Objective: To investigate the effects of hepatic radiofrequency ablation (RFA) in patients with malignant liver disease with respect to inflammation activation and stress response.

Materials and Methods: In an observational trial, we investigated the physiologic parameters of 17 patients (20 interventions) who underwent percutaneous RFA under general anesthesia after applying total intravenous anesthesia. TNFα, IL-6, IL-8, IL-10, adrenaline and noradrenaline, liver enzymes, lactate and creatine kinase were determined pre-interventionally after induction of anesthesia (T1), 90 minutes after initiation of RFA (T2), immediately after the conclusion of the procedure (T3), and 24 hours after the procedure (T4).

Results: A significant increase in body temperature ($p < 0.001$), and mean arterial pressure ($p = 0.001$) were measured intraoperatively (T2) and the day after the procedure (T4). Increased levels of IL-6 were measured at T3 and T4 ($p = 0.001$). IL-10 increased immediately after the procedure (T3; $p = 0.007$). IL-6 levels correlated well with the total energy applied ($r = 0.837$). Significant increases in the levels of adrenaline and noradrenaline were present at T3 and T4 ($p < 0.001$). The RFA-induced destruction of hepatic tissue was associated with increased levels of AST, ALT, GLDH and LDH.

Conclusion: Percutaneous RFA of hepatic malignancies causes an inflammatory and endocrine activation, similar to the systemic inflammatory response syndrome. These effects have to be taken in account when dealing with patients susceptible to sepsis or multi-organ failure.

Over the last two decades an increasing number of minimally invasive, local ablative therapies have been established, challenging the role of surgical resection (1). Radiofrequency ablation (RFA) in particular, has increasingly been employed with promising results (2, 3). With the recent ablation techniques, all regions of the liver can effectively be treated by RFA (4, 5).

The excessive cytokine release from performing the cryoablation is known to result in systemic inflammatory or stress response include acute renal and liver failure, as well as acute respiratory distress syndrome (7, 8). When compared with cryoablation, hepatic RFA presents with a lower expression of tumor necrosis factor α (TNFα) and interleukin (IL)-1β (6).

However, from previous studies on intraoperative RFA, contradictory results on pro- and anti-inflammatory cytokines and systemic stress response have been reported (9, 10). There are only a few, unsystematic data regarding the inflammatory response after percutaneous RFA. These data suggest cytokines to play a role in post-ablation...
hypoxemia (11). Cytokines are also speculated to influence post-RFA coagulopathy and thrombopenia (12). The currently available data, however, is not sufficient to come up with robust recommendations for patient management and we feel that more data on this issue is needed.

Therefore, the purpose of this prospective study was to systematically investigate the effects of RFA on stress and inflammation in patients undergoing percutaneous treatment for hepatic tumors under general anesthesia with total intravenous anesthesia (TIVA).

MATERIALS AND METHODS

From August 1 to 31, 2007 all patients scheduled for percutaneous RFA for treatment of hepatic cancer or metastases were recruited for this explorative prospective cohort study. The investigative protocol was approved by the Institutional Review Board and informed consent was obtained from every patient before enrollment.

Demographics

Seventeen patients (M:F = 9:8; mean age, 61.5 ± 11.7; range, 38–78 years) treated by CT-guided RFA for non-resectable hepatocellular carcinoma (HCC; n = 4) and liver metastases from colorectal cancer (n = 7), breast cancer (n = 3), gastric cancer (n = 1), uterine cancer (n = 1), and leiomyosarcoma (n = 1) were included in this study. Patients suffered from a variable number of lesions of different sizes, with a total of 28 lesions treated in 20 treatment sessions. The general condition and anesthesia-related risks were classified according to the American Society of Anesthesiology (ASA) grading system (Table 1). All patients with metastatic disease had undergone resection of the primary tumor, and 14 patients had been pre-treated, either by chemotherapy (n = 6), combined surgical resection of liver metastases plus chemotherapy (n = 3), or surgical resection of liver metastases without chemotherapy (n = 5). None of the patients had undergone systemic chemotherapy within four weeks prior to the intervention.

