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Favorable Tissue Effects of Quantum Molecular Resonance Device (Vesalius®) Compared with Standard Electrocautery

A Novel Paradigm in Lung Surgery

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Key Words
Quantum molecular resonance · Electrosurgery · Lung surgery

Abstract
Background: Electrosurgical devices are largely employed in thoracic surgery but their use is burdened by extensive necrosis and second intention healing. ***Methods:*** A rat model of thoracotomy was performed on 46 adult male rats using a standard electrocautery or a new quantum molecular resonance (QMR) instrument called Vesalius®. Skin, muscle and lung specimens were obtained immediately and 2 weeks after surgery to evaluate acute and late effects. ***Results:*** Both in the short- and long-term study, Vesalius produced less severe tissue damage than that of standard electrocautery. ***Conclusions:*** The use of the QMR device may provide an alternative to gold-standard electrosurgical devices in thoracic surgery.

Introduction

Classical electrocautery (EC) represents a technique to quickly cut and coagulate tissues without pressure, simply by passing high-frequency currents [1]. The electrosurgical generator is a device that produces frequencies of about 500 kHz with standard 100–300 W. The use of low frequencies implies warming of the tissues surrounding the incision: abrupt temperature increases reaching often 800°C and consequently it can determine extensive necrosis and tissue cooking [2]. Therefore, second intention healing and postoperative complications may occur.

Major efforts are being carried out to develop novel strategies to improve the properties of electrodevices [3, 4]. The quantum molecular resonance (QMR) constitutes the theoretical basis of a new surgical instrument called Vesalius® (Telea Ing., Vicenza, Italy).

According to the QMR principle, the energy is transmitted to the tissue packed into quanta, the energy of each quantum being proportional to the frequency of the current provided and it is therefore higher than a standard EC. Furthermore, the spectrum of frequencies used by Vesalius produces an amount of energy adequate to

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break the molecular bonds in the biological tissue, avoiding the development of high temperature. In other words, the energy transmitted by Vesalius is converted almost exclusively into potential energy (by breaking the molecular bonds) and not into kinetic energy (which would lead to an increase of local temperature) [5]. Therefore, the resulting incision comes from direct breakage of molecular bonds; as a result, the surrounding tissues maintain a low temperature allowing clean cuts and easy healing, with no chance for keloid formation [6]. Coagulation itself results from protein denaturation instead of tissue warming.

The reason for intense research of new devices to employ in lung surgery is the need to avoid extensive pleural abrasion and parenchymal damage at the hilum and at the fissures during the dissection procedures, which are often responsible for postoperative air leakages [7]. The most recent technology introduced in thoracic surgery is the Harmonic Scalpel, an ultrasonically-activated device which can coagulate and cut the vessels or tissues without passing an electric current [8]. However, this device is not currently widely used in surgical practice yet.

Materials and Methods

Animals

A total of 46 adult male Sprague-Dawley rats weighing 250–300 g (Charles River, Monza, Italy) were used in the experiments. The rats were divided into two groups of 23 each according to the equipment used in the surgical procedure: standard EC (Valleylab) or Vesalius scalpel. Ten out of the 23 rats in each group were used for the short-term study and were killed immediately after surgery (group A). The remaining 13 animals in each group were killed 2 weeks after surgery (group B) to explore long-term damage. All the procedures involving animals and their care were conducted in accordance with institutional guidelines in compliance with national and international laws and policies.

