The effect of modulated electro-hyperthermia on temperature and blood-flow in human cervical carcinoma

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Presented at 36th ICHS, Budapest, 2018

Cite this article as:

Cho DH. (2018): The effect of modulated electro-hyperthermia on temperature and blood-flow in human cervical carcinoma; Oncothermia Journal 24: 482-484

www.oncothermia-journal.com/journal/2018/The_effect_of modulated_electro_hyperthermia.pdf

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Introduction

Mild hyperthermia has been known to enhance the response of tumors to radiotherapy or chemotherapy by increasing tumor blood flow, thereby increasing tumor oxygenation or drug delivery. The purpose of this study was to assess the changes in temperature and blood flow in human cervical cancer in response to regional heating with modulated electro-hyperthermia (mEHT).

Methods

The pelvic area of 20 patients with cervical carcinoma was heated with mEHT. The peri-tumor temperature was measured using an internal organ temperature probe. The tumor blood flow was measured using 3D color Doppler ultrasound by determining the peak systolic velocity/end-diastolic velocity ratio (S/D ratio) and the resistance index (RI) within blood vessels.

Results

The mean peri-tumor temperature was 36.7 ± 0.2°C before heating and increased to 38.5 ± 0.8°C at the end of heating for 60 min. upon heating for 30 and 60 min, respectively, and was 37.1 ± 0.3°C at 30 min after heating. The S/D ratio was 1.65 ± 0.20 at baseline, 1.40 ± 0.13 and 1.22 ± 0.09 upon heating for 30 and 60 min, respectively, and 1.40 ± 0.16 at 30 min after heating. The RI was 0.40 ± 0.12 before heating, 0.29 ± 0.11 and 0.19 ± 0.06 upon heating for 30 and 60 min, respectively, and 0.30 ± 0.10 at 30 min after heating. The marked declines in RI and S/D values strongly demonstrated that heating significantly increased tumor blood perfusion.

Conclusion

Regional heating of the pelvic area with mEHT significantly increased the peri-tumor temperature and improved the blood flow in cervical cancer. This is the first demonstration that the blood flow in cervical cancer is increased by regional hyperthermia. Such increases in temperature and blood flow may account for the clinical observations that hyperthermia improves the response of cervical cancer to radiotherapy or chemotherapy.

Keywords: intra-tumor blood flow, peri-tumor temperature, electro modulated-hyperthermia

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INTRODUCTION

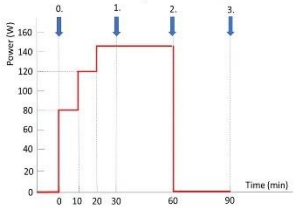
Mild hyperthermia has been known to enhance the response of tumors to radiotherapy or chemotherapy by increasing tumor blood-flow, thereby increasing tumor oxygenation or drug delivery. The purpose of this study was to assess the changes in temperature and blood-flow in human cervical cancer in response to regional heating with modulated electro-hyperthermia (mEHT).

METHOD

The pelvic area of 20 patients with cervical carcinoma was heated with mEHT. The peri-tumor temperature was measured using an internal organ temperature probe. The tumor blood-flow was measured using transvaginal 3D color Doppler ultrasound by determining the peak systolic velocity/end-diastolic velocity ratio (S/D ratio) and the resistance index (RI) within blood vessels.

Regional hyperthermia was performed using an mEHT device (EHY-2000, Oncotherm GmbH, Troisdorf, Germany). We have previously used this device to elucidate the effect of regional heating on the pharmacokinetics of an orally administered drug. Patients were placed in a supine position on a couch, and a 30-cm diameter circular electrode was lightly coupled to the pelvic area. All patients underwent two-dimensional simulation to measure the size of the tumour. The pelvic area was heated at 80 W for the first 10 min, 120 W over the next 10 min and 150 W for the remaining treatment time (40 min).

The measurement points of the study



Baseline characteristics of patients (N½20) assigned to treatment

Characteristics	Number of patients (*N* = 20)
Age (years)	
Range	30–81
Median	50.5
ECOG performance status	
1	12 (60%)
2	8 (40%)
Presentation of tumour	
Exophytic	14 (70%)
Endophytic	6 (30%)
Size of tumour (cm)	
Horizontal x	
Range	2.4–10.0
Median	5.05
Vertical y	
Range	2.0–8.0
Median	4.15
Depth z	
Range	2.9–8.0
Median	4.50
Stage	
IIb	10 (50%)
IIIa	2 (10%)
IIIb	6 (30%)
IVa	1 (5%)
IVb	1 (5%)
Pathology	
Adenocarcinoma	6 (30%)
Squamous cell carcinoma	13 (65%)
Carcinosarcoma	1 (5%)
Haemoglobin (g/dl)	
Range	6.4–13.2
Median	10.41
Mild anaemia[a] (11.0–12.9)	6 (30%)
Moderate anaemia[a] (8.0–10.9)	10 (50%)
Severe anaemia[a] (<8)	2 (10%)
Non-anaemia (≥13)	2 (10%)
Haematocrit (%)	
Range	19.0–38.0
Median	31.35
CA 19-9 (U/ml)	
Range	1.1–33.8
Median	7.89
CA 125 (U/ml)	
Range	5.5–111.6
Median	45.45

[a]WHO classification.

