British Journal of Anaesthesia **113** (6): 985–92 (2014)
Advance Access publication 30 August 2014 · doi:10.1093/bja/aeu256

BJA

Anaesthetic management during open and percutaneous irreversible electroporation

K. Nielsen[1†], H. J. Scheffer[2†], J. M. Vieveen[3], A. A. J. M. van Tilborg[2], S. Meijer[1], C. van Kuijk[2], M. P. van den Tol[1], M. R. Meijerink[2] and R. A. Bouwman[3,4*]

[1] Department of Surgery, [2] Department of Radiology and [3] Department of Anesthesiology, VU University Medical Center, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands
[4] Department of Anaesthesiology, Catharina Hospital, Michelangelolaan 2, 5623 EJ Eindhoven

* Corresponding author. E-mail: ra.bouwman@gmail.com

Editor's key points

- Irreversible electrocorporation is a novel tumour ablation technique involving repeated application of electrical energy.
- The electrical pulses have the potential to cause seizures, arrhythmias, and muscle contractions.
- The authors report the incidence of complications among 28 patients undergoing the technique.
- They found no major complications and a low incidence of minor complications.

Background. Irreversible electroporation (IRE) is a novel tumour ablation technique involving repetitive application of electrical energy around a tumour. The use of pulsed electrical gradients carries a risk of cardiac arrhythmias, severe muscle contractions, and seizures. We aimed to identify IRE-related risks and the appropriate precautions for anaesthetic management.

Methods. All patients who were treated with IRE were prospectively included. Exclusion criteria were arrhythmias, congestive heart failure, active coronary artery disease, and epilepsy. All procedures were performed under general anaesthesia with complete muscle relaxation during ECG-synchronized pulsing. Adverse events, cardiovascular effects, blood samples, cerebral activity, and post-procedural pain were analysed.

Results. Twenty-eight patients underwent 30 IRE sessions for tumours in the liver, pancreas, kidney, and lesser pelvis. No major adverse events occurred during IRE. Median systolic and diastolic blood pressure increased by 44 mm Hg (range −7 to 108 mm Hg) and 19 mm Hg (range 1–50 mm Hg), respectively. Two transient minor cardiac arrhythmias without haemodynamic consequences were observed. Muscle contractions were mild and IRE caused no reactive brain activity on a simplified EEG. Pain in the first 24 h after percutaneous IRE was generally mild, but higher pain scores were reported after pancreatic treatment (mean VAS score 3; range 0–9).

Conclusions. Side-effects during IRE on tumours in the liver, pancreas, kidney, and lesser pelvis seem mild and manageable when current recommendations for anaesthesia management, including deep muscle relaxation and ECG synchronized pulsing, are followed. Electrical pulses do not seem to cause reactive cerebral activity and evidence for pre-existing atrial fibrillation as an absolute contra-indication for IRE is questionable.

Keywords: ablation techniques; anaesthesia, general; EEG, electroencephalography; electroporation, methods; liver neoplasms, surgery; pancreatic neoplasms, surgery

Accepted for publication: 13 May 2014

Irreversible electroporation (IRE) is a novel tumour ablation technique based on the local application of an electrical field between two or more electrodes inserted around a tumour. Multiple cycles of short, extremely high-voltage electrical pulses alter the transmembrane potential of tumour cells, leading to the creation of nanoscale defects in the lipid bilayer of the cell membrane, increasing membrane permeability. With the appropriate electrical parameters (90 pulses of 70 μs; electric field strength 1500 V cm^{-1}; delivered current 20–50 A), the membrane permeability becomes permanent and the cell eventually dies because of loss of homeostasis.[1 2] Because cell death in IRE is based on electrical energy rather than thermal energy, the technique has two advantages over thermal ablation techniques like radiofrequency ablation (RFA). First, whilst IRE effectively destroys all cells within the ablation area, the extracellular matrix is preserved. As a consequence, vascular, biliary, and nervous structures rich in extracellular collagenous and elastic structures remain intact.[3 4] Secondly, IRE is unaffected by the so-called heat-sink effect, in which incomplete tumour ablation may occur near large vessels as a result of loss of heat via blood flow.[5] Therefore, IRE may represent an effective alternative

† K.N. and H.J.S. contributed equally.

for tumours that cannot be resected or thermally ablated because of unfavourable location. In light of the promising results of the first trials investigating the safety and efficacy of IRE in different organs, we anticipate that the therapeutic use of IRE will expand rapidly in the near future.[6–9]

