WHOLE BODY HYPERTHERMIA BY EXTRACORPOREAL CIRCULATION IN SPONTANEOUSLY BREATHING SARCOMA PATIENTS: HEMODYNAMICS AND OXYGEN METABOLISM

Short Title: Spontaneous Breathing in Whole Body Hyperthermia

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ABSTRACT

Purpose: This phase I study was performed to evaluate the feasibility and toxicity of a new method of extracorporeal perfusion-induced whole body hyperthermia (WBHT) in patients with advanced sarcoma avoiding the need of intubation and general anesthesia.

Methods: One double-lumen femoral venous access was inserted by Seldinger´s technique to obtain WBHT (41.8°C for 120 minutes) via an extracorporeal circuit. No concomitant chemotherapy was applied. Up to 4 treatments of WBHT were performed under moderate sedation in 6 spontaneously breathing patients. Invasive hemodynamic monitoring was performed by use of a pulmonary artery catheter.

Results: After their first WBHT session, 2 patients were excluded from further treatment due to transient liver toxicity or catheter related complication, so a total of 12 cycles remained for analyses. In all patients, conscious sedation resulted in sufficient spontaneous respiration without the need of mandatory ventilation. Median time to reach the target temperature was 84 minutes (range 60-142). Hemodynamic changes revealed the expected hyperdynamic state: Heart rate, cardiac index and stroke volume index significantly increased ($p < 0.05$), whereas blood pressure and systemic and pulmonary vascular resistance index significantly decreased ($p < 0.05$). A net fluid balance of 5822 $\pm$ 1766 ml as well as norepinephrine (mean; 0.062 $\mu g.kg^{-1}.min^{-1}$) were necessary to maintain the mean arterial blood pressure > 60 mm Hg.

Conclusion: Our data demonstrate the feasibility of this method of extracorporeal WBHT without mandatory ventilation. Hemodynamic side effects in spontaneously breathing patients during perfusion-induced WBHT seem less severe than those observed in radiant heat WBHT.

Keywords: Whole Body Hyperthermia; Extracorporeal Circulation; Hemodynamics; Oxygen Metabolism; Cancer.

INTRODUCTION

Although definite data from phase III studies are missing yet, loco-regional as well as whole-body hyperthermia (WBHT) has become an additional modality in the treatment of refractory malignant disorders, demonstrating enhanced thermal sensitivity of malignant cells and an improvement in therapeutic index of certain cytotoxic agents when combined with hyperthermia (1-7).

A series of phase I and II studies demonstrated the efficacy and safety of WBHT at an optimum target temperature of 41.8 $\pm$ 0.2 °C in combination with chemotherapy (8-13), but in addition, there are sporadic hints that WBHT might be of clinical benefit even without cytotoxic agents (14-16).

In contrast to radiant-heat (RH) techniques, WBHT by extracorporeal circulation (ECC) uses a centrifugal pump and a heat exchanger integrated in the circuit to elevate the temperature of the drawn blood, formerly from an artificial arterio-venous shunt applied by surgeons (13, 17, 18).

Recently, the feasibility and safety of ECC through a veno-venous circuit has been demonstrated (5, 19). Due to a lower flow than arterio-venous, no evidence of relevant hemolysis or coagulation disturbances was observed, but this approach was characterized by use of two different cannulas. However, all patients on ECC had to undergo general anesthesia including intubation and mechanical ventilation due to the study protocols.

To date, no data on WBHT by using veno-venous ECC without general anesthesia and ventilatory support do exist. This method would possibly result in lower hemodynamic side effects such as hypotension or tachycardia, and could therefore, with acceptable technical amount, be introduced in cancer centers.

The aim of the present study was to investigate the feasibility and toxicity of veno-venous ECC-WBHT in cancer patients by use of moderate sedation enabling spontaneous breathing. Moreover, we focused on hemodynamics and oxygen metabolism, and hypothesized, that hemodynamic side effects are not that pronounced compared to intubated patients undergoing WBHT as previously published.

