 kHz was delivered using 'Indiba Activ 902' (Indiba S. A., Barcelona). This therapeutic device was factory calibrated and pretested for accuracy of output. The peak power of the device was 200 Watts (W) (or 450 Volt-Ampere (VA)). It

delivers continuous-wave radiofrequency energy in two modes: A 'capacitive (CAP) mode' and a 'resistive (RES) mode', using metallic electrodes via a coupling medium.

PSWT device

PSWT was delivered using 'Bosch Ultramed' (Robert Bosch GmbH, Germany) that operates at 27.12 MHz. The pulse duration (PD) was fixed at 400 µs, repeating at (pulse repetition rate; PRR) 15–200 Hz. The peak power (PP) can be varied from 100 to 1000 Watts (W). The desired mean power (MP) can be obtained by manipulating these pulse parameters. The device was calibrated prior to the study.

Doppler ultrasound and Sonoelastography

Blood flow to the deeper tissues (two centimetres or more from the skin) was monitored using Doppler ultrasound that provided information on the velocity, volume and intensity of blood flow. The indices of tissue extensibility (measurements of relative hardness/softness of tissues) were obtained using Sonoelastography. An 'Esaote MyLab70 XVG' (Esaote S.p.A, Genoa, Italy) ultrasound scanner was used alongside a linear array probe 'LA523' that supports a frequency range of 4–13 MHz (Esaote S.p.A, Genoa, Italy) to collect the data. Sample ultrasound images obtained from one of the participants are shown in Figure 2.

Insert Figure 2 here

Other devices

Blood pressure (BP) and pulse rate (PR) were monitored using a digital BP monitor (Omron M2, Omron Healthcare Europe B.V., Netherlands) and core temperature using an infra-red (IR) tympanic thermometer (Braun ThermoScan IRT 4520, Braun GmbH, Germany). A body composition monitor (Omron BF508, Omron Healthcare Europe B.V., Netherlands) was used to obtain the anthropometric data. Room temperature and humidity were monitored using an electronic thermohygrometer (RS 212-124, RS Components Pte Ltd., Singapore).

Experimental procedure and Data acquisition

The participants were asked to avoid food, beverages and strenuous exercises before the start of sessions to minimise physiological inconsistencies. They attended one treatment condition per session in a random order. A minimum gap of 48 hours was ensured between sessions. Similar times (±1 hour) of the day were chosen for all sessions of a participant. The

participants were screened using an eligibility questionnaire including questions relating to any recent injury or illness and accepted contraindications to RF therapy (pregnancy, malignancy, metal or electronic implants in the body). Subsequently, their 'skin thermal sensitivity' and the ability to distinguish between warm and cold was tested using test tubes filled with water at approximately three different temperatures (± 0.5 $^{\circ}$C): 45 $^{\circ}$C (warm), 35 $^{\circ}$C (neutral) and 25 $^{\circ}$C (cold). After this screening, demographic and anthropometric data were collected.

Participants were then positioned in supine after changing to shorts or other loose fitting clothes. The skin over the medial aspect of both thighs were prepared and marked. While the skin and experimental setting was being prepared the participants acclimatised for 20 minutes in supine. For all participants the right leg was chosen for the study, while the untreated left leg served as control. Blood flow and Sonoelastography measurements were performed pre and post intervention. Core temperature, BP and PR were also concurrently monitored. For each participant, blood flow was identified by manoeuvring the ultrasound probe over the lower anteromedial aspect of the quadriceps femoris muscle. Once most prominent pulsatile (arterial) flow was identified, skin markings were used to maintain accuracy of probe placement and ensure repeatability. For Sonoelastography measurements, a fixed probe position was adopted for all participants. The probe was placed parallel to the longitudinal axis of thigh, perpendicular to the skin in the middle lower part of the marked area. Minimal probe pressure and liberal amount of conductive gel were used to avoid any undue compression of the tissues.

For all participants, the machine settings remained the same for both pre and post treatment measurements. Data clips were recorded up to five seconds for both Doppler and Sonoelastography measurements during each assessment, which were then broken down into image frames for analysis. Prior to this study, intra-rater reliability for both Doppler and Sonoelastography measurements was established in a pilot study on 12 participants. The ICCs (3,1) for all measurements relating to blood flow (Doppler) were 0.818 – 0.987 with 95% CI, and within 0.957 – 0.998 with 95% CI for all measurements relating to tissue compliance (Elastography).

Radiofrequency Intervention

The CRMRF treatment was delivered for 15 minutes (5 minutes in CAP mode followed by 10 minutes in RES mode) using 20 ml coupling medium for each mode. The return plate electrode was smeared with 20 ml coupling medium and positioned under the calf muscle belly. The dosage was adjusted based on participant feedback. For CRMRF high, the intensity was gradually increased till the participants reported moderate yet comfortable heating, which was then maintained throughout the session. For CRMRF low, the intensity was maintained at a sub/minimally-thermal level throughout. For CRMRF placebo, the device output was turned off after the participants reported thermal onset (within the first minute). For the control condition the participants rested on the treatment plinth for 15 minutes. The nearest available PSWT dose to the mean CRMRF high dose (42.37 W) used in this study was 47 W (PD–400 µs, PRR–200 Hz, PP–600 W). Hence, 47 W was delivered for 15 minutes to all 15 participants who attended PSWT group, using a drum (monode) applicator placed 1.5 cm from the skin.

Data Analysis

Ultrasound images were computationally analysed using MATLAB (MathWorks, Massachusetts) algorithms to process the colour image data into numerical data. For every image frame the MATLAB algorithms generated two types of data: the 'pixel count' (total number of coloured pixels) in the 'region of interest' (ROI) indicating the blood volume information, and the 'colour intensity index' (sum of colour intensity values of all the coloured pixels in the ROI). In the final analysis, the pixel count was expressed in 'kilo pixels' (pixel count divided by 1000) and the colour intensity index as the 'mean colour intensity index per pixel' by dividing the sum of colour intensity values of a frame by the total number of pixels in that frame. In colour Doppler, the 'colour intensity index' indicated the relative velocity of blood flow, where higher the index higher was the velocity. In power Doppler, the pixel count represented the overall 'blood volume' and the colour intensity index represented the 'blood flow intensity'. Higher the pixel count and/or index, higher were the blood flow. The degree of tissue compliance (level of hardness/softness) data from Sonoelastography was analysed similarly to the Doppler data although the MATLAB algorithms varied depending on the machine colour scales and their pixel values. The analysis of all machine colour scales using MATLAB is further illustrated in Figure 3.

