

## Electrochemotherapy and heart function: Treatment in a patient with implantable cardioverter defibrillator/pace-maker

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der general anesthesia and particular attention we put on the interference with the functioning of the heart. The synchronization algorithm currently implemented in Clinoporator Vitae device coupled with the external triggering device AccuSync proved to be effective in preventing external stimulation of the heart during the so-called vulnerable period of the ventricles. As a result all electroporation pulses in our study were delivered outside the vulnerable period and no heart arrhythmias or any other pathological morphological changes were observed. The safety of treatment was demonstrated also by absence of side effects during and after ECT.

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**Key words:** General anesthesia; Electrochemotherapy; Pace-maker; Implantable cardioverter defibrillator; Tumor ablation; Metastatic skin cancer

### Abstract

Electrochemotherapy (ECT) is a recently described therapy that relies on the permeation of cancer cell membranes by electrical pulses to enhance cytotoxic drug penetration. It has been successfully used in the treatment of primary and metastatic skin cancer. Systemic chemotherapy is the most commonly used therapeutic strategy, and the prevailing orientation calls for the administration of the maximum tolerated dose; however, considerable limitations exist including toxicities to healthy tissues and low achievable drug concentrations at tumor sites. We reported a case of an 83-years-old patient with a laterocervical metastasis of a squamous epidermoidal lip cancer. The patient had a complex medical history and an implantable cardioverter defibrillator (ICD)/pace-maker. The lesion was localized in the supraclavicular right side with a distance from the pace-maker/ICD about 5 cm, but the nodule was not deeply located. The ECT was performed un-

**Core tip:** We reported a case of treatment with electrochemotherapy (ECT) for a metastatic skin cancer in a patient with a complex cardiological history. The safety of the treatment was demonstrated by absence of side effects during and after ECT.

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### INTRODUCTION

Electrochemotherapy (ECT) is a therapeutic technique that relies on high-intensity electrical currents to reversibly increase cell membrane permeability (electroporation)

and to enhance the penetration of cytotoxic drugs into neoplastic cells<sup>[1]</sup>.

Bleomycin sulphate has been successfully used in combination with ECT in primary skin cancer, in the treatment of metastases of melanoma and squamous cell carcinoma, such as in Kaposi's sarcoma<sup>[2]</sup>. ECT is reported as an efficient and safe method, it causes only minor side effects in the patients such as transient lesions in areas in direct contact with the electrodes and acute localized pain due to contraction of muscles next to the electrodes. When tumor nodule is too large or is in the neck the ECT is painful and needs general anesthesia.

Mali *et al*<sup>[3]</sup> studied the effects of ECT of tumors located close to the heart and they examined the influence of electroporation pulses on functioning of the heart of human patient by analyzing the electrocardiogram. They found no arrhythmias or other pathological morphological changes during the application of electrical pulses and the only demonstrated effect was a transient R-R interval decrease.

Mir *et al*<sup>[4]</sup> defined the standard operating procedures in order to safely and conveniently treat by ECT patients with cutaneous and subcutaneous nodules. In the section "patient selection" the authors covered the criteria that must be checked during the pre-inclusion visit for the treatment by ECT and the presence of a pace-maker was considered a precluding element for a treatment on the anterior chest wall.

Here we present a case of 83-years-old male patient with laterocervical metastasis of a squamous epidermoidal lip cancer, with an implantable cardioverter defibrillator (ICD)/pace-maker undergoing to ECT.

## CASE REPORT

A 83-years-old male (body weight: 71 kg; height: 168 cm) was admitted to our Ear Nose Throat Surgical Unit for the ECT treatment of a laterocervical metastasis, a massive lesion, measuring 43 mm in diameter, aching, extended into the submandibular gland region, masseter and platysma muscle. In 2010, the patient was operated for a squamous epidermoidal lip cancer removal in the same University Hospital. His medical history was significant for a post-ischemic dilatative cardiomyopathy, permanent atrial fibrillation, chronic renal failure and chronic obstructive pulmonary disease. Past surgical history included: inguinal hernia repair in 1956, myocardial revascularization and left ventricular aneurysmectomy in 1985, biventricular pace-maker/ICD implant in 2009 (St. Jude Medical). In addition to oral anticoagulant therapy, the usual treatment was: digoxin 0.125 mg 1 cp/die, carvedilol 25 mg 1 cp × 2, perindopril arginine 10 mg 1 cp/die, candesartan cilexetil 8 mg 1 cp/die, furosemide 25 mg 1 cp × 3, metolazone 10 mg 1 cp/die, ezetimibe/simvastatin 10/40 mg 1 cp/die, pantoprazol 40 mg 1 cp/die, sertraline 50 mg 1 cp/die. Preoperative evaluation of the patient revealed a good blood pressure control, mild