PATIENTS AND METHODS

Patients

The present study was designed for 10 patients with metastatic soft tissue sarcoma and progressive disease within 6 months after at least 2 cycles of anthracycline- and ifosfamide-based chemotherapy. The study was approved by the Local Ethical Review Board, since at the time of study initiation no standard salvage therapy was available. All patients provided signed informed consent. However, enrollment had to be prematurely terminated after 6 patients due to the approval of the novel cytostatic agent trabectidin.

All of these 6 patients had a Karnofsky Scale >80%, normal cardiac and pulmonary function, and normal laboratory parameters.

Patients were scheduled to undergo 4 sessions of ECC-WBHT every 4 weeks unless prohibitive toxicity (as stated in Methods / Toxicity assessement) occurred or restaging after 2 cycles showed evidence of progressive disease.

Treatments were performed at an intensive care unit (ICU). After assessing the tolerability of the ECC under normothermic conditions for 30 minutes, the heating procedure was performed as described below to achieve the target core temperature of 41.8 ± 0.2°C within 90 minutes. This temperature was maintained for 120 minutes and thereafter decreased by active cooling down to physiological levels.

Patients were followed overnight in the ICU and then transferred to an open ward. Discharge from hospital took place 48 hours after ECC-WBHT.

Methods

General Procedure

To maintain peripheral oxygen saturation (SpO_2) >95 % and oxygen tension (PaO_2) >85 mmHg oxygen was insufflated. To ensure airway patency an oropharyngeal tube (Guedl tube) was used during conscious sedation. A reflective template was wrapped around the patients to minimize heat loss. The patients´ head and neck were cooled by a local cooling device (Hilotherm; Orthomed Medizintechnik GmbH, Vienna, Austria).

Medication and fluid replacement

Patients received standardized medication (10, 20-22) as given in Table 1. Sedation was titrated to maintain a Glasgow Coma Scale of 8 – 10 during the study period. Crystalloids were administered with a temperature of 45°C to maintain mean arterial blood pressure (mABP) >60 mmHg, urinary output >1ml.kg^{-1}.h^{-1} and pulmonary capillary wedge pressure (PCWP) between 8 and 15 mmHg. Norepinephrine was allowed if mABP was <60 mmHg in patients with PCWP >10 mmHg and systemic vascular resistance index (SVRI) <1600 dyn.sec.m^2.cm^{-5}.

Extracorporeal Circulation (ECC)

ECC was composed of a single serving centrifugal pump (RotaFlow, Jostra AG, Hierlingen, Germany) in conjunction with the Jostra RotaFlow Console and a custom-made tubing set (HLM Tubing Set, Jostra AG), primed with unfractionated heparin (70 U.kg^{-1}) in order to maintain an activated partial thromboplastine time above 60 seconds. In addition, a specifically designed heat exchanger (HEC 44, Jostra AG; flow rate up to 1.5 l.min^{-1}) connected to a water bath was integrated in the circuit and used for elevation of blood temperature to 48°C as well as for postprocedural cooling. According to the literature (23), a temperature of 48°C was chosen, known to be able to rapidly increase body core temperature whithout severe hemolysis. Active cooling was performed by setting the heat exchanger to 37°C.

The whole equipment conformed to the legal requirements determined by the "EU guidelines for Medical Products" 93/42/EWG.

Catheters for establishing and monitoring WBHT

After sedation was achieved, an arterial indwelling catheter (REF SAC-00820, Arrow International, PA, USA) was inserted via the radial artery. A 9 French (9F) triple-lumen polyurethane sheath (AVA HF Advanced Venous Access Device, Edwards Lifesciences GmbH, Unterschleissheim, Germany) was inserted via the internal jugular vein and was used for fluid replacement and for a 7.5F pulmonary artery catheter (Swan-Ganz CCOombo V; Edwards Lifesciences GmbH) for hemodynamic and temperature monitoring. A double-lumen ECC cannula (Cannula for neonatal veno-venous ECMO, M1510-88, 15 F, Jostra AG) was inserted into the femoral vein by use of the Seldinger´s technique. For monitoring of body temperature a 1529 Chub E4 thermometer (Hart Scientific, USA) with ultra sensitive thermistor probes (D-0S4 and D-S18, Exacon Scientific, Denmark) was used. Thermometers were placed in the esophagus, rectum and axilla. Probes were calibrated in a homogeneous waterbath (Micro Bath 7102, Hart Scientific) with a standard temperature probe (Hart 5764, Hart Scientific) using the Steinhart and Hart equation (24).