All data were analysed using IBM SPSS Statistics ((Version 20) IBM Corporation, USA). Two separate data analyses, with three CRMRF and control groups (17 participants) and with

all five groups (15 participants) were undertaken. The data sets from all five experimental conditions were tested for normal distribution. To ascertain any statistically significant differences between conditions, group data were compared using either two-way (intervention and time) repeated measures analysis of variance (ANOVA) at two time points (baseline, post treatment) or using the non-parametric alternative Friedman's two-way ANOVA by ranks, where the data sets violated the assumptions of normality (Shapiro-Wilk test). Statistical significance was set at $p \leq 0.05$ (0.8 P, 95% CI). A post-hoc analysis was conducted using G*Power (Version 3.1) to determine the power.

Insert Figure 3 here

Results

All participants completed the treatments and the accompanying assessments. Both types of interventions were well tolerated, with no reports of any adverse events. The demographic and mean (SD) anthropometric data are reported in Table 1. Mean (SD) treatment doses, room temperature and humidity are reported in Table 2. The study was conducted in thermoneutral conditions. To illustrate the levels of variation among participants, the individual dosage data from the three radiofrequency groups are plotted in Figure 4.

Insert Table 1 here

Insert Table 2 here

Insert Figure 4 here

Blood Flow Volume

Figures 5(a–b) shows the mean (SD) blood flow volumes recorded at the two time points and the percentage changes of mean.

Insert Figures 5a & 5b here

Blood flow volume data were analysed by Friedman's two-way ANOVA by ranks. In the four-group analysis, a significant main effect for the interventions was found at post treatment [$\chi^2 (3) = 13.659$, $p=0.003$]. Therefore, the applied dose influenced the changes in blood flow volume. At baseline the groups did not differ significantly, except between the control and placebo groups (Friedman, $p=0.009$). In the five-group analysis similar result was

9

obtained for the main effect [$\chi^2(4) = 20.000$, $p<0.001$]. The five groups were not significantly different at baseline.

Within the CRMRF high group there was a substantial rise in blood flow volume from baseline to post treatment (Wilcoxon, $p=0.001$, $r=0.60$). A significant increase, although less strong was noted also in the CRMRF low group (Wilcoxon, $p=0.006$, $r=0.47$). No such meaningful changes in blood flow volume were noted in the other three groups. Key results of pairwise comparisons between groups are reported in Table 3.

Insert Table 3 here

Blood Flow Intensity

Figures 6(a–b) shows the mean (SD) blood flow intensities recorded at the two time points and the percentage changes of mean.

Insert Figures 6a & 6b here

Blood flow intensity data were analysed by Friedman's two-way ANOVA by ranks. In the four-group analysis, a significant main effect for the interventions was found at post treatment [$\chi^2(3) = 14.788$, $p = 0.002$]. Therefore, the applied dose influenced the changes in blood flow volume. At baseline the groups did not differ significantly. In the five-group analysis similar result was obtained for the main effect [$\chi^2(4) = 18.240$, $p=0.001$]. The five groups were not significantly different at baseline.

Within the CRMRF high group there was a substantial rise in blood flow intensity from baseline to post treatment (Wilcoxon, $p=0.001$, $r=0.55$). No such meaningful changes were noted in the blood flow intensity recordings of the other four groups. Key results of pairwise comparisons between groups are reported in Table 4.

Insert Table 4 here

Blood Flow Velocity and Tissue Extensibility

No significant main effects, interactions or changes within groups were noted for any of the intervention groups for any time point in either the four or the five-group analysis for blood flow velocity and the tissue extensibility measures.

Other results

No significant variations were ever noted in core temperature, BP or PR under any test condition.

The post-hoc analysis revealed that the overall power obtained for both statistical analyses on blood flow volume and intensity were over 80%.

Discussion

Although numerous studies have investigated the effects of radiofrequency-based treatment in animal models as well as in humans, there is insufficient evidence to demonstrate the effects of radiofrequency below the shortwave frequency band. Two recent reviews on the use of radiofrequency-based EPAs in therapy-related clinical practice published by the same authors found no clinical studies on acute conditions for frequencies below shortwave (23) and only a limited number of such studies on chronic conditions (26). The current study addressed the issue of physiological effects of both types of frequency ranges of RF by performing due comparisons between CRMRF that operates at 448 kHz in continuous mode and PSWT that operates at 27 MHz in pulsed mode.

Recently, the skin thermal responses to incremental doses of CRMRF were reported by us in an experimental study (16). The current study reports other thermophysiological responses such as changes in deep blood flow as well as changes in tissue compliance (up to over two cm depths from the skin), in response to the application of multiple doses of CRMRF therapy and a comparable high dose of PSWT. In terms of the mode of energy delivery PSWT may not be directly comparable to CRMRF since the former is pulsed while the latter is continuous. Besides, PSWT is not known to cause extremely high thermophysiological responses due to a "washout" of the heat energy from the tissues during its "off cycle". However, the comparisons have been made for the aforementioned reasons.

The within-group changes (the changes within each experimental condition) in tissue response and the results of the between-group pair-wise comparisons (the comparisons between the experimental conditions) reported in tables 3 and 4 show that a high dose of CRMRF can significantly increase the blood flow volume (effect size, $r = 0.60$) and the blood flow intensity ($r = 0.55$) in deeper tissues. Although less significant, even a low dose of CRMRF can increase the blood flow volume at depth ($r = 0.47$). In contrast, exposure to an equivalent high dose of PSWT failed to induce any such effects on either the volume or the intensity of blood flow in deeper tissues. Either type of RF failed to significantly increase the

blood flow velocity. Since similar studies that employed RF at frequencies lower than shortwave have not been reported previously, the authors are unable to make any direct comparison with existing literature.

Studies in the past have suggested that the differences in blood flow responses secondary to electromagnetic field (EMF) exposure are mainly due to the differences in their ability to penetrate tissues and the level of rise in local tissue temperature. Radiofrequency-based EPAs are proposed to be more penetrative and are anticipated to influence blood flow at various depths (9, 12, 16) compared to low penetrative infrared radiation (IRR) that has been shown to increase cutaneous circulation (34, 35). Previous research with shortwave has proposed that a tissue temperature rise to levels in excess of 40 °C may be necessary to increase muscle blood flow (36). Temperature of the tissues was not directly monitored in the current study; however, it is unlikely to have risen to levels above 40 °C. Skin temperature responses secondary to CRMRF exposure has already been reported by us (16). The peak temperature attained by Kumaran and Watson (2015) that used much higher CRMRF doses than those reported in this study was below 40 °C (16).