Surgical Procedure

Rats were anesthetized by intramuscular injection of tiletamine hydrochloride and zolazepam hydrochloride (700 μg/kg) [9] plus subcutaneous injection of xylazine (150 μg/kg) [10]. Animals were then placed in dorsal recumbency on a grounding pad that allowed the return current to dissipate over a relatively large surface area. For the EC, the dispersive electrode was pre-gelled, flexible, self-adhering, while the Vesalius device does not need direct contact between the animal and the plate, thus preventing eventual burns. Animals were intubated with a 16-gauge endotracheal catheter connected to a small animal ventilator (SAR-830 ventilator, CWE Inc., Ardmore, Pa., USA) set at a respiratory rate of 75/min and 200 ml/min airflow. The anterior and lateral chest walls were shaved and prepped in a sterile fashion. Lateral thoracotomy was performed as follows: a 3-cm incision was made on the skin of the lateral chest between the 4th and 5th ribs 1 cm from the parasternal line. The deep and superficial muscles covering the ribs were retracted to expose the intercostal muscle. The intercostal muscle plane and the pleura were passed through using the cutting and cauterization properties of the device until the pulmonary parenchyma was exposed. All these procedures were performed with particular attention to preserve the anatomic planes. The blunt tines of a small self-retaining retractor (Mueller, McGaw Park, Ill., USA) were placed under the 4th and 5th ribs and the retractor was opened to produce rib separation of about 10 mm. To avoid undesired pulmonary damage, ventilation was briefly stopped allowing the lung to collapse during this last procedure. A standard transversal lesion of about 4–5 mm in length was then carried out on the lung parenchyma with the scalpel using the same cutting and coagulating power (40 W) throughout the study. Methylene blue was then applied to the lung parenchyma to mark the lesion for future identification. We carefully evaluated the presence of air leak by shedding a small amount of saline solution on the operative field. A 4-cm long piece of silicone (0.047 inch diameter) rubber tubing was placed inside the pleural space. The deep muscles covering the ribs were closed with 5-0 silk sutures, with secure muscle apposition around the tubing. Air was aspirated from the pleural cavity with a 5-ml syringe attached to the tubing to restore normal intrapleural pressure. The tubing was then removed from the pleural space and the exit point immediately sealed with a 5-0 silk suture. Once spontaneous ventilation was restored, the Y-connector was detached from the endotracheal catheter, the superficial muscles covering the ribs were then apposed with 3-0 silk sutures, the skin was closed with 2-0 nylon sutures, and the endotracheal catheter was removed after the animal moved spontaneously.

During the immediate postoperative course, animals were monitored closely and received subcutaneous injections of cephazolin (1 g/kg) and proper analgesic treatment in the form of intramuscular tramadol (1 g/kg). The animals were then allowed to feed ad libitum and were maintained in a controlled environment.

Histology and Image Analysis

To study the immediate tissue effects of electrosurgery and QMR surgery, 10 animals (group A) were killed 5 min after the parenchymal lung lesion was carried out. To study the reparative processes, 13 animals (group B) were killed 14 days after surgery. Skin, muscle and lung specimens were obtained from tissues involved in the surgical procedures and placed into tubes filled with 4% paraformaldeyde for histological hematoxylin-eosin (HE) staining, using a standard procedure. At time 0, tissues were frozen in liquid nitrogen and stored at –80°C until processing for apoptosis assay (n = 5 per group). The short-term study (time 0 after surgery) was conceived to evaluate the amount of necrosis created by each device. Necrosis was defined as the presence of typical morphological arrangements due to cell death: eosinophilic coloration, vacuolization of the cytoplasm and the presence of pyknosis or absence of the nuclei.

The long-term study (14 days after surgery) was conceived to evaluate the amount of inflammation, especially granulomatous [11], characterized by aggregates of epithelioid cells, usually with surrounding lymphocytic infiltration.

In both cases, a discrete semiquantitative scoring system was used, ranging from 0 to 3 (0 = no necrosis or inflammation; 1 = necrosis or inflammation extending up to 30% of the section: 2 =

