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Benign electrocardiographic changes and diaphragmatic contractions while using the NanoKnife: A case report

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ABSTRACT

Introduction: The NanoKnife is a relatively new non-thermal tumor ablation tool. It is based on the creation of nanoscale defects in the cell membrane lasting long enough to induce cell death. Although considered a minimally invasive technique, side effects are still possible. Case Report: We describe a patient who had benign electrocardiography (ECG) changes in the form of tall T-waves with no apparent hemodynamic consequence. The patient also had regular right diaphragmatic contractions that slightly affected ventilatory curves during positive pressure ventilation, without clinical implications. Conclusion: Irreversible electroporation represents a new method for tumor ablation. It appears to be safe and promising, especially with the application of advanced ECG-synchronizing devices. This example shows that we should be careful when implementing new techniques and that we should add our experiences to a global database to enhance the learning process.

Keywords: Benign arrhythmia, Diaphragmatic contraction, General anesthetic, NanoKnife, Neuromuscular blockade

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INTRODUCTION

The NanoKnife is a relatively new non-thermal tumor ablation tool. It is based on the creation of nanoscale defects in the cell membrane lasting long enough to induce cell death. Although considered a minimally invasive technique, side effects are still possible. We describe a patient who had benign electrocardiography (ECG) changes and diaphragmatic contractions.

CASE REPORT

A 59-year-old male was listed for an open NanoKnife procedure for a head-of-the-pancreas tumor that was locally advanced and considered inoperable. The patient was a non-insulin dependent diabetic with no other significant medical history. He was a non-smoker and drank no alcohol. His medications included Gliclazide and Creon and he had no known drug allergies.

The surgical approach was a midline incision above the umbilicus to access the pancreas and apply the electrode for the NanoKnife. Standard monitoring was applied prior to induction of anesthesia (SpO_2, blood pressure, 3-lead electrocardiography (ECG), airway gases). Electrodes for the NanoKnife were placed, synchronized with the ECG

and checked prior to induction of general anesthesia. An intravenous cannula was sited and intravenous induction was achieved with a combination of midazolam, fentanyl, propofol, and atracurium after pre-oxygenation. The patient's trachea was intubated with a standard 8-mm cuffed endotracheal tube. Anesthesia was maintained with oxygen, air, and desflurane. Intraoperatively, analgesia was provided with paracetamol and morphine boluses. Paralysis was monitored with a standard nerve stimulator placed on the patient's forehead, and further boluses of atracurium were administered as required.

Intraoperatively, we noticed ECG interference, shown in Figure 1. This was in the form of excessively high T-waves, with no obvious effect on hemodynamic status. The patient had a regular heart rhythm, checked by manual palpation of the pulse, and no change in blood pressure, which was frequently checked.

We also noticed rapid contraction of the diaphragm, apparently caused by the NanoKnife. Although a peripheral neurostimulator confirmed that the patient was paralysed, atracurium bolus was given in an attempt to stop the frequent diaphragmatic contractions. As seen in Figure 2, the diaphragmatic contractions affected his ventilation slightly. End tidal CO_2, ventilatory pressure, and volume curves showed small undulations caused by involuntary, regular diaphragmatic contractions during NanoKnife ablation. The muscle relaxant boluses did not resolve the diaphragmatic contractions. As soon as the NanoKnife was removed from the tumor, all the changes described disappeared.

Postoperative analgesia was provided with titrated intravenous morphine boluses in the recovery ward. Regular paracetamol combined with codeine phosphate were administered, with oral morphine as required. He went home on day the third post-surgery.

DISCUSSION

Irreversible electroporation (IRE) represents a new, minimally invasive, non-thermal tumor ablation technique based on the creation of nanoscale defects in cell membranes, lasting long enough to induce cell death [1]. During IRE high voltage direct current (DC) shocks are passed via the electrodes placed near the tumor tissue. This creates an electrical field density high enough to disrupt the cell membrane structure and form irreversible membrane holes. This leads to the disequilibrium of cellular electric potentials Typically pulses are in the range of 1000–3000 V at 20–50 A, lasting 70–100 μs (100 μs pause between pulses) [1–3].