Hemodynamic guidance

Continuous monitoring of vital functions included respiratory rate and heart rate, body surface and core temperature, ECG, mABP, central venous (CVP) and pulmonary arterial pressure (PAP), cardiac output, SpO_2 and mixed venous oxygen saturation (SvO_2). At prespecified time points (baseline, after 30 minutes on normothermic ECC, after reaching a body core temperature of 40°C, at 41.8°C, and at the end of the heating period) systemic and pulmonary vascular resistance, stroke volume, PCWP, and arterial and mixed venous blood gas analyses were assessed too.

Toxicity assessment

Laboratory parameters including complete blood count, serum chemistry, renal parameters (creatinine, BUN, and creatinine clearance), hepatic enzymes (AST, ALT, GGT, and bilirubin), coagulation parameters (prothrombin time, partial thromboplastin time, fibrinogen, d-dimer, and

antithrombin III-activity) and hemolysis parameters (lactate dehydrogenase, and free hemoglobin) were assessed during the procedure, after 24 and 48 hours as well as on days 8 and 28 of each treatment cycle. Physical examination and assessment for side-effects were additionally performed at the same time points. Toxicity was graded in accordance with the National Cancer Institute Common Toxicity Criteria.

Data Analysis Methods

Data are presented as Mean ± Standard Deviation (SD) unless otherwise stated. All confidence intervals for parameters to be estimated were constructed with a significance level of <0.05 (i.e. a 95% confidence level). Reliability analysis and t-test for paired variables were performed to assess changes in measured hemodynamic parameters. All statistical analyses were performed using the SPSS statistical software package (SPSS Inc., Chicago, IL, version 15.0). A p-value <0.05 was stated as significant.

RESULTS

General Feasibility

Twelve cycles of veno-venous ECC-WHBT were accomplished (Table 2). Heating was commenced 30 minutes after starting the ECC, target temperature of 41.8°C was achieved within a median of 85 minutes (range, 60 – 140) by flow rates ranging between 0.8 and 1.5 $l.min^{-1}$, and was held for 120 minutes. Temperature distribution was homogenous (Figure 1), active cooling down to approximately 37°C took about 30 minutes.

To sustain the hemodynamic goals 1484 ± 291 $ml.h^{-1}$ of fluids were necessary, resulting in an overall substitution of 7754 ± 1653 ml. The net fluid balance was 5822 ± 1766 ml per heating period. In 10 cycles low doses of norepinephrine (median 0.062 $\mu g.kg^{-1}.min^{-1}$; range 0 – 0.139 $\mu g.kg^{-1}.min^{-1}$) were required to maintain a mABP > 60 mm Hg, but could rapidly be tapered after reaching normothermia.

In all patients, conscious sedation resulted in sufficient spontaneous respiration with a significant increase in respiratory rate. Oxygen insufflation ranged between 2 and 4 $l.min^{-1}$. Daily chest x-rays as routinely performed at our ICU revealed no evidence of upcoming pneumonic infiltrates.

Toxicity

In general, treatment was well tolerated and toxicities as depicted in Table 3 were within those usually observed in WBHT trials (e.g. thrombocytopenia, transient elevation of liver parameters).

In all patients thrombocytes significantly decreased with the nadir at 24 hours after ECC-WBHT ($p < 0.05$), but spontaneously resolved within the following days (Figure 2).

There was no evidence of cardiovascular side effects such as arrhythmia or congestive heart failure. In one cycle of ECC-WBHT, a moderate troponin-T elevation was observed, but without any signs of ischemia in the 12-lead-ECG.