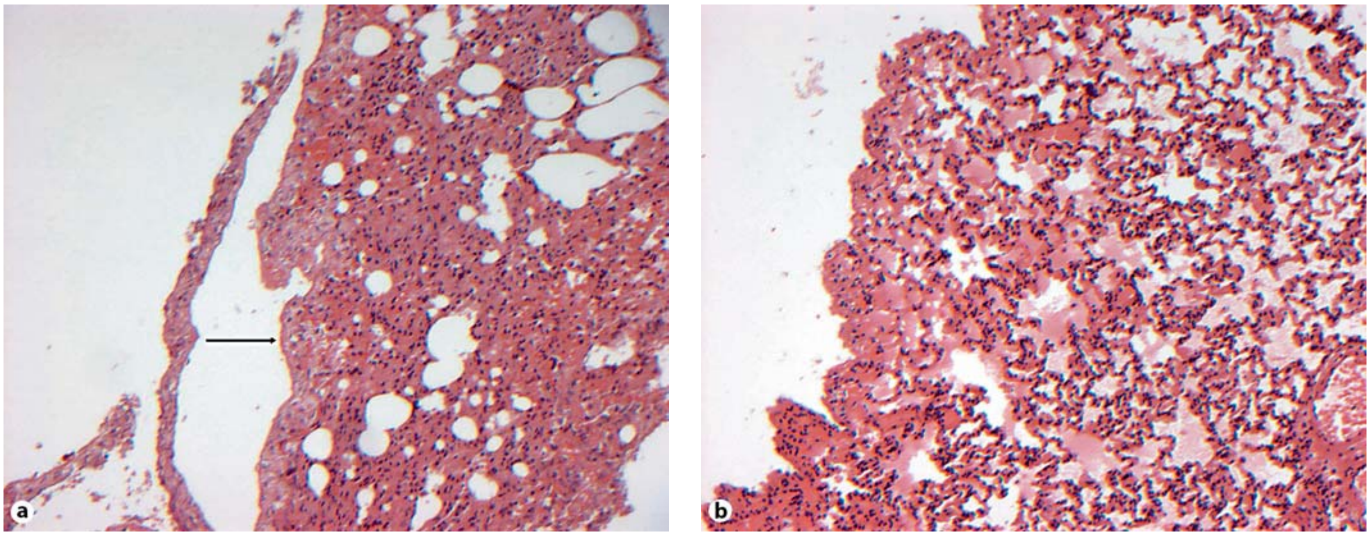

Fig. 1. Tissue damage in the group A. **a** Lung parenchyma with a small necrotic focus (black arrow) from an EB-treated rat (score 1). HE, orig. magnif. ×25. **b** Areas of normal parenchyma without necrosis (score 0) in a Vesalius®-treated rat. HE, orig. magnif. ×25.

necrosis or inflammation extending 30–50% of the section area; 3 = more than 50% of the section exhibiting necrosis or inflammation). To avoid interpretation biases, all histologic sections were analyzed by the same trained pulmonary pathologist throughout the study, who was blind to the study groups.

Apoptosis Assay

Apoptosis of parenchymal cells was evaluated using a commercially available PCR kit for DNA ladder assay (Maxim Biotech, Inc., San Francisco, Calif., USA) according to the manufacturer's protocol.

Statistical Analysis

Data are expressed as mean ± SE. Mann-Whitney's U test was used to compare scores from different groups. SPSS Version 11.0 was used and statistical significance was accepted if the null hypothesis could be rejected at $p \leq 0.05$.

Results

Tissue Damage in Group A

The short-term study evaluated the immediate degenerative tissue effects in the anatomical structures involved in the surgical procedures. Qualitative evaluation of HE-stained sections revealed differences between the two devices, which were further investigated by semi-quantitative analysis. Immediate effects in the EC-treated rats consisted of irreversible cell death attributable to both direct damage and tissue warming. Cell death was primarily due to coagulative rather than colliquative necrosis. The general tissue architecture was roughly preserved, and areas with extensive necrosis remained in contact with vital areas. In the Vesalius-treated animals, immediate effects showed almost no sign of cell death, while the major abnormal finding was the presence of some areas of atelectasy, in which typical alveolar collapse was associated with parenchymal compacting (fig. 1).

From a quantitative point of view, the necrosis score was significantly lower in the Vesalius- than in EC-treated animals in skin specimens (0.5 ± 0.21 vs. 1.3 ± 0.32, p = 0.03), muscle specimens (0.4 ± 0.21 vs. 1.2 ± 0.34, p = 0.04) and lung specimens (0.2 ± 0.13 vs. 0.7 ± 0.15, p = 0.01) (fig. 2a). DNA fragmentation assay revealed no difference in terms of pulmonary cell apoptosis between Vesalius- and EC-treated animals (0.47 ± 0.07 vs. 0.41 ± 0.01, p = 0.49) (fig. 2b).