Hence, extrapolating our previous findings to the results of this study it may be argued that the significant rise in deep blood flow volume and flow intensity obtained with the high dose CRMRF might have been achieved with a potentially modest rise in tissue temperature. This is further vindicated by the rise in blood flow volume even with the low dose CRMRF where the rise in tissue temperature must have been minimal. This potentially suggests that a substantial rise in tissue temperature may not be required for CRMRF to achieve increased deep blood flow. Moreover, it needs to be taken into account that the Doppler measurements were only able to be recorded about five minutes after the end of the intervention owing to the skin preparation time and the time taken to locate blood flow, which meant that any blood flow responses during and immediately after the treatment were not accounted for. Therefore, based on the current and previously reported (16) results on CRMRF and the existing shortwave literature (36), it is proposed that unlike SWT the CRMRF may be capable of increasing and sustaining blood flow at depth at substantially lower tissue temperatures. This suggests that CRMRF is potentially capable of inducing a sustained influence on the physiological processes relating to deep blood flow with mechanisms that are either thermal or nonthermal or both.

Considering the above argument, it is implied that compared to CRMRF a substantially higher dose of treatment and hence a substantially higher amount of energy (potentially generating a high thermal response as explained) may be needed for PSWT to produce effects similar to that of CRMRF. In other words, PSWT may lack any notable nonthermal effect on deep blood flow in the absence of significant tissue heating. This is justified by the mixed reports on the deep circulatory effect of PSWT available from the literature (15, 37), which indicate that when compared to the doses in this study; a substantially higher dose of PSWT may be required to increase blood flow at depth. In fact, PSWT was designed to deliver pulsed RF energy to provide physiological benefits without an undue rise in tissue temperature. It appears from the results of this study that a low dose CRMRF can potentially achieve the same benefits more effectively than PSWT without unduly raising the tissue temperature despite being a continuous-mode RF therapy. It is therefore assumed that the type of applied energy might also be a critical factor beside the temperature change, in deciding the level of tissue response.

With regards to tissue extensibility, early work has shown that heat changes the behaviour of collagenous tissues making it more viscoelastic (38, 39), and reduces spasm in muscles (40). However, for a notable effect, the tissue temperature will need to be raised at least to the level of 40 ºC (41). Contrary to blood flow, there were no significant effects on tissue extensibility with any of the interventions in this study. Nonetheless, it may be noted that the Sonoelastography measurements were performed after the blood flow measurements were taken, thus any effect during or immediately after the intervention should clearly have been missed. This clearly is a limitation of this study. Besides, all participants in this study had normal muscle tone with no concomitant injury. People affected by conditions that may be compromising their tissue extensibility, or even asymptomatic people who are presented with increased tone in their muscles could behave differently to the subjects of this study.

The results also indicate a dose-response relationship, with the high dose CRMRF inducing a more pronounced physiological response than the low dose CRMRF. The mean dose delivered to the high dose group was twice as that of the low dose group. In addition, there were small variations in dosage within the groups itself as a fixed dose was not delivered to every participant in the group (dosing varied based on the participants' thermal perception and thermal tolerance). Since only two active doses of CRMRF were employed, recommendations on the optimum dosage parameters could not be identified. It has also not been possible to identify why some participants were able to receive a higher dose of

CRMRF when compared to the others. It is proposed that the thermal sensory perception of the individual may have been responsible for the level of energy uptake. The thermal perception is a normally distributed phenomenon in a normative sample. Additional studies will need to be carried out to further identify the dosage and other intervention parameters.

Although the study used a crossover design employing participants with a wide age range (25–66 years, with a mean (SD) age of 45.71 (12.70) years) and varying physical activity levels, there were several study limitations too. Besides the short delay in obtaining the post treatment data, there were no follow-up assessments and the physiological responses during the intervention phase were not mapped, unlike in some of the previous shortwave studies (13, 14, 37) where peripheral blood flow was monitored during the intervention. The PSWT session was not randomised, not fully blinded and was always the fifth session for all participants. Also, the study was only single-blind as the researcher (BK) who performed the interventions and assessments remained unblinded. Together, the above factors may somewhat limit the validity of the findings. Future studies should be fully randomised, double-blinded, employ follow-ups and minimise the time delay in starting the post treatment measurements. Additionally, to facilitate a full understanding of the physiological responses, the measurements should be enabled during the treatment delivery where possible.

Conclusions

The results of this study suggest that a high as well as low dose of CRMRF can significantly enhance blood flow volume at depth, while only the high dose can enhance both the volume and intensity of flow. An equivalent high dose of PSWT failed to show any impact on either parameter, which meant that overall CRMRF induced a significantly more pronounced physiological response out of the two types of radiofrequency-based EPAs. None of the treatment conditions had any impact on the deep blood flow velocity. The extensibility of tissues (relative hardness and softness), core temperature, BP and PR were not affected by either type of RF treatment.

Based on the presented results the hypothesis proposed on the effects of CRMRF on deep blood flow was accepted, but not for tissue extensibility. The more pronounced physiological effects of CRMRF in healthy participants compared to PSWT may be indicative of its potentially greater clinical benefits; however, caution should be exercised in extrapolating these findings to patient populations who could respond differently to the same intervention.

Further studies that address the limitations of this study, that explore additional physiological responses and clinical studies that involve patient groups are therefore necessary.

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Table 1: Demographic and mean (±SD) anthropometric data from the 17 participants who received localised 448 kHz Capacitive Resistive Monopolar Radiofrequency (CRMRF) treatment.

Sample	Demographic data			Mean (±SD) anthropometric data				
	Mean (±SD) age (years)	Gender: Males	Gender: Females	Height (m)	Weight (kg)	Body fat (%)	Visceral fat	BMI
17	45.71 (12.70)	7	10	1.70 (0.08)	71.48 (10.02)	30.32 (7.61)	7.24 (2.54)	24.68 (2.71)

SD – standard deviation; kg – kilogram; m – metre; BMI – body mass index.

Table 2: Mean (±SD) treatment doses received by the participants in the five experimental groups, and mean (±SD) room temperature and humidity during the experimental sessions.

	CRMRF High	CRMRF Low	CRMRF Placebo	Control	PSWT
RF dosage in Watts (W)	42.37 (4.64)	18.77 (3.82)	2.79 (1.23)	0	47
Room temperature (°C)	25.12 (1.14)	25.53 (1.11)	25.35 (1.06)	25.18 (1.04)	24.30 (0.56)
Humidity (%)	41.21 (6.38)	41.06 (7.40)	39.68 (6.24)	41.79 (6.50)	32.70 (4.37)

CRMRF – Capacitive Resistive Monopolar Radiofrequency; PSWT – Pulsed Shortwave Therapy; RF – radiofrequency.