During the whole study period, there was no clinical or laboratory evidence of major coagulation activation or bleeding tendency. Moreover, there was no evidence of hemolysis as indicated by unchanged levels of lactate dehydrogenase or free hemoglobin (data not shown).

There were 2 serious adverse events leading to prolonged hospitalization and discontinuation of further WBHT: In one patient transient liver failure occurred, resolving within 10 days after conservative management. In another patient, placement of the pulmonary artery catheter resulted in intravascular burling, requiring surgical removal. However, the patient had to be excluded from further treatment due to time violation of the protocol.

Hemodynamic alterations, oxygen metabolism, and acid-base state

During the heating period significant increases in heart rate, cardiac index and stroke volume index ($p < 0.05$) were observed accompanied by significant decreases of mABP, SVRI and pulmonary vascular resistance index ($p < 0.05$). CVP, PAP and PCWP remained unchanged.

Normothermic ECC did not alter any hemodynamic parameter (Figure 3).

Oxygen delivery and oxygen consumption significantly increased during WBHT ($p < 0.03$), therefore not alterating oxygen extraction (Figure 4).

PaO_2 and SaO_2 remained above the requested limit during the whole study period. Respiratory rate initially dropped, but then significantly increased during heating ($p < 0.05$) and remained elevated during the heating period (Figure 5).

Arterial pH, although showing significant changes over the time period, remained within normal range. After a moderate increase on normothermic ECC, $paCO_2$ significantly decreased to a steady state during the hyperthermic plateau phase ($p < 0.05$). Standard bicarbonate and base excess continuously decreased ($p < 0.05$) till the end of WBHT (Figure 5).

A significant elevation of serum lactate up to 2.6 $mmol.l^{-1}$ accompanied the increase of temperature ($p < 0.05$). Interestingly, also normothermic ECC led to a moderate but not significant increase (Figure 5).

DISCUSSION

In this study we could demonstrate the feasibility of a new type of veno-venous perfusion induced WBHT. All patients tolerated ECC-WBHT well and are still alive. In 2 patients serious adverse events led to exclusion for further investigation, but in only one patient this event was directly related to WBHT. All other patients could be discharged 48 hours after each cycle.

At no time throughout the whole study period the need for intubation or mechanical ventilation arose. Although conscious sedation without intubation might increase the risk of silent aspiration (25), we could not observe any radiological evidence of pneumonic infiltrates. Therefore, spontaneously breathing might be considered as safe in patients undergoing ECC-WBHT.

As expected, perfusion induced WBHT provoked peripheral vasodilatation, accompanied by increases in heart rate and cardiac index. These findings are in accordance with the hemodynamic effects observed with external heating devices (26-30), and exhibit analogies to the systemic inflammatory response syndrome or even sepsis (31). The extracorporeal circuit alone did not seem to exert hemodynamic alterations.

Interestingly, hemodynamic data in patients undergoing ECC-WBHT are rare (15, 18). In most protocols using extracorporeal devices (13, 15, 23), norepinephrine was administered, but the dosage was not given and the net fluid balance during the heating procedure remained unclear.

In our investigation, a volume need of about 6000 ml was adequate to compensate hypovolemia, as indicated by unchanged CVP, PAP and PCWP during the hyperthermic period. However, this significant lower volume necessity than in comparable RH-WBHT trials (7290 to 11500 ml; 26-29) as well as the lower norepinephrine support (0.062 vs. 0.113 $\mu g.kg^{-1}.min^{-1}$) might be explained by the fact, that in these latter studies hemodynamics might have been impaired by intubation and mechanical ventilation (25). Since data of invasive hemodynamic monitoring of patients undergoing RH-WBHT without intubation are missing (10, 20, 32, 33), a comparison with our results is impossible.

Overall, to our estimation this study succeeded in developing a method of systemic hyperthermia without the need of intubation and mechanical ventilation. Moreover, the modified perfusion technique used herein, i.e. a single cannula access by the use of the Seldinger´s technique, also reduces invasiveness. Hemodynamic side effects observed in the present study were as expected and acceptable, so further studies can be performed in a less invasive way (eg. by omiting the pulmonary artery catheter). Except thrombocytopenia with its nadir on day 2 (i.e. 24 hours after ECC-WGHT), the observed toxicities did not exceed those described in literature. Moreover, since platelet count spontaneously resolved within a few days, the temporary thrombocytopenia might not interfere with concomitant application of cytotoxic agents.