Tissue Damage in Group B

The long-term study evaluated the reparative processes 2 weeks after surgery. Cumulative mortality rate at 2 weeks was relatively low (1 animal per group, 7%). For both devices, the main pathologic finding was the presence of a chronic inflammatory process characterized by giant epithelioid cells. In the skin and muscle samples, small necrotic areas and fibroblast-rich foci were also found. Especially in EC-treated rats, lung specimens

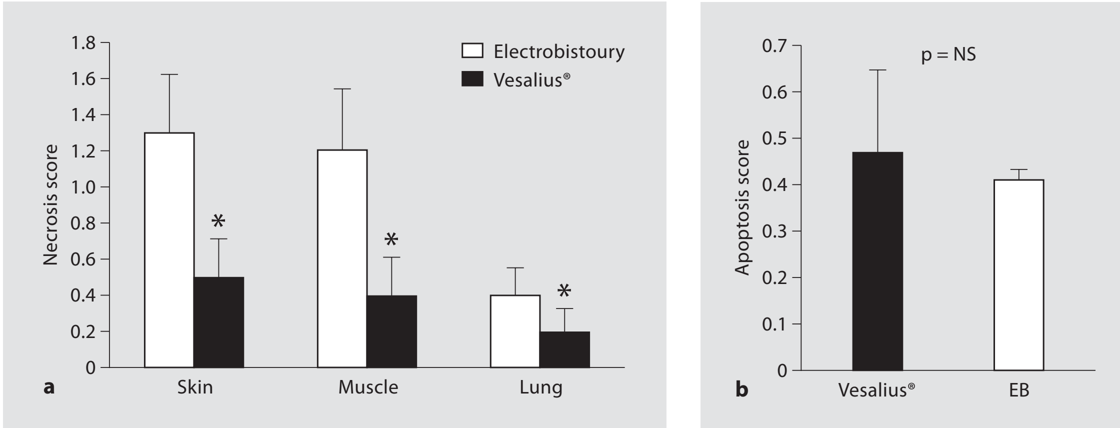

Fig. 2. Necrosis score and apoptosis assay at time 0. **a** Reduced necrosis score at time 0 in electrobistoury and Vesalius®-treated animals in skin and muscle samples. **b** The study of apoptosis in pulmonary parenchyma evaluated with the DNA ladder assay. On average, no differences were found in lung cell apoptosis between electrobistoury and Vesalius-treated tissues. * $p < 0.05$; NS = not statistically significant.