dyspnoea, permanent atrial fibrillation. A trans thoracic echocardiography showed global hypokinesia with a dilated left ventricle, aortic-mitral and tricuspidal regurgitation, pulmonary arterial pressure of 50 mmHg and left ventricular ejection fraction 35%. Chest X-ray revealed cardiomegaly, ventilatory stripes and micronodular opacities with calcifications. A subsequent abdomen computed tomography scan was positive for abdomen harvest fluid. Laboratory data showed: haemoglobin 9.1 g/dL, hematocrit 30.1%, red-blood-cells  $3.35 \times 10^6/\mu\text{L}$ , creatinine 1.6 mg/dL, glycaemia 115.3 mg/dL, urea 111.5 mg/dL, prothrombin time 54%, partial thromboplastin time 38.9 s, international normalized ratio 1.44. Other haematological parameters were within the normal range.

The procedure was performed under general anesthesia. The patient was considered in class III of American Society of Anesthesiologists physical status classification<sup>[5]</sup> and showed predictive elements of a difficult airway (Mallampati score III, a reduced extent of the mouth opening and a reduced motility of the neck with a flexion-extension angle  $< 90^\circ$ ). After the positioning of a large-diameter *iv* cannula, the patient was monitored (SpO<sub>2</sub>, EKG, non-invasive blood pressure) and a magnet was placed on the ICD (it was located near the neoplastic mass  $< 10$  cm). Two pads were applied and connected to an external cardioverter/defibrillator unit. We started the infusion of remifentanyl 0.05-0.10  $\mu\text{g}/(\text{kg} \cdot \text{min})$  (Ultiva 5 *iv* 5 mg, GlaxoSmithKline S.p.A., Verona, Italy) and propofol (Propofol Ibi 1% 10 mg/mL, Istituto Biochimico Italiano, Milan, Italy), 2-3 mg/( $\text{kg} \cdot \text{h}$ ) giving supplemental oxygen through a nasal cannula at the rate of 4 L/min. After 5 min and adequate atomization of topical 4% lidocaine (Ecocain 10 g/100 mL spy, Molteni Dental, Florence, Italy), we performed an awake fiberoptic tracheal intubation. After the intubation, the induction of anesthesia was obtained with propofol (Propofol Ibi 2% 20 mg/mL, Istituto Biochimico Italiano, Milan, Italy) 1.5 mg/kg and cis-atracurium 0.1 mg/kg (Nimbex 2, GlaxoSmithKline S.p.A., Verona, Italy). Desflurane 5%-6% (Suprane, Baxter S.p.A, Rome, Italy) in a mixture of oxygen/air (60%/40%) and remifentanyl 0.1-0.2  $\mu\text{g}/(\text{kg} \cdot \text{min})$  was used for the maintenance of anesthesia and a large oropharyngeal cannula was inserted in the mouth to prevent tongue lesions during the electric pulses delivering. Five minutes after the induction, a needle electrode (type III, six needles forming a hexagon and one needle at its center with an 8 mm gap between them) was inserted into the metastatic nodule and connected to the electrical pulse generator (Cliniporator Vitae, Igea, Modena, Italy) which generates square-wave electric pulse of variable amplitude with 1-5000 Hz delivery frequencies. In the same time, another operator administered *iv* bleomycin sulphate (TEVA API, LGM Pharma, Sicor S.r.l. Milan, Italy) at a concentration of 1000 UI, 0.25 mL (250 UI)/ $\text{cm}^3$  slowly and, 8 min after, a run of 4 square-wave electrical pulses (1000 V amplitude, 5000 Hz, 100 microseconds per pulse) was delivered. The procedure

was repeated three times and the duration of ECT was approximately of 40 min. Throughout the treatment all parameters resulted stable and we didn't observed complications. At the end of ECT treatment we stopped the infusion of remifentanyl and the administration of desflurane, the patient returned rapidly to a spontaneous breathing and the endotracheal tube was removed after 5 min. The patient was transferred to the post-anesthesia care unit and was monitored for 24 h. The patient was discharged from the hospital after the revision of the pacemaker/ICD.