Table 3: Key results from the pairwise comparisons on blood flow volume responses across the five experimental groups.

Comparisons involving PSWT group are based on 15 participants, while all others are based on 17 participants. Data were not significantly different at baseline, except between the placebo and control groups. Statistical significance was set at $p \leq 0.05$ (Friedman's two-way ANOVA).

Comparison		Test statistic	Adjusted significance value (p)	Effect size (r)	Power (P)
CRMRF high vs.	CRMRF low	0.353	1.000 (NS)	0.137	
	CRMRF placebo	1.176	0.047	0.456	0.815
	Control	1.412	0.009	0.547	0.920
	PSWT	2.067	0.003	0.654	0.961
CRMRF low vs.	CRMRF placebo	0.824	0.377 (NS)	0.319	
	Control	1.059	0.101 (NS)	0.410	
	PSWT	1.867	0.012	0.590	0.924
PSWT vs.	CRMRF placebo	0.600	1.000 (NS)	0.190	
	Control	0.467	1.000 (NS)	0.148	

CRMRF – Capacitive Resistive Monopolar Radiofrequency; PSWT – Pulsed Shortwave Therapy; NS – non-significant.

Table 4: Key results from the pairwise comparisons on the blood flow intensities across five experimental groups.

Comparisons involving PSWT group are based on 15 participants, while all others are based on 17 participants. Data were not significantly different at the baseline. Statistical significance was set at $p \leq 0.05$ (Friedman's two-way ANOVA).

Comparison		Test statistic	Adjusted significance value (p)	Effect size (r)	Power (P)
CRMRF high vs.	CRMRF low	0.471	1.000 (NS)	0.182	
	CRMRF placebo	0.824	0.377 (NS)	0.319	
	Control	1.647	0.001	0.638	0.972
	PSWT	2.000	0.005	0.632	0.951
CRMRF low vs.	CRMRF placebo	0.353	1.000 (NS)	0.137	
	Control	1.176	0.047	0.456	0.815
	PSWT	1.467	0.111 (NS)	0.464	
PSWT vs.	CRMRF placebo	0.800	1.000 (NS)	0.253	
	Control	0.067	1.000 (NS)	0.020	

CRMRF – Capacitive Resistive Monopolar Radiofrequency; PSWT – Pulsed Shortwave Therapy; NS – non-significant.

Figure 1: Schematic representation of the five study groups. Groups 1–4 were represented by all 17 participants, with each participant assigned a random order of attendance. Group 5 was represented by 15 participants only, at non-random and was always the last (fifth) session.
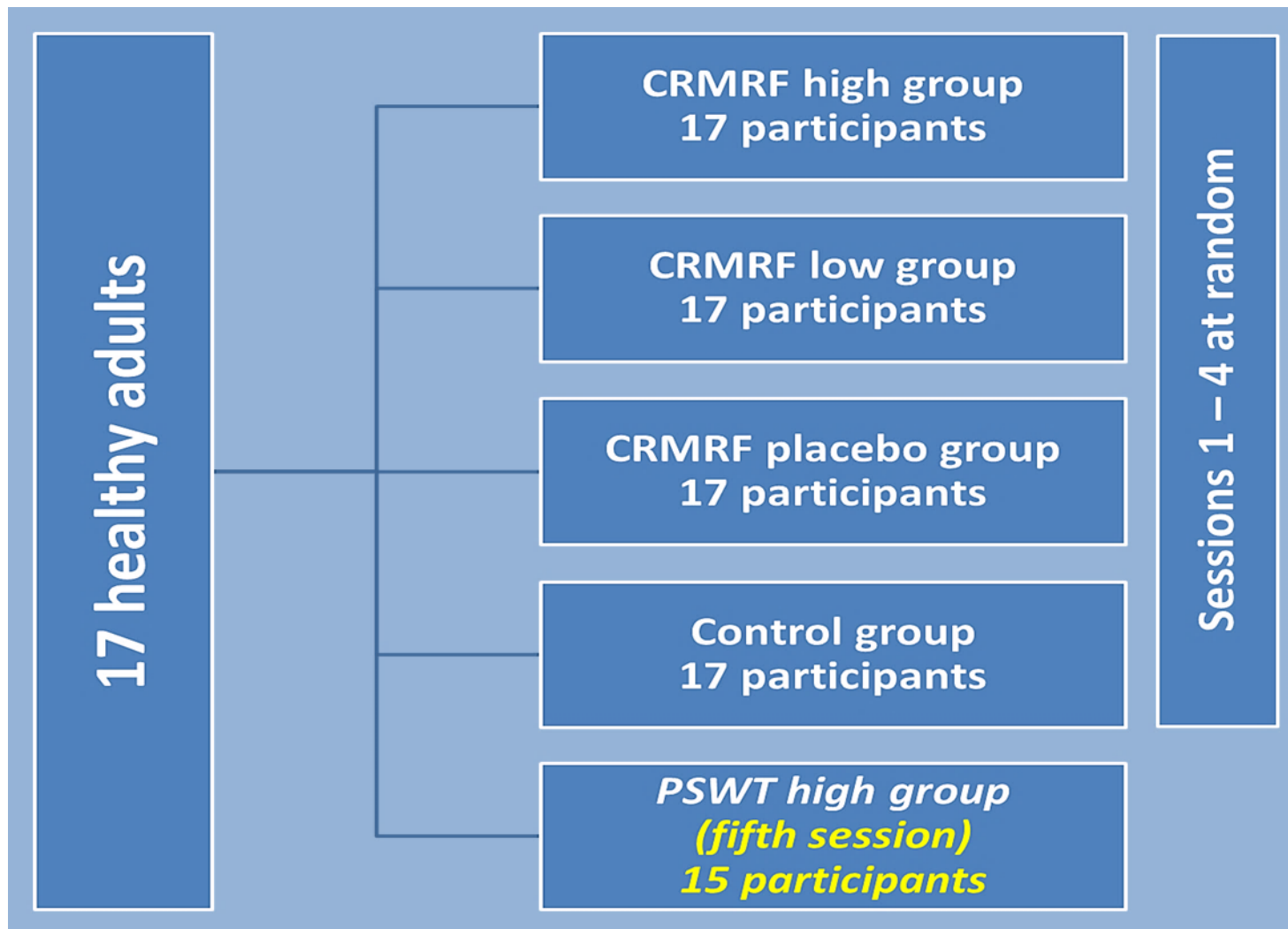
Figure 2: Sample images showing the Doppler

Ultrasound and Ultrasound Elastography recordings from one participant (Number 14) before and after receiving the 'CRMRF high' intervention.