There are two main advantages of IRE compared to other thermal ablation techniques (such as radiofrequency ablation). The extracellular matrix, biliary, vascular and nervous tissue is preserved in IRE. Some degree of destruction of these structures is inevitable using thermal based techniques. Secondly, complete tumor ablation is prevented in certain areas using thermal techniques due to the 'heat-sink' effect. Heat is lost by high local blood flow near large vessels. This effect is negligible using IRE [2, 3].

Although efficacious for ablating tumors that cannot be operated on in a 'classical' manner, or with thermal-ablation methods, removal of tumors with IRE carries some of its own risks. Specifically, the creation of permanent nanoholes in cell membranes and the disruption of cell homeostasis leads not only to destruction of malignant tissue, but also of all cells within the range of the applied high-energy electric field [2, 3]. It is also possible to create reversible membrane defects with lower energies due to the effects of the electric field's spatial dispersion, which leads to the phenomenon of reversible electroporation and dysfunctional, but viable, cells.

In animal experiments by Rubinski et al. [1], electrical field modeling led to the conclusion that the electrical field strengths over 600 V are necessary to create irreversible

Figure 1: ECG interference: excessively high T-waves.

Figure 2: Involuntary diaphragmatic contractions during NanoKnife pulses.

electroporation (i.e., cell death), and field magnitudes between 100 V and 600 V can induce reversible membrane permeability. In similar animal experiments [4], authors performed mathematical analysis and came to almost the same values. The energies required for IRE was minimum 500 V, with field strengths between 100V and 500 V led to the reversible electroporation. However, the results were influenced by tissue characteristics (volume and conductivity), the distance between electrodes and exact voltages applied. It is difficult to extrapolate these findings on humans.

In anesthesia there are interactions between IRE pulses and myocardial and skeletal muscle, as well as central nervous system excitable tissue cells. We would like to focus attention on the influence of IRE on the electrical functioning of the heart, and especially on the propensity of IRE to create malignant heart arrhythmias.

It is known that the heart's action potential consists of an absolute and a relative refractory period, defined by the sensitivity and susceptibility of the myocardium to the applied electrical potential [5]. During the absolute refractory period, even the strongest electrical stimuli cannot induce an action potential in the myocardial cell, and this interval lasts from the beginning of the QRS complex to the beginning of the T-wave. However, during the relative refractory period, supramaximal stimuli (such as IRE pulses) can provoke premature action potentials with the possibility for malignant ventricular arrhythmias, and in heart electrophysiology this time interval is referred to as the "vulnerable period" [6]. For heart atria, this period coincides with the S-wave, during which IRE pulses could, theoretically, lead to self-limiting supraventricular arrhythmias (i.e. paroxysmal supraventricular tachycardia, atrial flutter and fibrillation) [7].

The ventricular vulnerable period is clinically more dangerous; this period encompasses the whole T-wave on the ECG. During this interval, applied supramaximal stimuli could lead to malignant heart arrhythmias, including ventricular extrasystole (VES), ventricular tachycardia (VT), and ventricular fibrillation (VF) [6, 7]. It is thus important to synchronize IRE pulses with the ECG R-wave, which allows the supraphysiological electrical stimulus to fall during the absolute refractory period, and before the ventricular vulnerable period (i.e. before the beginning of the T-wave) [4].

Ball et al. confirmed the importance of ECG synchronization [1], who recorded the effect of IRE pulses on electrical heart activity during ablation of liver, kidney, and lung tumors. Without synchronization, brief episodes of VT with a fall in arterial pressure were noticed, followed by normalization of the heart rhythm and hemodynamics immediately after stopping IRE pulses. However, when an ECG synchroniser was used, no cardiac arrhythmia was recorded.