Table 1. Summary of Patient Characteristics, Radiofrequency-System and Applied Energy

| Patient No. | Procedure | Sex | Age | Weight | ASA | Primary Tumor | Lesions | Size (cm) | Probe | Energy (kJ) |
|-------------|-----------|-----|-----|--------|-----|---------------|---------|-----------|-------|------------|
| 1           | 1         | F   | 75  | 80     | 2   | CR            | 1       | 2 × 2     | LeVeen | 226.2      |
| 2           | 2         | M   | 60  | 80     | 2   | CR            | 1       | 2 × 2.5   | LeVeen | 1281.6     |
| 3           | 3         | M   | 49  | 70     | 2   | CR            | 1       | 3.5 × 4   | LeVeen | 2202.2     |
| 4           | 4         | F   | 38  | 67     | 2   | B             | 3       | 3 × 3     | LeVeen | 1519.2     |
|             |           |     |     |        |     | 2.8 × 3       |         | 2.5 × 2   |       |            |
| 5           | 5         | M   | 78  | 65     | 2   | CR            | 1       | 2 × 1.8   | LeVeen | 1572.0     |
| 6           | 6         | M   | 60  | 78     | 2   | CR            | 2       | 3 × 2.5   | LeVeen | 744.6      |
|             |           |     |     |        |     | 2.3 × 2.7     |         | 3 × 2.8   | HiTT   | 1404.0     |
| 7           | 7         | F   | 45  | 47     | 1   | U             | 4       | 2.5 × 2   | HiTT   | 1919.0     |
|             |           |     |     |        |     | 2 × 2         |         | 2 × 1.6   |       |            |
|             |           |     |     |        |     | 1.2 × 1       |         |           |       |            |
| 8           | 9         | F   | 65  | 75     | 2   | B             | 1       | 3.8 × 4   | LeVeen | 1556.4     |
| 9           | 10        | F   | 61  | 62     | 2   | CR            | 1       | 1.6 × 1.6 | LeVeen | 511.2      |
| 10          | 11        | M   | 69  | 100    | 3   | HCC           | 1       | 3.2 × 3   | LeVeen | 760.8      |
| 11          | 12        | F   | 70  | 55     | 2   | CR            | 1       | 2 × 1.5   | LeVeen | 1368.0     |
| 12          | 13        | M   | 63  | 70     | 2   | CR            | 1       | 4 × 3.5   | LeVeen | 678.0      |
| 13          | 14        | M   | 54  | 60     | 3   | HCC           | 1       | 3.1 × 3   | LeVeen | –          |
| 14          | 15        | M   | 69  | 78     | 2   | HCC           | 1       | 2 × 2     | LeVeen | 1530.0     |
| 15          | 16        | M   | 49  | 81     | 3   | G             | 1       | 3.5 × 3.2 | LeVeen | –          |
| 16          | 17        | M   | 65  | 75     | 2   | B             | 1       | 3 × 2     | LeVeen | 537.6      |
| 17          | 18        | F   | 51  | 47     | 2   | B             | 2       | 2.5 × 2.3 | LeVeen | 1590.0     |
|             |           |     |     |        |     | 2 × 1.8       |         |           |       |            |
| 18          | 19        | M   | 77  | 64     | 2   | HCC           | 1       | 4.5 × 3.3 | LeVeen | 485.4      |
| 19          | 20        | M   | 69  | 97     | 2   | HCC           | 1       | 3 × 3     | LeVeen | 369.0      |

Note.— 1 = Patients 2, 8 and 10 were treated twice, ASA = American Society of Anesthesiology, B = breast, CR = colorectal, G = gastric, HCC = hepatocellular carcinoma, L = leiomyosarcoma, No. = number, U = uterus
Biochemical Analysis

Anesthesia Management

Study Protocol

After informed consent had been obtained, patients were enrolled 48 hours before the intervention. Inclusion criteria included less than five metastatic or three HCC lesions per lobe, a tumor size of less than 5 cm, and no extrahepatic tumor (13). Exclusion criteria were portal vein thrombosis and contraindications to percutaneous puncture, i.e. ascites, or coagulopathy with an international normalized ratio (INR) > 1.5 or a platelet count < 50,000 (10^9/L).