The data shown are: Colour Doppler images showing the peak velocity of blood flow (top left), Power Doppler images showing the peak volume and peak intensity of blood flow (bottom left), and Elastography images showing the hard, intermediate and soft tissue structures (right). The images were computationally analysed using MATLAB codes (MathWorks, Massachusetts, USA) to convert the colour image data into numerical data.

Pre-intervention
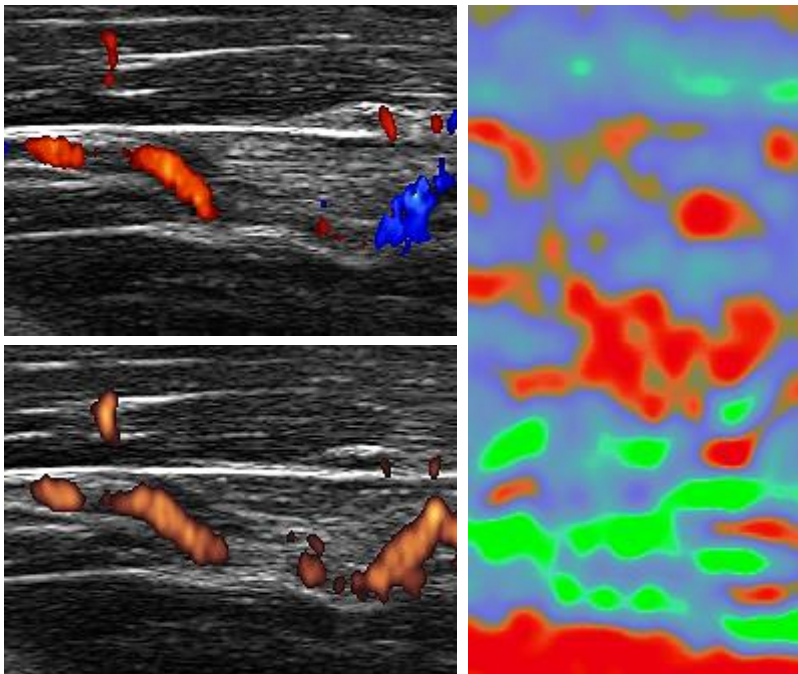
Post intervention
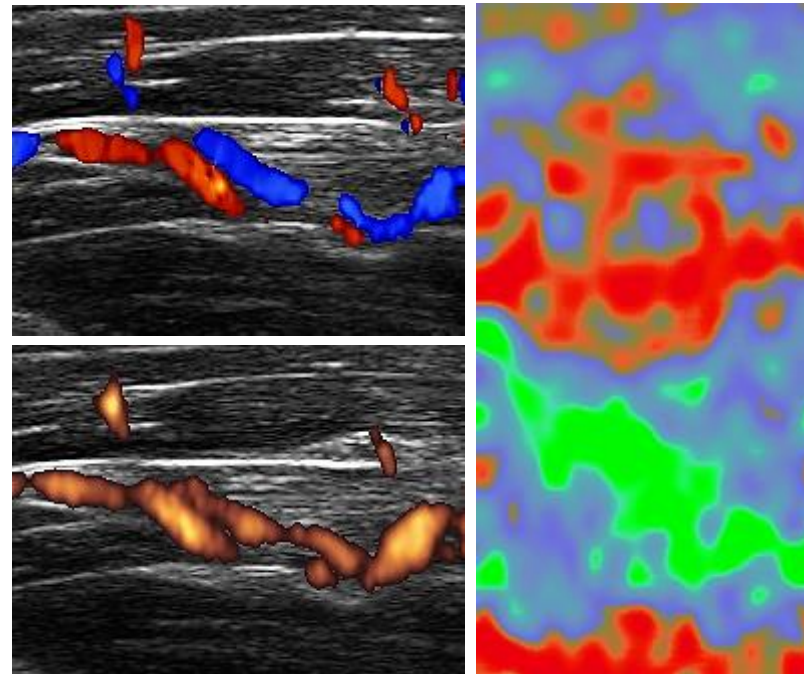
Figure 3: Images (left) and graphs (right) showing the analysis of colour Doppler (top), power Doppler (middle) and Elastography (bottom) colour scales. For colour and power Doppler, a linear relation was identified between the intensity of colour on the scale and the amount of 'green' component (as plotted) of the corresponding RGB (red, green and blue) spectrum. Red and blue components did not follow this linear relation and were hence not used for the analysis of either colour or power Doppler. The x-axis shows the 'pixels' from the top to the bottom of the scale on the left and the y-axis shows the corresponding value of 'green' from the RGB scores. For Elastography, which was divided into 'hard', 'intermediate' and 'soft' categories, all three colour components (red, blue and green respectively) were analysed and used for interpretation as shown in the graph.
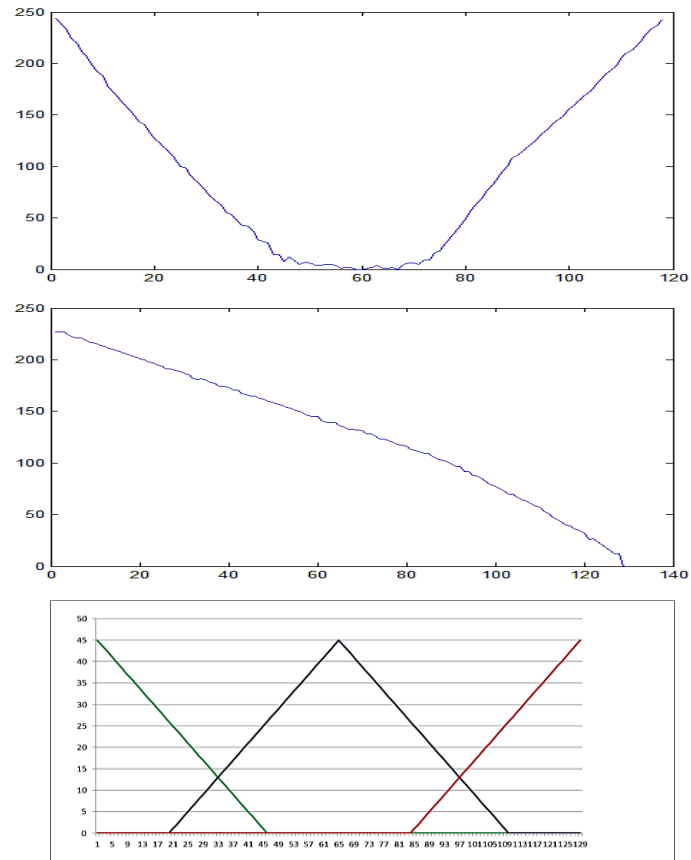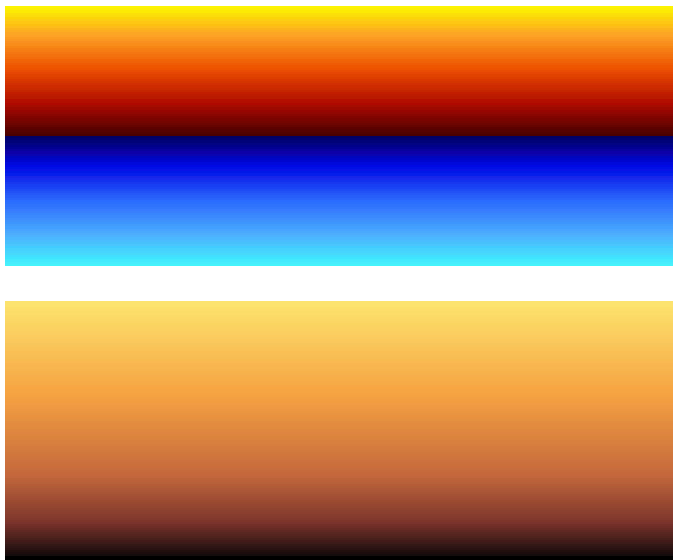
Figure 4: Data from CRMRF high, CRMRF low and PSWT high groups, showing the <u>individual</u> treatment doses delivered.