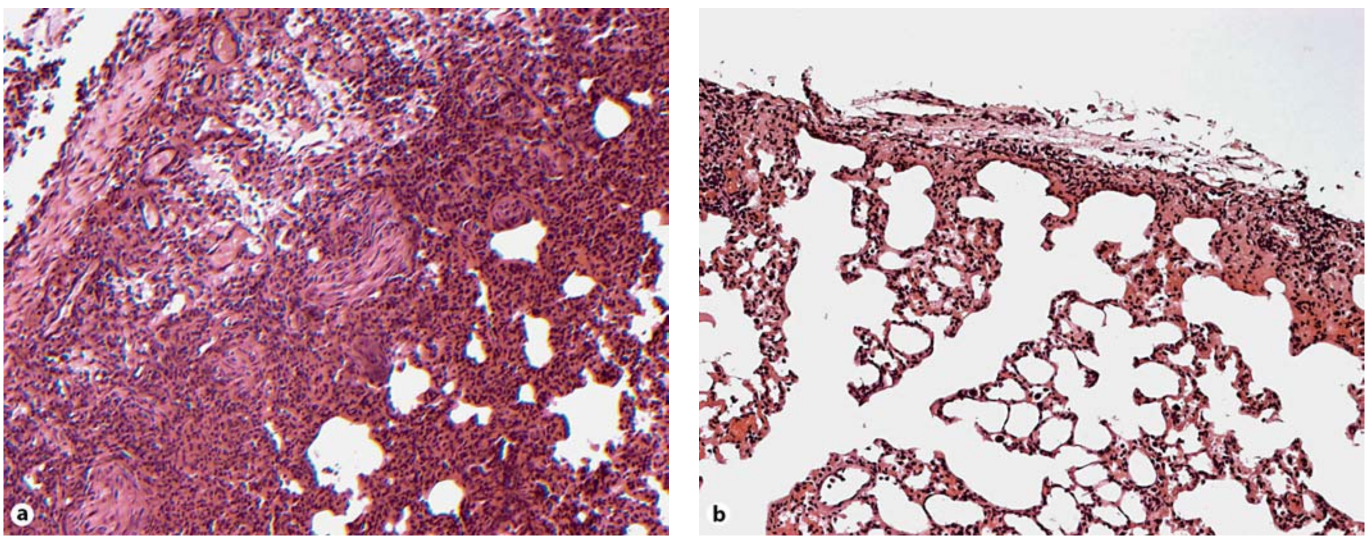

Fig. 3. Tissue damage in the group B. **a** Lung specimen from EB-treated rat with diffuse inflammatory process (score 2). **b** Lung parenchyma treated with Vesalius® without any signs of inflammation (score 0). HE, orig. magnif. ×25.

showed chronic inflammation, sometimes extending to the subpleural and interstitial tissues. In 30% of skin and muscle samples persistent necrotic areas, in some cases extensive, were evident. Moreover, despite aseptic procedures and adequate antibiotic treatment, extensive necrosis and acute inflammatory response due to pyogen infection caused evident purulent lesions. This intense reaction often produced tenacious adhesions between the pleuropulmonary tissue and the overlying muscle plane (fig. 3a, b).

While similar reparative events took place with both devices, the inflammatory stimulus seems to be weaker when the QMR device was used. Consistently, in the Vesalius-treated rats, inflammatory scores were significantly lower than in EC-treated rats, particularly in muscle tissue (2.38 ± 0.17 vs. 3 ± 0, $p = 0.005$) and in the pulmo-

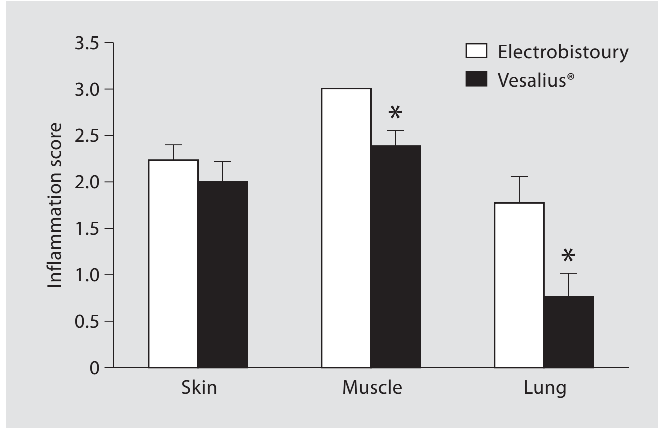

Fig. 4. Inflammation score at time 14. Inflammation was significantly lower in muscle and lung samples treated with Vesalius® in comparison with electrobistoury samples. * $p < 0.05$.

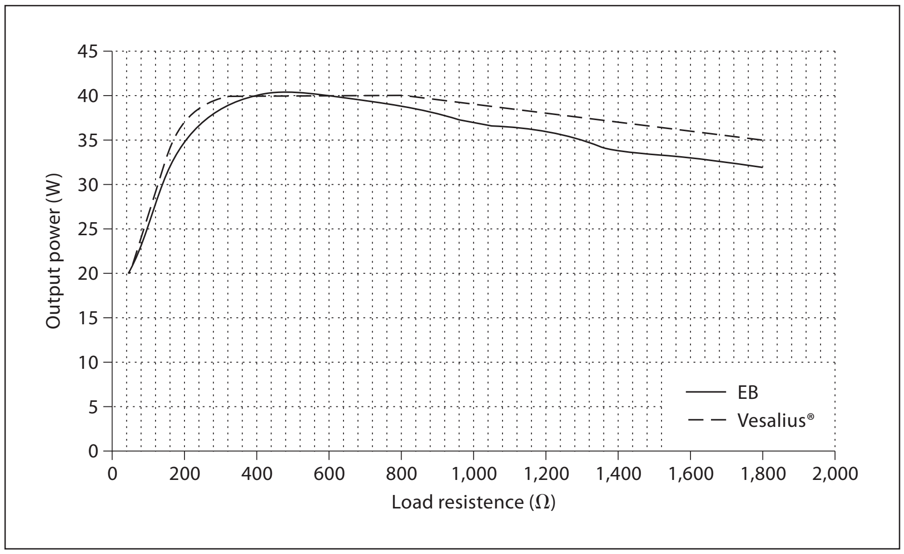

Fig. 5. Output power analysis: the output power of the Vesalius® and EB with both instruments set at 40 W is similar when the devices work at the normal tissue impedance (300–500 Ω). Output power was measured with the use of a wattmeter.