After enrollment, patient vital signs, body temperature, and blood samples were obtained. Four measurement time points (T1-T4) were defined as follows:

- **T1** = pre-interventionally after induction of anesthesia,
- **T2** = intra-interventionally, 90 min after initiation of RFA,
- **T3** = post-interventionally after finishing the procedure, and
- **T4** = post-interventionally the following day (22–24 h after initiation of RFA).

Hemodynamic measurements, body temperature (Infrared Ear-Thermometer, First Temp Genius®), Sherwood Medical, UK), and blood samples were obtained at all time points T1-T4. All blood samples were immediately cooled down to 4°C and centrifuged. The plasma fraction was separated, aliquoted, and stored at −70°C until analysed.

Biochemical Analysis

Plasma samples were assayed by ELISA (Immumite 1000®, DPC Biermann, Bad Nauheim, Germany) for TNFs, IL-6, IL-8, and IL-10. Serum samples for catecholamines (adrenaline, noradrenaline) were stored on ice and transferred to the laboratory for prompt high pressure liquid chromatography (HPLC) analysis (Alliance HPLC Systems, Waters Corporation, Milford, MA). Blood samples for liver enzymes, creatine kinase (CK) and lactate were taken at the same time.

Anesthesia Management

All procedures were performed under general anesthesia according to our hospital routine protocol, including oral premedication with 0.1 mg/kg midazolam (Midazolam ratiopharm, Ratiopharm, Ulm, Germany) and monitoring of ECG, invasive blood pressure, pulse oximetry, and capnometry. Pre-oxygenation anesthesia was induced by the injection of 0.1 mg/kg piratramide (Dipidolor®), Janssen-Cilag, Neuss, Germany), 1–2 mg/kg propofol (Propofol-ratiopharm, Ratiopharm) and 0.2 mg/kg cisatracurium (Nimbex®, GlaxoSmithKline Uxbridge, UK). The patient’s trachea was intubated and anesthesia was maintained intravenously with 5–10 mg/kg/h propofol (Propofol-ratiopharm, Ratiopharm) and 0.1–0.3 μg/kg/min remifentanil (Ultiva®, GlaxoSmithKline). Patients were mechanically ventilated (Servo 900C, Siemens Elema, Solna, SE), in the volume controlled mode, with a tidal volume of 8 ml/kg and a respiratory rate to target an end-tidal partial carbon dioxide pressure (EtCO₂) of 34–40 mmHg. For hemodynamic management, 2 ml/kg/h of Ringer’s solution were infused. A foley catheter was placed in the bladder (Rüsch Sensor Silicon®, Rüsch, Belp, CH) to measure body temperature and fluid balance. With removal of the RF probe, the infusions of propofol and remifentanil were discontinued. Upon emergence from anesthesia, the patient was extubated and brought to the post-anesthetic care unit until full recovery.

Radiofrequency Ablation Procedure

First, a standardized non-contrast CT (SOMATOM Volume Zoom, Siemens, Forchheim, Germany) of the liver was performed to visualize the lesion (4 × 2.5 mm, 120 kV, 150 mAs/eff). Next, the RF-probe was placed under CT-guidance using 3 mm sequential images.

Two different generators, RF-3000 (Boston Scientific, Natick, MA) and Elektrotom HiTT 106® (Integra, Plainboro, NJ) were used (Table 1). The probes used were either mechanically expandable (LeVeen, Boston Scientific, Natick, MA) or employed saline infusion (HiTT needle electrode, Integra, Plainboro, NJ). The probe size was individually adapted to the size of the lesion. Ablation was performed according to the protocols recommended by the vendors at two positions using the so called pull-back technique (12, 14). At the end of the procedure, the

| Table 2. Summary of Clinical Parameters |
|-----------------|-----------------|-----------------|-----------------|
|                | T1              | T2              | T3              | T4              |
| Heart rate (bpm) | 68.2 ± 14.8     | 69.6 ± 17.1     | 71.6 ± 13.6     | 84.3 ± 18.6^AC |
| MAP (mmHg)      | 77.9 ± 13.7     | 91.9 ± 14.4^a   | 96.2 ± 13.3^a   | 96.1 ± 14.8^a   |
| Temperature (°C) | 36.4 ± 0.5      | 37.8 ± 0.9^bc   | 36.2 ± 0.63     | 37.3 ± 0.9^bc   |

Note: — ^a = significant difference in comparison to, T1, ^b = significant difference in comparison to, T2, ^c = significant difference in comparison to, T3, MAP = mean arterial pressure
Changes in heart rate, mean arterial pressure, and temperature prior to ablation (T1), 90 minutes after Initiation of ablation procedure (T2), immediately after conclusion of procedure (T3), and 24 hours after procedure (T4)
probe was slowly withdrawn while tract ablation was performed. In the RF-3000 system, the applied energy was estimated as the product of time (s) and power (W), while it was displayed on the HiTT106® system.