Participants 9 & 10 did not attend the PSWT group.
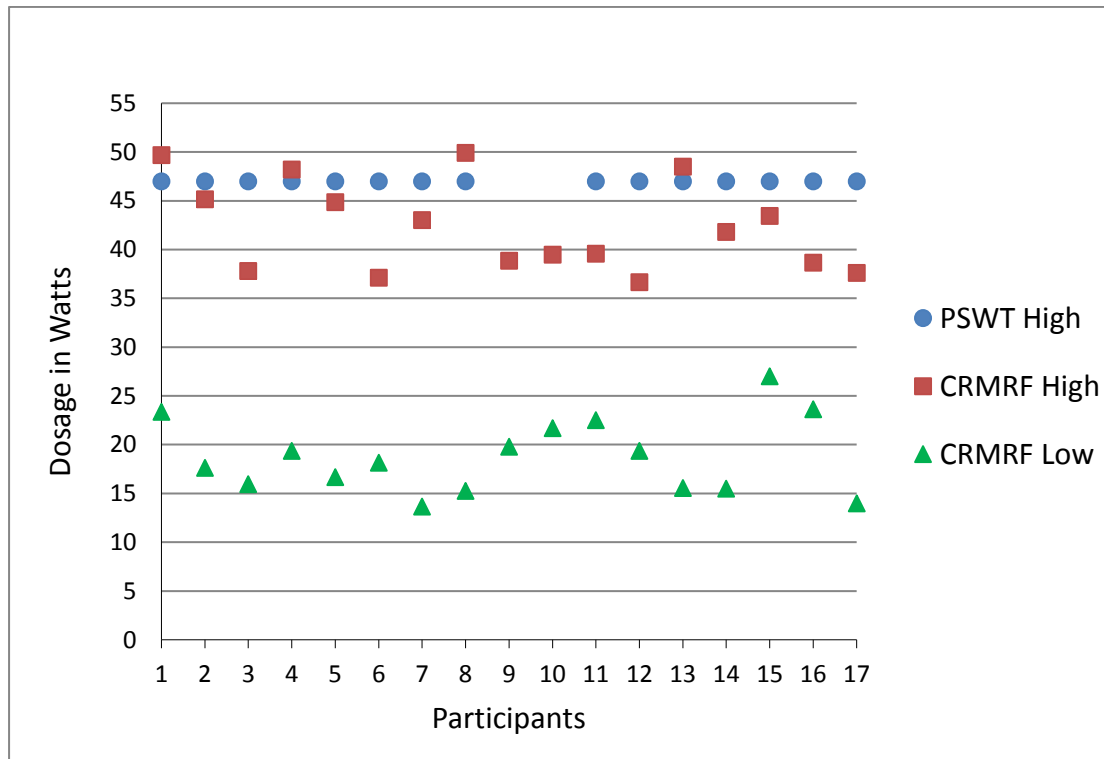
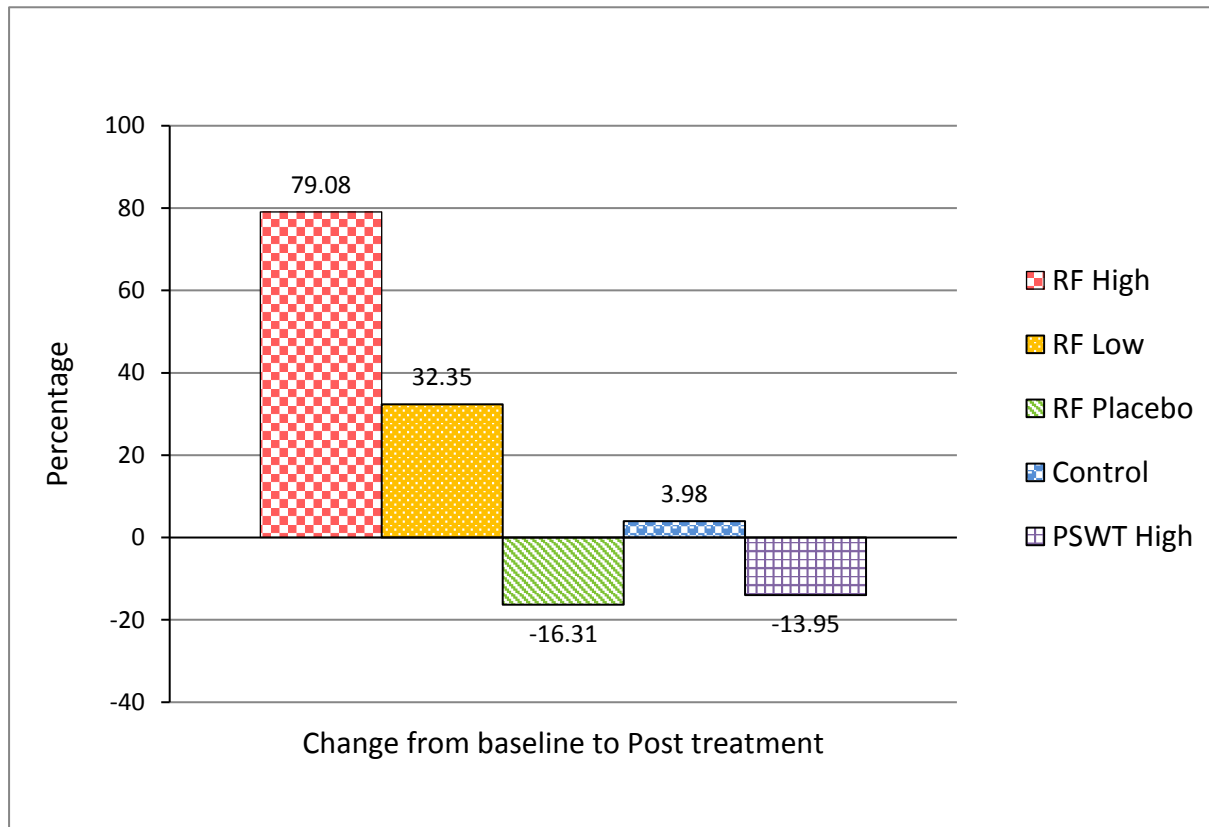**Figure 5a:** The mean (±SD) deep blood flow volume responses showing the baseline and post treatment data from all five groups.