nary parenchyma (0.77 ± 0.25 vs. 1.77 ± 0.29, $p = 0.015$). No statistically significant difference was found in skin samples (2.00 ± 0.21 vs. 2.23 ± 0.16, $p = 0.21$) (fig. 4).

Discussion

With this research we demonstrate that QMR bistoury is suitable for surgical procedures involving skin, muscle and lung tissue. The main finding of our work is that, in rats, tissue damage related to the use of Vesalius was significantly lower than that deriving from the use of an electrobistoury, both in the short- and long-term study. These results are consistent with the theory of QMR, implemented in the Vesalius device: the absence of free energy excess prevents tissue heat damage and allows clean-cut and coagulate maneuvers.

It should be noted that few works have been carried out in animal models [12, 13]. Our study was conceived to explore two related aspects of surgical damage, which are relevant in the field of thoracic surgery: immediate degenerative effects and late reparative processes. During the surgical procedure, the presence of vital vascular and neural anatomic structures in the thorax requires precise and non-traumatic devices to carry out arduous procedures. The postoperative period is often characterized by local inflammation and necrosis, causing neurogenic pain [14], reduced ventilation and cough reflex that lead to respiratory distress and a higher incidence of infections [15].

Our findings showed that necrosis was significantly reduced by using Vesalius in the short-term analysis. In lung tissue, where necrotic damage was marginal, apoptotic injury was also investigated. In comparison with electrobistoury, the Vesalius-treated samples showed a similar apoptosis rate, suggesting that reduced necrosis is not mirrored by increased apoptosis and that tissue dieresis is carried out with an absolute reduction in cell death.

These favorable immediate tissue effects translate into reduced inflammation 2 weeks after the surgical procedure: extensive necrotic damage resulting from the use of electrobistoury led to stronger inflammatory responses in the long term [16].

The equivalence of the preset energy was the fundamental assumption that allows the two surgical devices to be compared. The actual output power of the devices is function of the power values set by the operator during the procedure and of impedance of the biological tissue (fig. 5). Commonly, surgical scalpels are designed considering a tissue impedance range of 300–500 Ω. With these data, the output energy would be virtually identical with both instrument sets at 40 W. In the current study, we employed only the pre-specified energy level of 40 W in order to reproduce as close as possible the events taking place in the clinical setting. Furthermore, we did not vary energy levels to reduce the number of variables and to increase the statistical power. Finally, the pathological evidence that, despite the same energy output, Vesalius determined lower necrosis in all tissues, which is linked to the immediate effect of the power applied, suggested that there was no need to vary the energy levels.

In the present study we did not explore molecular mechanisms of tissue damage. In the setting of both acute and chronic damage, the study of heat-shock protein regulation may provide additional proof of the favorable effects of QMR. Moreover, the systemic and local inflammatory response may be evaluated in terms of cytokine and chemokine release or expression.

Limitations of the Study

Employing a rat model simplifies experimental research because of the low cost, prompt availability, easy care, and low mortality rate. Nevertheless, the small animal size prevented us from performing a suitable lung resection. As a consequence, the results are not directly transferable to humans being difficult to explore outcomes related to surgery, such as pain [17], air leakage and disventilatory syndrome, which are clinically relevant in patients. Moreover, we cannot exclude that local complications could partially explain the differences in the long-term study. However, the surgical procedure was simplified as much as possible; therefore we tend to attribute the histopathological changes to the device used, which was the only difference between groups. Further investigation with Vesalius should be performed on larger animal models such as rabbits or pigs, allowing more complex thoracic procedures and comprehensive evaluation [18].

In conclusion, this first-line study was carried out to investigate the rational for use of a surgical device based on a new technology (quantum molecular resonance – QMR). On this basis, it may be considered a starting-point for wider projects.

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