Statistics

Data are presented as the mean and standard deviation. A repeated measures ANOVA was performed to test for differences. In case of significant results, a post hoc analysis was performed using Scheffe’s procedure. A Pearson’s correlation was used to determine a statistical relationship. Statistical significance was forest a $p < 0.05$. All statistical operations were performed using SPSS for Windows 17.0 (SPSS Inc, Chicago, IL).

RESULTS

Stable TIVA was achieved in all patients and RFA was successfully completed. Total procedure time and duration of energy deposition were $152 \pm 22$ (113–186) minutes and $101 \pm 7$ (92–112) minutes, respectively. There were two major and one minor complication. In one patient, a puncture-related hepatic artery bleeding was successfully treated by transarterial coil embolization. Another patient with previously known severe hepato-pulmonary syndrome developed an intra-hepatic abscess and died despite adequate percutaneous drainage 33 days after the procedure from septic multi-organ failure. In one patient, a fully reversible paresis of the right arm occurred, which was due to the positioning of the arm above the head. In two patients treated with the RF-3000 system, there was no data for computing the amount of applied energy. These patients were excluded from the correlation analysis. The mean energy applied in the remaining patients was $1125.3 \pm 587.2$ kJ.

Clinical Parameters

There were no significant changes in heart rate during the interventions, but heart rate was significantly increased on the first post-interventional day ($p = 0.038$). Mean arterial blood pressure was significantly lower after induction of anesthesia at T1, when compared to all other points ($p < 0.001$). Body temperature increased significantly during the procedure, but was normal again in the post-anesthetic care unit. Temperature was again slightly elevated on the first post-interventional day ($p < 0.001$) (Table 2).
Cytokine Levels

No significant changes could be detected for TNFα and IL-8 levels. IL-6 increased during (T2; \( p > 0.05 \)) and after (T1 vs. T3; \( p = 0.003 \)) the intervention and remained high at the next day (T1 vs. T4; \( p = 0.001 \)). IL-10 increased significantly between T1-T3 (\( p = 0.007 \)) and T2-T3 (\( p = 0.014 \)), and started to decrease the following day (T4), but remained above the pre-interventional level (\( p = 0.019 \)) (Fig. 1, Table 3). Post-interventional IL-6 levels strongly correlated with the applied energy (\( r = 0.837 \), \( p = 0.01 \)). There was also a weak correlation between the plasma levels of adrenaline and the anti-inflammatory cytokine IL-10 after the intervention (\( r = 0.583 \), \( p = 0.022 \)).

Catecholamine Levels

Post-interventional adrenaline levels were significantly elevated in the recovery room (T1 vs. T3; \( p < 0.001 \)), but decreased to pre-interventional levels on the next day. In contrast, noradrenaline was elevated on the first post-interventional day only (\( p < 0.001 \)) (Fig. 2, Table 3).

Serum Chemistry

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels increased during the procedure (\( p = 0.021 \)), and continued to further increase the next day (\( p < 0.001 \)). Lactate dehydrogenase (LDH) increase was delayed to the first post-interventional day (\( p < 0.001 \)). No significant changes could be demonstrated for alkaline phosphatase (AP), pseudocholinesterase (PCHE), and glutamate dehydrogenase (GLDH) levels. There was an increase in CK, starting directly after the procedure (T1 vs. T4; \( p = 0.001 \)). Lactate was slightly, but significantly greater the day after the procedure (T4; \( p = 0.007 \)) (Table 4).