Further investigations of this method in combination with chemo- and/or radiotherapy in patients with refractory malignant disorders are therefore warranted.

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Table 1. Study Medication

Medication	Dosage	Indication
Midazolam	0.1 $mg.kg^{-1}$ bolus, 0.03 $mg.kg^{-1}.h^{-1}$ continuous infusion	Moderate sedation allowing spontaneous breathing
Thiopental sodium	3 $mg.kg^{-1}.h^{-1}$	Seizure prophylaxis
Droperidol	2.5 mg	Sedative and antiemetic effect
Lidocain	50 mg bolus, 3 $mg.min^{-1}$ continuous infusion	Antiarrhytmic effect
Esomeprazole	40 mg	Stress ulcer prophylaxis
Metoclopramide	10 mg	Antiemetic prophylaxis
Moxifloxacine	400 mg po for 5 days	Postprocedural infection prophylaxis
Famciclovir	500 mg bid for 5 days	Postprocedural prophylaxis in pts. with history of herpes virus infection

Table 2. Number of Treatment Cycles

Pt. #	Sex	Age	Number of Cycles	Reason of Discontinuitation
1	f	34	2	Progressive Disease
2	m	41	4	End of Study
3	f	44	1	Grade 2 Liver Failure
4	f	31	2	Progressive Disease
5	m	21	1	Catheter related Problems
6	f	52	2	Progressive Disease

Table 3. Incidence of WHO-Toxicity in ECC-WBHT (number of events in 12 treatment sessions)

Adverse Events / Toxicity NCI CTC	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hypocalcemia	1 (8)	5 (42)	-	-
Hypophosphatemia	-	3 (25)	6 (50)	-
Hypomagnesemia	4 (33)	-	-	-
Hypopotassemia	5 (42)	-	-	-
Hypermagnesemia	4 (33)	-	-	-
Hyperchloremia	1 (8)	-	-	-
Hypersodiemia	1 (8)	-	-	-
Hyperbilirubinemia	4 (33)	2 (17)	3 (25)	-
Hypalbuminemia	6 (50)	-	-	-
Elevated lipase	1 (8)	1 (8)	2 (17)	-
AST elevation	4 (33)	3 (25)	2 (17)	2 (17)
ALT elevation	4 (33)	1 (8)	3 (25)	2 (17)
GGT elevation	2 (17)	1 (8)	-	-
Elevated phosphatase	2 (17)	-	-	-
Amylase elevation	-	-	4 (33)	-
Hypoglycemia	1 (8)	-	-	-
Hyperglycemia	1 (8)	-	-	-
Creatinine elevation	1 (8)	-	-	-
CPK elevation	4 (33)	3 (25)	-	1 (8)
Troponin T elevation	-	1 (8)	-	-
Anemia	5 (42)	-	-	-
Thrombocytopenia	3 (25)	2 (17)	4 (33)	3 (25)
Leukopenia	3 (25)	1 (8)	-	-
Neutropenia	1 (8)	-	-	-
Hemolysis	4 (33)	-	-	-
PTT prolongation	3 (25)	-	-	-
DIC	-	1 (8)	-	-
Proteinuria	4 (33)	1 (8)	1 (8)	-
Liver failure	-	1 (8)	-	-
Infection (herpes labialis)	2 (17)	1 (8)	-	-
Fatigue	2 (17)	7 (58)	-	-
Cough	2 (17)	-	-	-
Fever	4 (33)	-	-	-
Hypotension	-	1 (8)	-	-
Nausea	1 (8)	-	-	-
Burn	1 (8)	-	-	-
Diarrhea	2 (17)	4 (33)	-	-