RESULTS

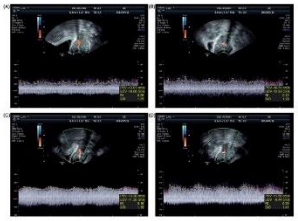
The mean peri-tumor temperature was 36.7 ± 0.2°C before heating and increased to 38.5 ± 0.8°C at the end of heating for 60 min upon heating for 30 and 60 min, respectively, and was 37.1 ± 0.3°C at 30 min after heating. The S/D ratio was 1.65 ± 0.20 at baseline, 1.40 ± 0.13 and 1.22 ± 0.09 upon heating for 30 and 60 min, respectively, and 1.40 ± 0.16 at 30 min after heating. The RI was 0.40 ± 0.12 before heating, 0.29 ± 0.11 and 0.19 ± 0.06 upon heating for 30 and 60 min, respectively, and 0.30 ± 0.10 at 30 min after heating. The marked declines in RI and S/D values strongly demonstrated that heating significantly increased tumor blood perfusion.

The main values of starting characteristics divided into subgroups to show the cohort properties of the treated population.

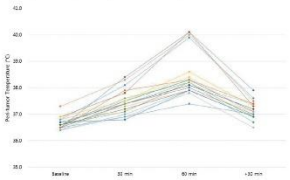
A	Mass size <5 cm (*n* = 11)	Mass size ≥5 cm (*n* = 9)	*p* value
RI index	0.38 ± 0.07	0.42 ± 0.015	0.65
S/D ratio	1.34 ± 0.17	1.65 ± 0.21	0.68
Peri-tumour temperature (°C)	36.58 ± 0.16	36.57 ± 0.24	0.21
SUVmax	10.36 ± 2.52	15.52 ± 5.32	0.27
Haemoglobin (g/dl)	11.4 ± 1.4	9.7 ± 1.3	0.0027
Haematocrit (%)	33.2 ± 3.9	27.6 ± 3.5	0.0021
CA 125 (U/ml)	37.7 ± 18.6	45.9 ± 31.5	0.88
CA 19-9 (U/ml)	7.3 ± 6.4	12.4 ± 8.1	0.04
B	SUVmax <10 (*n* = 14)	SUVmax ≥10 (*n* = 6)	*p* value
RI index	0.35 ± 0.069	0.42 ± 0.13	0.12
S/D ratio	1.57 ± 0.201	1.68 ± 0.19	0.13
Peri-tumour temperature (°C)	36.57 ± 0.16	36.71 ± 0.89	0.2
SUVmax	8.33 ± 1.02	14.55 ± 4.72	–
Haemoglobin (g/dl)	9.9 ± 1.6	11.5 ± 1.7	0.047
Haematocrit (%)	29.8 ± 4.1	33.4 ± 5.6	0.07
CA 125 (U/ml)	45.0 ± 28.6	33.2 ± 19.4	0.45
CA 19-9 (U/ml)	10.1 ± 7.9	8.0 ± 8.5	0.11
C	Tumour nature Endophytic (*n* = 6)	Tumour nature Exophytic (*n* = 14)	*p* value
RI index	0.39 ± 0.082	0.40 ± 0.13	0.91
S/D ratio	1.63 ± 0.21	1.66 ± 0.20	0.49
Peri-tumour temperature (°C)	36.6 ± 0.15	36.71 ± 0.24	0.071
SUVmax	10.81 ± 2.43	13.49 ± 0.53	0.015
Haemoglobin (g/dl)	11.0 ± 1.8	10.7 ± 1.8	0.32
Haematocrit (%)	32.6 ± 5.3	29.9 ± 4.5	0.19
CA 125 (U/ml)	42.9 ± 21.2	40.8 ± 28.9	0.62
CA 19-9 (U/ml)	9.4 ± 8.2	9.5 ± 8.1	0.93
D	Squamous cell carcinoma (*n* = 13)	Non-squamous cell carcinoma (*n* = 7)	*p* value
RI index	0.37 ± 0.07	0.45 ± 0.017	0.32
S/D ratio	1.64 ± 0.20	1.67 ± 0.20	0.72
Peri-tumour temperature (°C)	36.7 ± 0.24	36.6 ± 0.97	0.87
SUVmax	12.18 ± 2.0	13.61 ± 7.5	0.94
Haemoglobin (g/dl)	10.7 ± 1.4	9.9 ± 1.4	0.32
Haematocrit (%)	31.2 ± 4.10	29.7 ± 4.8	0.45
CA 125 (U/ml)	37.2 ± 22.8	49.7 ± 32.3	0.58
CA 19-9 (U/ml)	6.9 ± 4.8	14.2 ± 10.6	0.13

Significant deviations were observed only in haemoglobin and haematocrit concentrations by mass and by SUVmax subdivisions.