## DISCUSSION

Recently the ECT was considered as part of strategies for the control of cancer. This technique has been demonstrated to be an effective and well-tolerated therapy for cutaneous and subcutaneous lesions of different histological types with response rate of 80% and long lasting complete responses of 70%<sup>[6,7]</sup>. The present case report illustrates the difficulty in the management for cancer control in a patient with several organ dysfunctions. Surgery, radiotherapy and chemotherapy are invasive therapeutic approaches and are associated with significant adverse effects and they was not suitable for our patient.

The pace-maker/ICD constituted another limit for ECT. The American Society of Anesthesiologist published an updated task force Practice Advisory in conjunction with the Heart Rhythm Society in 2011 that provides expert recommendations for perioperative management of patients with cardiac implantable electronic devices<sup>[8]</sup>. According these notices, a magnet can be secured over the pulse generator of an ICD to suspend the arrhythmia detection function of the ICD and prevent discharge. The main caveat to the routine use of magnets to temporarily deactivate an ICD revolves around whether or not there is a possibility that the magnet response of the ICD is programmed to ignore magnet application. It depends on medical technology company and the kind of device: some devices haven't such an option and magnet application should reliably deactivate the device while its removal reactivates it. Other devices have the option of programming the magnet response to off, which underscores the need to know how an implanted device is programmed. Even when the ICD has been deactivated by a magnet, its pacemaker function is not affected. In patients with a Pacemaker the application of the magnet has different consequences. Indeed when a magnet is secured over the pulse generator, the device paces in asynchronous mode (AOO, VOO, DOO), that is, the device paces at a frequency higher than the patient's spontaneous. In asynchronous pacing if the patient is not entirely pmk-dependent, a parasystolic rhythm given by the spontaneous activity could occur and it's likely to compete with the rhythm stimulated by the device. A stimulus delivered during the vulnerable period of a spontaneous cycle could lead to a dangerous arrhythmia. Although this possibility is rare and avoided thanks to a higher pacing

rate, it should be evaluated from time to time what is the management more appropriate for each individual patient<sup>[9]</sup>.

An increased probability for electroporation pulses interfering with the heart function is present. In recently published studies on non-thermal irreversible electroporation, different minor and major hemodynamic and cardiologic changes due to unsynchronized irreversible electroporation pulse delivery were reported, such as systolic hypertension, supraventricular tachycardia, ventricular tachycardia with pressure drop, ventricular fibrillation and changes in T wave<sup>[10]</sup>. Deodhar *et al*<sup>[11]</sup> showed that unsynchronized irreversible electroporation pulses delivered at less than or equal to 1.7 cm from the heart provoked fatal events whereas pulses delivered more than 3 cm from the heart did not provoke any changes on the electrocardiogram. On the other hand, they reported that synchronized irreversible electroporation did not provoke any events at more than 1.7 cm distance from the heart.

The lesion in our patient was localized in the cervical right side with a distance from the pace-maker/ICD < 10 cm, but the nodule was not deeply located. The choice to perform a general anesthesia was dictated by the clinical evaluation of the patient: tumor nodule with large dimension, painful, unpleasant sensation during procedure for muscle contraction in a patient with particular cardiac conditions and better administration of oxygen during the procedure. Our operating modalities, general anaesthesia and ECT were performed without complications. The synchronization algorithm currently implemented in Clinoporator Vitae device coupled with the external triggering device AccuSync proved to be effective in preventing external stimulation of the heart during the so-called vulnerable period of the ventricles. As a result all electroporation pulses in our study were delivered outside the vulnerable period and no heart arrhythmias or any other pathological morphological changes were observed.

The safety of the treatment was demonstrated by absence of side effects during and after ECT.

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