Figure 1. Temperature Curves

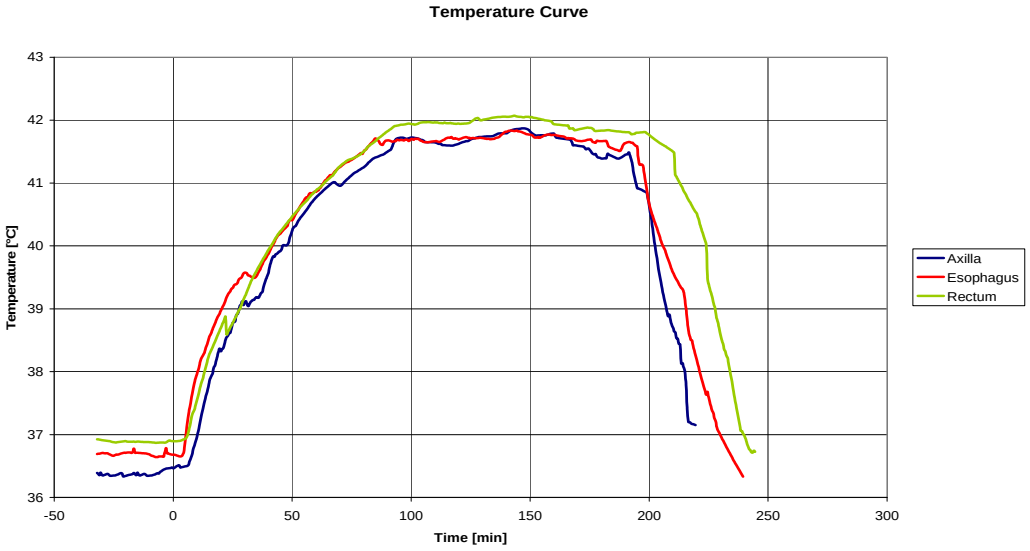


Figure 2. Platelet Count

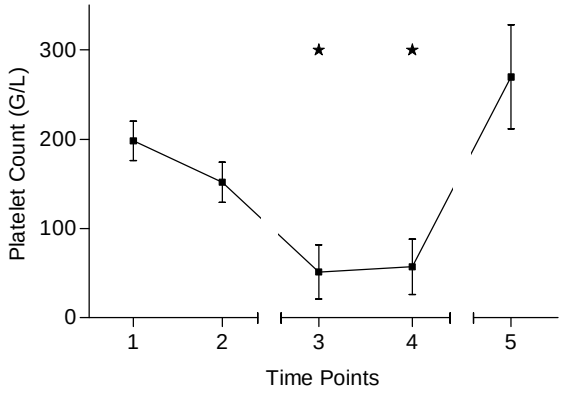


Figure 3. Hemodynamic changes

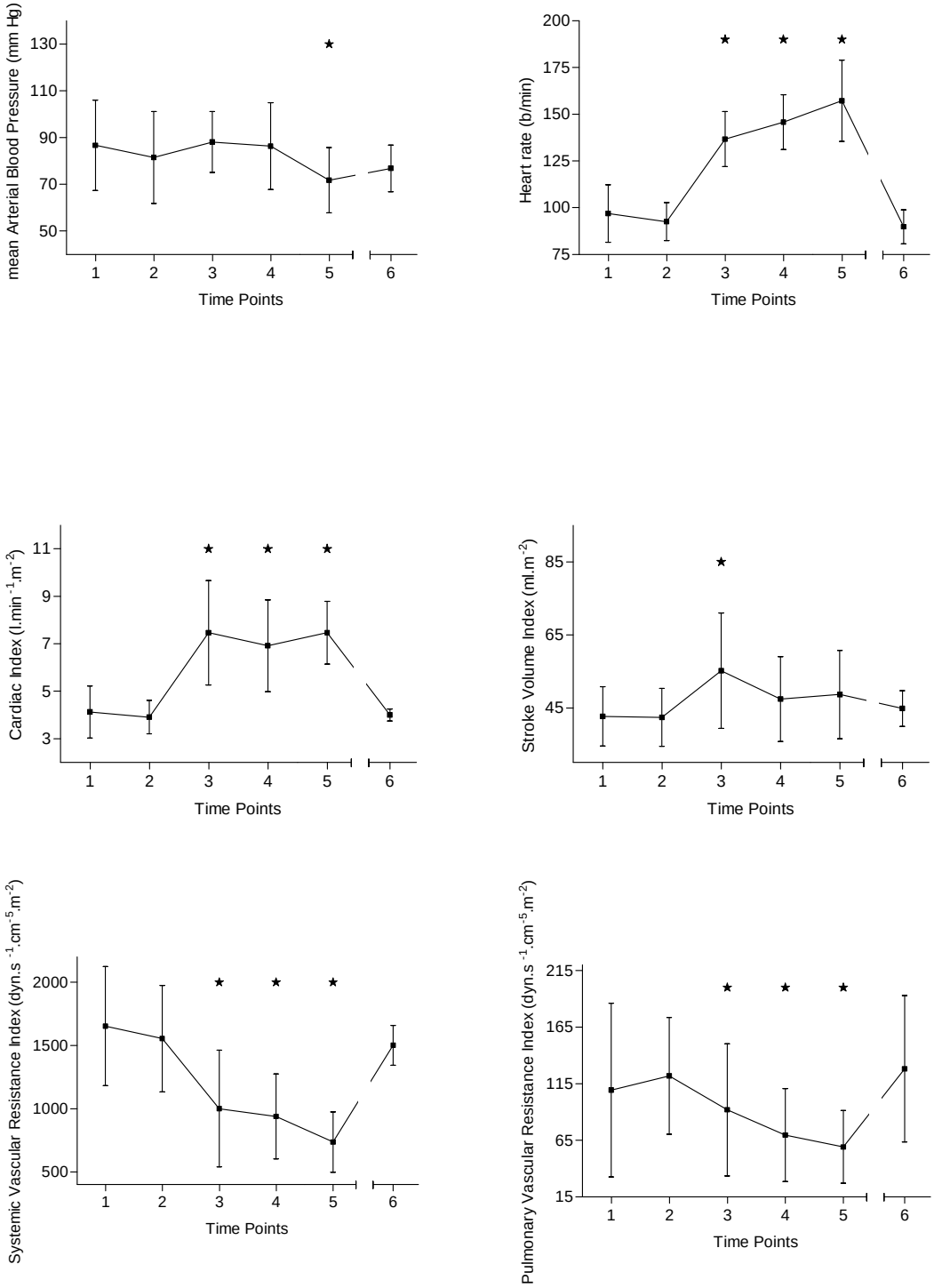


Figure 4. Oxygen Metabolism

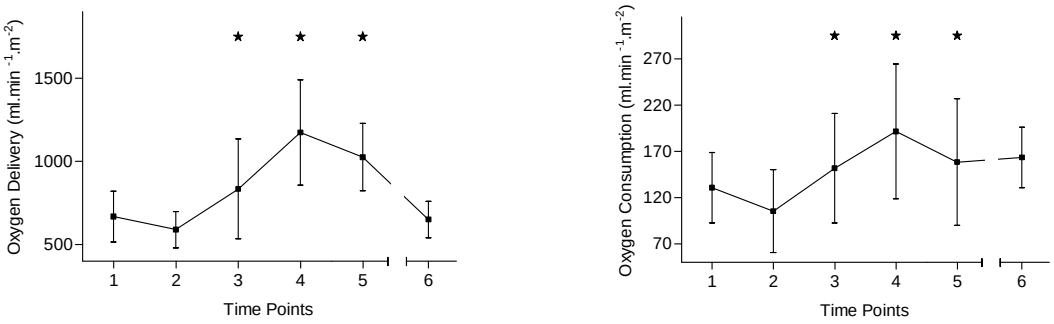
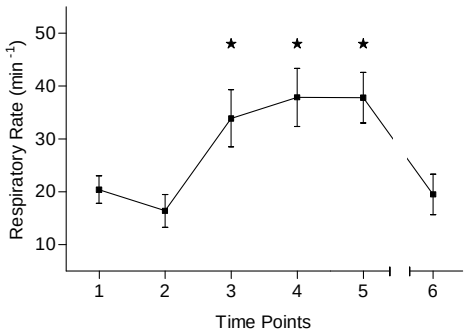
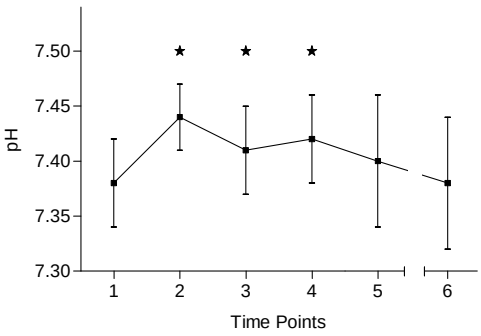
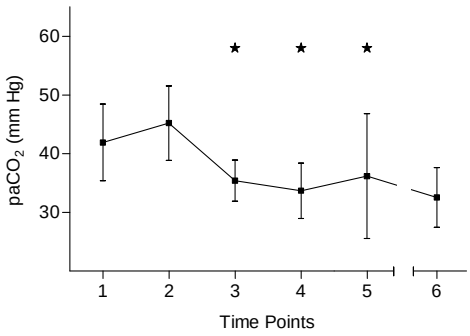
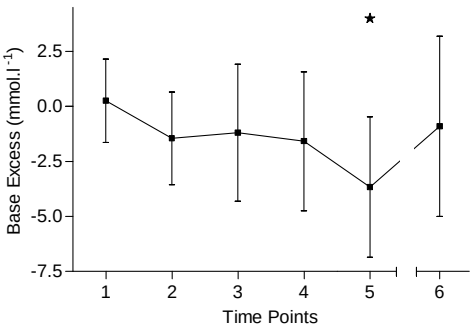


Figure 5. Acid-Base State









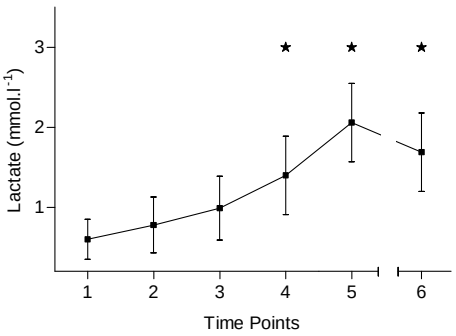


Figure Legends

Figure 1: Temperature distribution during ECC-WBHT measured in the axilla, the esophagus and the rectum. Data present mean values of all 12 WBHT cycles.