High-resolution Doppler measurements of a representation patient at baseline (A), 30 min into the heating procedure (B), 60 min into the heating procedure (C), and at 30 min after the heating procedure (D).



Peri-tumour temperatures were measured at 30 min before hyperthermia (baseline), at 30 min and 60 min during the hyperthermia procedure, and at 30 min after hyperthermia. The peri-tumour temperatures of all patients are shown.



Changes in the peri-tumour temperature, S/D ratio and RI index in cervical tumours

	Baseline	30 min	60 min	+30 min	*p* value[a]
Peri-tumour temperature (°C) (*n* = 20)	36.67 ± 0.22	37.47 ± 0.45*** (2.20 ± 1.10%)	38.46 ± 0.84*** (4.91 ± 2.01%)	37.13 ± 0.33* (1.26 ± 0.86%)	<0.0001
S/D ratio (*n* = 20)	1.65 ± 0.20	1.40 ± 0.13*** (−14.95 ± 5.21%)	1.22 ± 0.09*** (−25.09 ± 8.11%)	1.40 ± 0.16*** (−14.75 ± 8.32%)	<0.0001
RI index (*n* = 20)	0.40 ± 0.12	0.29 ± 0.11** (−27.67 ± 19.00%)	0.19 ± 0.06*** (−51.84 ± 13.14%)	0.30 ± 0.10* (−24.81 ± 10.58%)	<0.0001

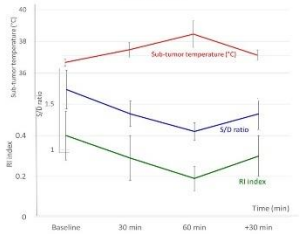
All changes measured in the study were significant and the values are characteristic of the heating process.
Mean ± SD.
[a]Repeated measures ANOVA.
Comparison with baseline: *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ (Bonferroni-corrected *p* values).

The peri-tumour temperatures, S/D ratios and RI indexes in squamous cell carcinoma (sqcc) and non-squamous cell carcinoma (non-sqcc)

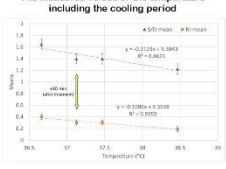
	Pathology		
Parameter/time point	Sqcc (*n* = 13)	Non-sqcc (*n* = 7)	*p* value[a]
Peri-tumour temperature (°C)			
Baseline	36.67 ± 0.24	36.66 ± 0.20	0.429
30	37.53 ± 0.44	37.36 ± 0.47	
60	38.39 ± 0.79	38.60 ± 0.97	
+30	37.15 ± 0.31	37.07 ± 0.38	
S/D ratio			
Baseline	1.64 ± 0.20	1.67 ± 0.20	0.5327
30	1.39 ± 0.13	1.41 ± 0.15	
60	1.24 ± 0.08	1.20 ± 0.10	
+30	1.38 ± 0.15	1.43 ± 0.19	
RI index			
Baseline	0.37 ± 0.07	0.45 ± 0.17	0.0439
30	0.29 ± 0.07	0.29 ± 0.17	
60	0.19 ± 0.05	0.19 ± 0.08	
+30	0.28 ± 0.06	0.33 ± 0.15	

Mean ± SD.
[a]Repeated measures ANOVA (pathology × parameter interaction *p* values).

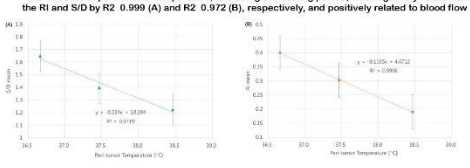
Average results in the various points of the measurements



The measured values of the temperature including the cooling period



The increase in peri-tumour temperature, excluding the cooling period, was negatively related to the RI and S/D by R2 0.999 (A) and R2 0.972 (B), respectively, and positively related to blood flow



Conclusion

Regional heating of the pelvic area with mEHT significantly increased the peri-tumor temperature and improved the blood-flow in cervical cancer. This is the first demonstration that the blood-flow in cervical cancer is increased by regional hyperthermia. Such increases in temperature and blood-flow may account for the clinical observations that hyperthermia improves the response of cervical cancer to radiotherapy or chemotherapy.