For the anaesthesiologist, the pulsatile application of electrical pulses with a very high voltage presents specific challenges, including the possible triggering of cardiac arrhythmias caused by increased cell membrane permeability of electroporated tissue, which opens a path for ion transport.[10] Also, severe muscle contractions and epileptic seizures could occur because of stimulation of muscular or nervous tissue.[11] Therefore, specific precautions in intraprocedural management are required in order to safely perform IRE. For example, as complete muscle paralysis is necessary to prevent muscle contractions, all IRE procedures require general anaesthesia and the use of neuromuscular blocking agents. Furthermore, to prevent arrhythmias, the electrical pulses must be administered synchronously to the heart rhythm, because external electrical stimuli delivered during the absolute refractory period of the heart are incapable of inducing an action potential.[10]

Current literature on anaesthetic management for IRE procedures is limited to a single publication by Ball and colleagues, who reported their initial experience in 21 patients treated with CT-guided percutaneous IRE for hepatic, renal, and pulmonary tumours and formulated guidelines for this procedure.[11] In our study, we aimed to broaden the experience of open and percutaneous IRE to an additional patient population with different tumour types and to confirm previous formulated guidelines for anaesthetic management. To this end, we specifically focused on IRE-related side-effects and the appropriate precautions with respect to anaesthetic management of open and percutaneous procedures in different organs.

Methods

This study was conducted with the approval of the Medical Ethics Committee of the VU University Medical Center. The study was designed and conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Patients

All patients treated with open or percutaneous IRE between August 2012 and September 2013 were prospectively included in a database and analysed. This included patients participating in the COLDFIRE-I trial, in which patients who were already undergoing surgical resection of colorectal liver metastases (CRLM) were treated with IRE during surgery 60 min before resection (Clincaltrials.gov registration number: NCT01799044). All other patients underwent IRE in the liver, pancreas, kidney, or lesser pelvis on clinical indication, because of proximity of the tumour to vital structures precluding surgical resection or thermal ablation. A designated multidisciplinary board determined local treatment. All patients had a histologically proven malignancy and underwent appropriate pre-procedural imaging. Inclusion criteria were ASA classification III or more and adequate bone marrow, hepatic, and renal function. Exclusion criteria were cardiac arrhythmias requiring anti-arrhythmic therapy or pacemaker/implantable cardioverter-defibrillator, a history of congestive heart failure (NYHA class higher than II), active coronary artery disease, uncontrolled hypertension, and epilepsy.

Anaesthetic management

Preoperative screening was performed with specific emphasis on contra-indications for IRE. Patients undergoing laparotomy received a thoracic epidural before surgery. The anaesthesia technique used was standardized to avoid bias. Based on personal preferences and also a practical issue (not all anaesthesia machines in the radiology department of our institution are equipped with proper scavening systems that allow the use of volatile anesthetics), total i.v. anaesthesia was induced with propofol (2 mg kg^{-1}), sufentanil (0.3 $\mu g\ kg^{-1}$), and rocuronium (0.6 mg kg^{-1}) and maintained with propofol and remifentanil.

The Accusync ECG-gating device (model 72; Milford, Connecticut) was connected to a 5-lead ECG to allow IRE pulses to be synchronized with the refractory period of the heart to avoid arrhythmias. Two defibrillation pads were placed and connected to a defibrillator as a precautionary measure. Immediately before IRE, complete muscle relaxation was confirmed by a train-of-four (TOF)-ratio of 0, using a peripheral nerve stimulator (TOF-Watch®, MIPM, Mammendorfer, Germany) to assess neuromuscular transmission. When necessary, an additional dose of rocuronium was administered.

After laparotomy, the epidural stayed *in situ* for at least 3 days. Pain control after percutaneous procedures was managed with acetaminophen combined with an NSAID (diclofenac) and an opioid (piritramide) if needed.

Safety analysis

All adverse events were graded according to the Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0). Cardiac rhythm, blood pressure, and saturation were continuously monitored. ECGs were monitored continuously until discharge from the recovery ward, and another 12-lead ECG was made 1 day post-IRE. Blood samples were evaluated with a special emphasis on serum electrolytes, renal function, and hepatic or pancreatic enzymes that could identify biochemical disturbances possibly caused by cellular destruction. These samples were drawn within 7 days before IRE, within 5 min after IRE and at least 1 day after the procedure. To monitor brain activity and the effect of pulses on the cerebrum before and during IRE, a simplified electroencephalogram (EEG) was made in six patients using the Thymatron System IV (Schwind Benelux Medical Electronics BV, Oosterbeek, The Netherlands). Post-procedural pain was scored three times a day during hospital admission, using the visual analogue scale (VAS).

Intervention

All procedures were performed by a board-certified interventional radiologist trained in IRE. Before IRE, the size and shape of the target lesion, including a 1 cm tumour-free