DISCUSSION

This study demonstrated a persistent increase in pro-inflammatory (IL-6) and a transient increase in anti-inflammatory cytokines (IL-10), with the increase in IL-6 being correlated with the amount of applied energy. This indicates a concomitant inflammatory response beyond

**Table 3. Cytokine and Catecholamine Levels at Different Points of Measurement**

| Parameter                  | Point of Measurement |
|----------------------------|----------------------|
|                            | T1               | T2               | T3               | T4               |
| TNFα (< 8.1 ng/L)          | 1.4 ± 4.3        | 1.3 ± 3.7        | 3.9 ± 6.7        | 2.3 ± 5.4        |
| IL 6 (< 10 ng/L)           | 2.8 ± 7.7        | 4.9 ± 9.6        | 21.8 ± 17.6      | 26.2 ± 31.7      |
| IL 8 (< 63 ng/L)           | 14.9 ± 14.3      | 28.8 ± 38.8      | 44.7 ± 48        | 21.9 ± 29.6      |
| IL 10 (< 10 ng/L)          | 0.8 ± 2.0        | 3.3 ± 7.2        | 41.3 ± 61.8      | 5.1 ± 6.6        |
| Adrenaline (165–468 pmol/L)| 210.5 ± 203.5    | 145.2 ± 115.7    | 741.3 ± 648.5    | 277.3 ± 270.9    |
| Noradrenaline (1.09–1.63 pmol/L) | 1.2 ± 0.9       | 1.1 ± 0.8        | 1.9 ± 1.1        | 2.6 ± 1.4        |

Note.—\(^\alpha\) = significant difference in comparison to T1, \(^\beta\) = significant difference in comparison to T2, \(^\gamma\) = significant difference in comparison to T4, TNF = tumor necrosis factor, IL = interleukin
Reference values are given in rectangular brackets. Significant differences in repeated measures ANOVA are indicated.

**Table 4. Serum Chemistry Levels at Different Points of Measurement**

| Parameter     | Point of Measurement |
|---------------|----------------------|
|               | T1               | T2               | T3               | T4               |
| AST (5–17 U/L)| 14.6 ± 10         | 78.8 ± 55.5      | 162.8 ± 131.5\(^\alpha\) | 293.6 ± 259.6\(^\alpha\) |
| ALT (5–23 U/L)| 14.9 ± 9.7        | 44.4 ± 44        | 83.9 ± 63.8      | 247.8 ± 234.8\(^\alpha\) |
| GLDH (0.1–4.0 U/L)| 4.9 ± 10.4      | 11.2 ± 17        | 30.2 ± 60.4      | 152 ± 333.1\(^\alpha\) |
| LDH (120–240 U/L)| 168.8 ± 31.7    | 259.2 ± 99.2     | 358.4 ± 160.2    | 545.5 ± 522.2\(^\alpha\) |
| PCHE (2000–7400 U/L)| 4506.1 ± 1214.6 | 4061.4 ± 1393    | 4298 ± 1092.4    | 4281.6 ± 1321 |
| AP (40–190 U/L) | 152 ± 105        | 144 ± 102.8      | 160 ± 104.6      | 180.4 ± 116.6   |
| CK (10–80 U/L)  | 30.7 ± 20.8       | 44.2 ± 38.6      | 109.9 ± 111.3    | 218.1 ± 230.7\(^\alpha\) |
| Lactate (1.1–1.8 mmol/L) | 1.03 ± 0.36     | 1.04 ± 0.32      | 1.34 ± 0.58      | 1.56 ± 0.55\(^\gamma\) |

Note.—\(^\alpha\) = significant difference in comparison to T1, \(^\beta\) = significant difference in comparison to T2, \(^\gamma\) = significant difference in comparison to T3, ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase, CK = creatine kinase, GLDH = glutamate dehydrogenase, LDH = lactate dehydrogenase, PCHE = pseudocholinesterase
Reference values are given in rectangular brackets. Significant differences in repeated measures ANOVA are indicated.
mechanistic heating (9, 10, 15). A cryoablation associated systemic inflammatory response syndrome (SIRS), with high mortality (35%) (6, 9, 15), which was characterized by multi-organ failure and coagulopathy, could not be detected in any of these RFA patients, and has not yet been reported after RFA. Therefore, the inflammatory and stress response measured in this cohort of patients undergoing percutaneous RFA of hepatic tumors has to be interpreted in the context of procedural, anesthetic and general considerations.