Nielsen et al. [3] also reported the occurrence of one VES and one ventricular bigeminy during ablation of liver and pancreatic tumors, despite using technically correctly applied ECG synchronisation. VES normalized after removal of the electrode closest to the heart, and ventricular bigeminy disappeared within 5 min after completing the procedure. Deodhar et al. [4] investigated the influence of IRE pulses with and without ECG synchronization on the occurrence of heart arrhythmias during experimental lung and myocardial ablations, as well as the effect of the distance of the ablation zone from the heart. They applied pulses with voltages of 1400V–2500V (depending of the distance between applicators) with duration of 70 microseconds, and a pause of 250 milliseconds between pulses in unsynchronized, or one heart beat in synchronized mode. They modeled and confirmed experimentally that the safe distance from the heart was 1.7 cm, even without ECG synchronization. However, when applied closer to the myocardium, in all cases malignant ventricular arrhythmias were recorded: i.e. transient VT and VF. Alternatively, using synchronisation, only 'minor' heart arrhythmias (ST-segment elevation, self-limited supraventricular tachycardia, T-wave changes) were noted, with no clinical consequence. However, the distance of 1.7 cm from the heart as a safety factor seems questionable because, as noted by the authors, this was measured with a static computed tomography (CT) image, and not using 'real-time' images of the heart with systolic-diastolic movement. Furthermore, the dielectric characteristics of the porcine lung tumor tissue may differ from the normal porcine tissue used in the experiment; thus, the resistance to spreading of the electromagnetic field have not been explored in sufficient depth to safely extrapolate to human situations.

In a recent case report [8], ventricular extrasystoles were recorded during the IRE ablation of liver metastases of the rectal adenocarcinoma. VES occurred as a result of failed synchronization of IRE pulses with the ECG R-wave, which subsequently fell during the relative refractory period (i.e., the vulnerable period of the heart). Although the VES were self-limited and without hemodynamic consequences, obviously the application of ECG synchronization does not *a priori* ensure absolute safety during IRE ablation near the heart.

It is also possible that extensive ablation of tumor tissue with a large mass or ablation of tumours in patients with renal impairment leads to imbalances in the acid-base status and electrolyte homeostasis, and hyperkalemia in particular. This could provoke serious heart arrhythmias, even if ECG synchronization of IRE pulses was applied correctly [2].

Furthermore, it is known that the application of high-energy electrical shocks during myocardial defibrillation can provoke a wide spectrum of arrhythmias, such as VT, VF, bradyarrhythmias, heart blocks, and myocardial stunning, which is believed to be caused by the reversible and irreversible electroporation of cardiomyocytes. Nikolski and Efimov [9] showed experimentally that resealing of the nanopores created by electroporation can last for seconds or even minutes after completion

of the procedure, which could create conditions for the emergence of focal or re-entry tachyarrhythmias via inhibition of the conduction pathways of the heart. This possibility demands constant vigilance from the anesthetist not only during the tumor ablation procedure, but also in the minutes that follow.

In our case, the tall T-waves may have been caused by hyperkalemia secondary to destruction of the tumour cell wall. In the neighboring zone of reversible electroporation there is a brief period of transient permeability of the cell membranes, which could also contribute to potassium load. The aforementioned study of Ball et al. [2] reported four patients developed acute hyperkalemia. One patient had resection of a very large tumor, and the other three patients had preexisting renal impairment. A second possibility is that ECG synchronization delivers a pulse 50 milliseconds after the registration of the preceding R-wave and well before the beginning of the T-wave. If the heart rhythm has a short QT-interval, the monitored ECG artificially summates IRE pulses with the T-wave. This leads to the false conclusion that the T-wave is pathologically altered, however the underlying cardiac rhythm is undisturbed. In our case, clinical and hemodynamic parameters remained within normal limits and no malignant cardiac arrhythmias were induced. We believe that this was the cause of the high T-waves.

To date, there have been several descriptions of diaphragmatic contractions following NanoKnife use in the literature [2, 9, 10]. In our patient, we presume that the NanoKnife stimulated nerves involved in diaphragmatic contraction. As the tumor and NanoKnife were more on the right side of the abdomen, only the right side of the diaphragm was affected.

CONCLUSION

Irreversible electroporation represents a new method for tumor ablation. It appears to be safe and promising, especially with the application of advanced ECG-synchronizing devices. However, theoretical modeling, experimental findings, and clinical experience in humans have shown that even with maximum precautions and using all appropriate safety measures, a real and permanent possibility of heart arrhythmias still exists.

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Author Contributions

Mariese Cooper – Acquisition of data, Drafting the article, Final approval of the version to be published
Stevan Mihailovic – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Zoka Milan – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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