The PSWT group results are based on 15 participants, while the other four groups' results are based on 17 participants. Statistically significant differences (at $p \leq 0.05$) when compared to the baseline are indicated by asterisks (*) above the error bars (Friedman's two-way ANOVA).
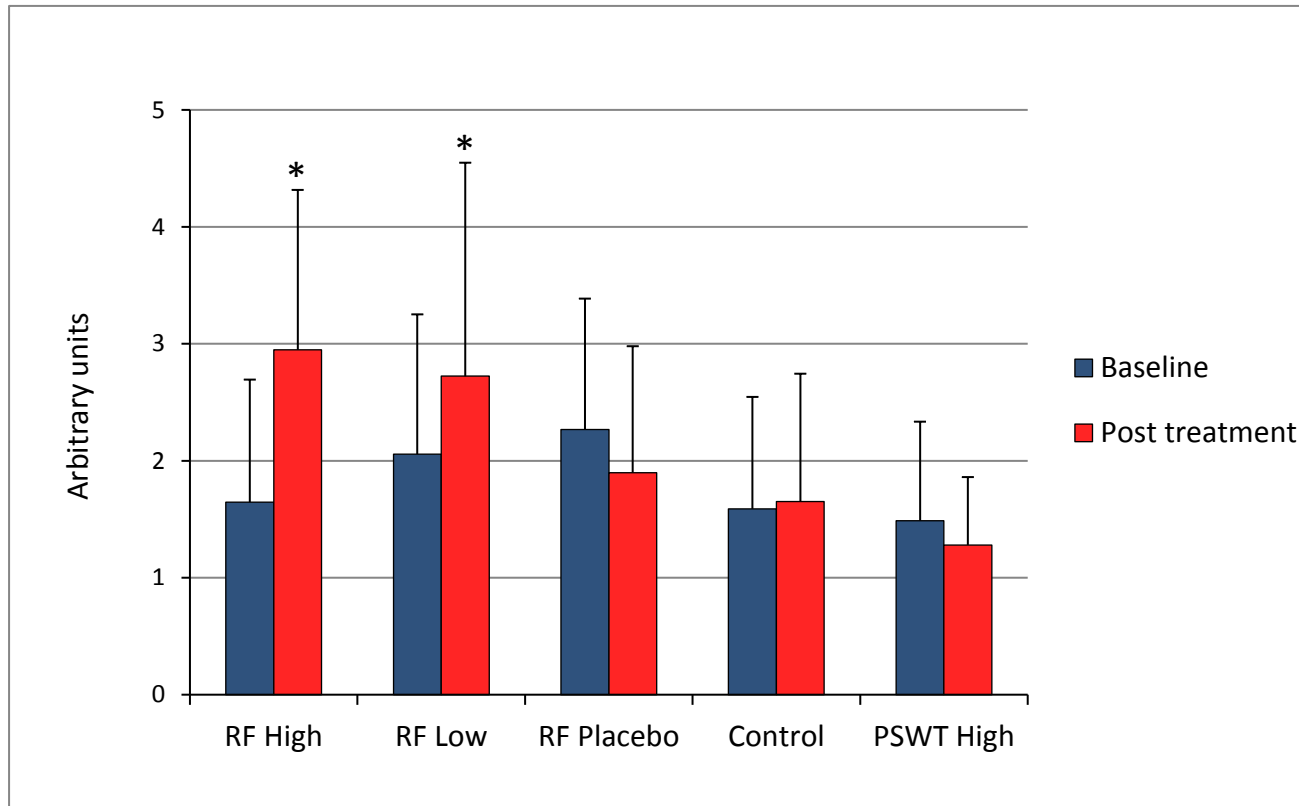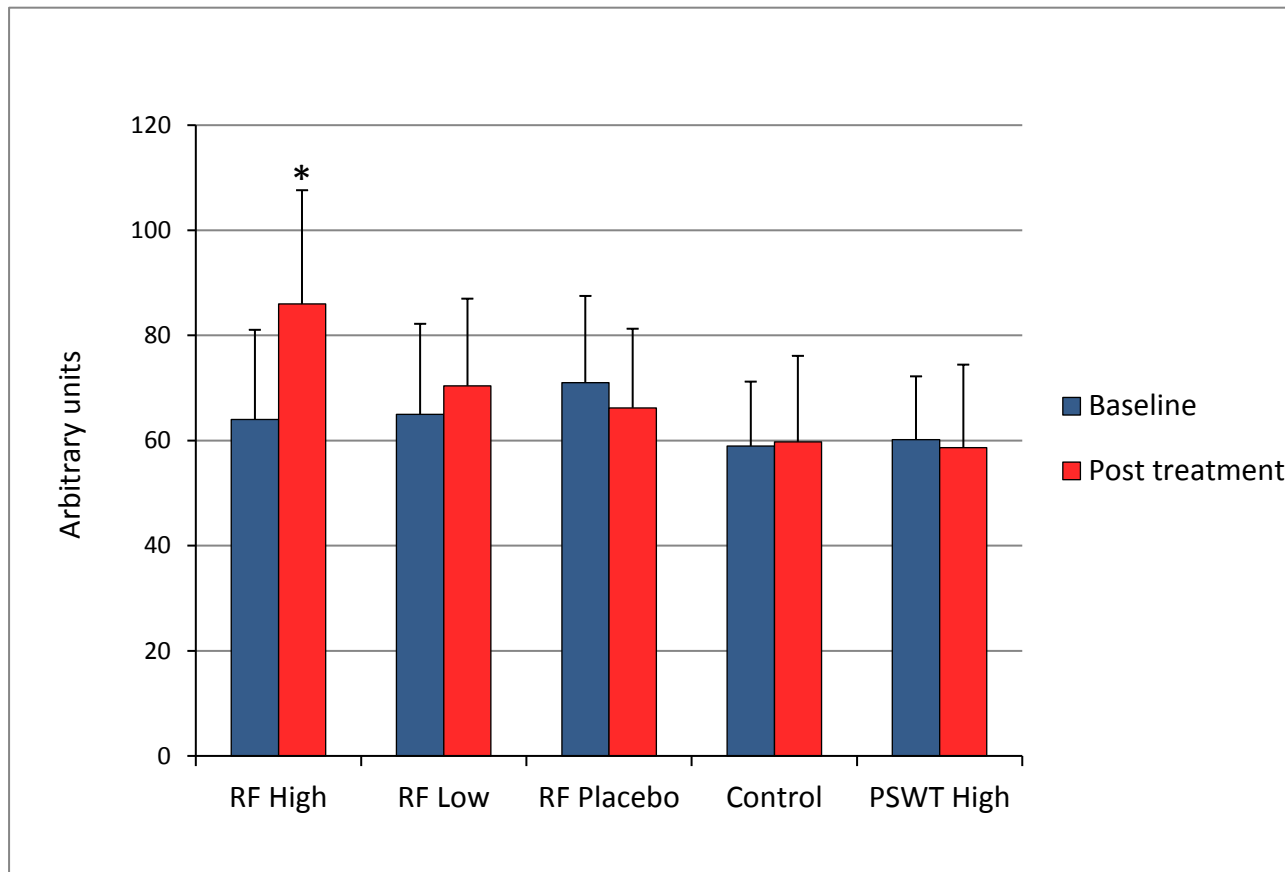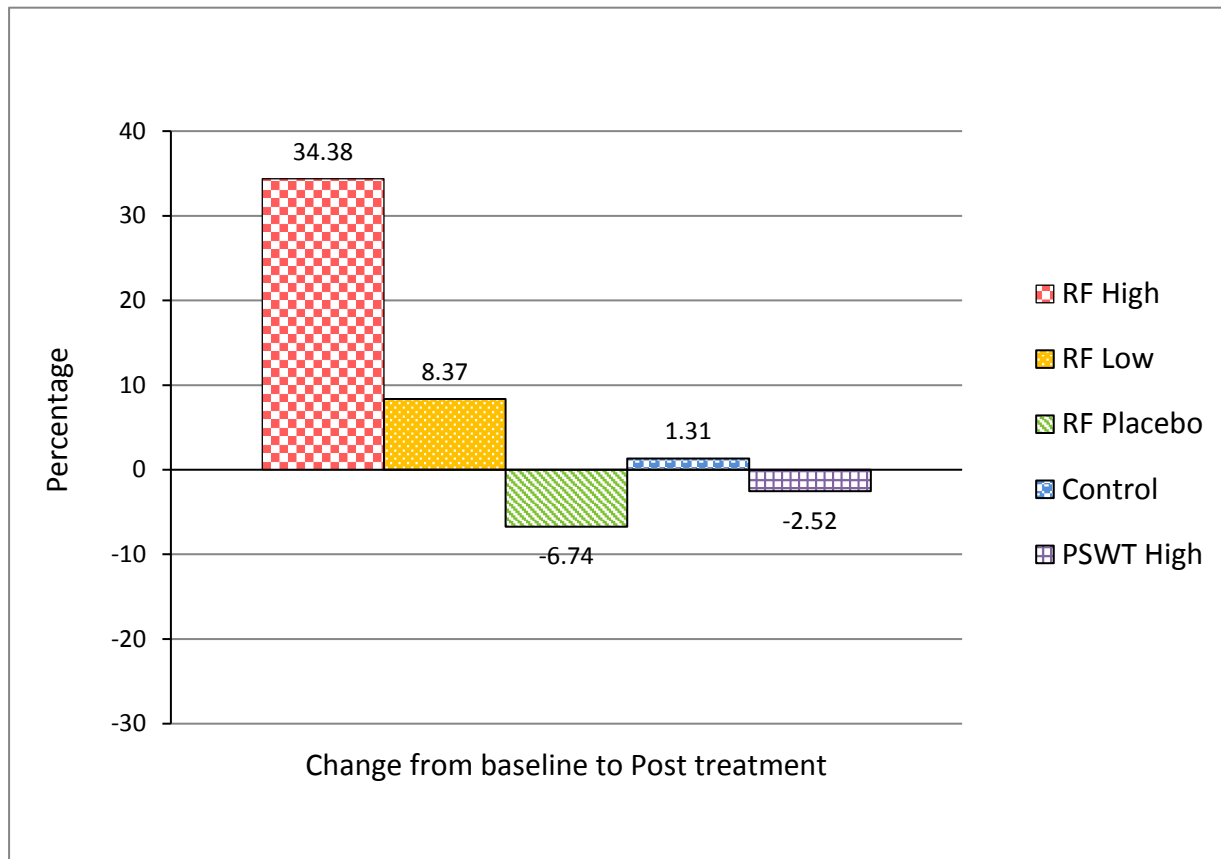
Figure 5b: Percentage change of the mean deep blood flow volume from baseline to post treatment for all five groups.