Extent and time course of the increase in liver enzymes and LDH are in agreement with previously published data, reflecting the response to the liver injury caused by ablation (16). Consistent with previous studies, we observed a significant increase in body temperature during and after percutaneous ‘hepatic RFA’ (17). However, a clear correlation between applied energy and increase in body temperature could not be established in this small patient population. The hypothesis of local hepatic hyperthermia, leading to systemic heating via intra-hepatic blood flow, comparable to a ‘heat exchanger’ (17), is supported by the transient normalization of body temperature measured immediately after the procedure. However, differences in tumor location and vascularization make it impossible to predict the systemic warming effect from the total amount of applied energy. Of note, no cooling techniques were used in this study.

The liver is a significant source of cytokines, which are produced in Kupffer cells (18–20). The release of cytokines may be depending on several conditions including the ablation technique and type of anesthesia. In a rat model, Chapman et al. (21) described a significantly higher increase in TNFa at 24 hrs after performing hepatic cryoablation when compared to RFA-treated animals. Jansen et al. (22) demonstrated that systemic inflammation induced by RFA or open partial liver resection are of the same moderate magnitude and not as exaggerated as frequently observed after cryoablation. The moderate inflammatory reaction observed in this study supports the findings of Schell et al. (10), indicating that the course of systemic inflammation after percutaneous RFA is typically moderate. These differences may be explained by differences in the mechanism of cell destruction. Cryoablation induces a rupture of the plasma membrane, resulting in a dispersion of intact cellular structures into the space of Disse and leading to a systemic spreading. RFA, in contrast, induces the coagulative destruction of intra cytoplasmatic structures and does not touch cellular surface integrity. Moreover, RFA results in local vessel occlusion, limiting the local and systemic spread of proinflammatory cytokines.

Interestingly, cytokine release is known to be influenced by the type of anesthesia and the ventilatory regimen. There is a significant correlation between balanced inhalational anesthesia and the increase of pro-inflammatory IL-6. The increase of IL-6 with TIVA has been reported to be markedly less when compared with the results observed in this study (23, 24). Therefore, the pro-inflammatory effect in this study effect is likely due to RFA. TIVA is also known to induce a significant increase of anti-inflammatory cytokines (25). The use of propofol and remifentanil in this study might have caused an anti-inflammatory effect, although both IL-6 and IL-10 activation were present.

The notable stress response is likely to have been attenuated by anesthesia. In previous investigations, maximum levels of stress hormones have been measured not during the surgical procedure, but immediately after termination of general anesthesia. This was attributed to the onset of postoperative pain, centralization, and shivering (26–29). These factors also need to be considered in RFA. One purpose of anesthesia is the modification of stress response to avoid surplus endocrine reactions and to preserve the compensatory mechanisms (26, 30). The mode of anesthesia is relevant, as endocrine stress response varies in different anesthetic regimens. It was found to be less attenuated with TIVA, compared with inhalation anesthesia (31). In this study, catecholamine levels were normal during the procedure, but increased post-interventionally, indicating that the stress response has been sufficiently suppressed during the procedure. Interestingly, the time courses of adrenaline and noradrenaline were different, peaking at different times. It has been speculated that propofol attenuates noradrenaline release (32, 33). This might have affected the suppression of noradrenaline production in the early post-interventional period, but not the first post-interventional day.

The study suffers several limitations. First, only a small number of patients with a broad variety of hepatic neoplasms were included in this explorative study. Nevertheless, there were relevant effects on inflammatory and stress response. Second, all procedures were performed under general anesthesia and there is no data on conscious sedation. Considering the effects on inflammatory and stress reaction, it has to be recognized that general anesthesia per se is not known to induce inflammation, and stress reaction is lowest with TIVA. Thus, the observed effects have to be considered to be due to the ablation procedure. However, we can only speculate if the results would be different in patients treated under conscious sedation. Finally, the energy applied with the RF-3000 system could only be estimated with incomplete
data on energy deposition in two procedures.

In conclusion, RFA of hepatic malignancies causes inflammatory and endocrine activation, similar to SIRS. In choosing the best management strategy, one has to consider that the extent of this response is extremely variable and is modulated by additional factors such as the type of anesthesia. As percutaneous RFA is often employed in fragile patients, these systemic reactions have to be taken into account when dealing with patients susceptible to sepsis or multi-organ failure.

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