Figure 2: Platelet count before (1) and immediately after ECC-WBHT (2), 24 (3) and 48 hours (3) thereafter, and 7 days after ECC-WBHT. Data present mean values $\pm$ SD of all 12 WBHT cycles, asterisks denote $p < 0.05$ vs. (1).

Figure 3: Hemodynamic changes during ECC-WBHT, evaluated at baseline (1), at 30 minutes on normothermic ECC (2), at 40°C body core temperature (3), at 41.8°C (4), at the end of 2 hours plateau phase at 41.8°C (5), and 24 hours after ECC-WBHT (6), respectively. Data present mean values $\pm$ SD of all 12 WBHT cycles, asterisks denote $p < 0.05$ vs. (1).

Figure 4: Oxgen metabolism during ECC-WBHT, evaluated at baseline (1), at 30 minutes on normothermic ECC (2), at 40°C body core temperature (3), at 41.8°C (4), at the end of 2 hours plateau phase at 41.8°C (5), and 24 hours after ECC-WBHT (6), respectively. Data present mean values $\pm$ SD of all 12 WBHT cycles, asterisks denote $p < 0.05$ vs. (1).

Figure 5: Acid-base state during ECC-WBHT, evaluated at baseline (1), at 30 minutes on normothermic ECC (2), at 40°C body core temperature (3), at 41.8°C (4), at the end of 2 hours plateau phase at 41.8°C (5), and 24 hours after ECC-WBHT (6), respectively. Data present mean values $\pm$ SD of all 12 WBHT cycles, asterisks denote $p < 0.05$ vs. (1).