The PSWT group results are based on 15 participants, while the other four groups' results are based on 17 participants. Statistically significant differences (at $p \leq 0.05$) when the groups were compared pairwise are given in Table 3 (Friedman's two-way ANOVA).

Figure 6a: The mean (±SD) deep blood flow intensity responses showing the baseline and post treatment data from all five groups.

The PSWT group results are based on 15 participants, while the other four groups' results are based on 17 participants. Statistically significant differences (at $p \leq 0.05$) when compared to the baseline are indicated by asterisks (*) above the error bars (Friedman's two-way ANOVA).

Figure 6b: Percentage change of the mean deep blood flow intensity from baseline to post treatment for all five groups.

The PSWT group results are based on 15 participants, while the other four groups' results are based on 17 participants. Statistically significant differences (at $p \leq 0.05$) when the groups were compared pairwise are given in Table 4 (Friedman's two-way ANOVA).

Acknowledgements

Competing Interests

Author Contributions

The first author (BK) is responsible for the study design, acquisition and analysis of data, and writing up this paper. The second author (AH) is responsible for creating the MATLAB codes and the computational analysis of data. The last author (TW) is responsible for the conception of the project, study design, critical revision of this manuscript and overall supervision of the research project. All authors have approved the final version of this manuscript and agree to be accountable for all aspects of the work, its accuracy and integrity. The authors also confirm that all persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.