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Towards a self-reporting coronary artery stent—Measuring neointimal growth associated with in-stent restenosis using electrical impedance techniques

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ABSTRACT

Implantable medical devices have become the standard method for treating a variety of cardiovascular diseases (NICE, 2003, 2009), such as coronary artery disease, where coronary artery stents are the device of choice (Fischman et al., 1994; Babapulle et al., 2004). One post-operative problem with these devices is the long-term monitoring of the device–tissue interface, with respect to the complications that often arise from in-stent restenosis. This monitoring, where it is available, is currently performed using imaging techniques such as contrast angiography, IVUS, CT and MRI. In this study we propose an alternative method for the non-invasive monitoring of restenosis in coronary artery stents. This preliminary study uses impedance spectroscopy to measure the electrical impedance of cells and tissues associated with the neointimal growth that characterises in-stent restenosis in coronary artery stents. An *in vitro* organ culture model, using a stent implanted in a section of pig coronary artery, simulated tissue growth inside a stent. Impedance measurements were made regularly over a 28-day culture period. In a novel step, the stent itself was employed as an electrode. Differences in electrical impedance could be seen between control (stent alone) and artery-embedded stents in culture, which were associated with the presence of biological tissue. This method could potentially be developed to produce a stent that was capable of self-reporting in-stent restenosis. The advantages of such a device would be that monitoring could be non-invasively and easily carried out, allowing more routine follow-ups and the early identification and management of any device complications.

1. Introduction

In recent times, coronary artery stents have become the medical device of choice for treating coronary artery disease (NICE, 2003, 2009). One of the key post-operative problems with such devices is the lack of long-term monitoring (Shedden et al., 2009) since once implanted the status of the device is difficult and inconvenient to determine, requiring angiography, CT or MRI procedures (if the stent is MRI compatible). It is well known that coronary artery stents can develop in-stent restenosis: a build-up of neointimal tissue inside the stent that causes re-narrowing of the artery. Drug eluting stents have served to reduce the incidence of restenosis significantly, but have introduced other problems, such as the possibility of late stent thrombosis (Babapulle et al., 2004; Stone et al., 2005, 2007). The complications associated with restenosis generally go undetected, until the patient has indicative symptoms such as chest pain. A method for monitoring the growth of neointimal tissue by measuring electrical impedance is proposed, which uses the surface of the stent as a sensor electrode. This method could be adapted for periodic monitoring of the stent status.

The concept of using electrical impedance to monitor cell proliferation and tissue growth and type has been studied *in vitro* and *in vivo* (Beetner et al., 2003; Scholz and Anderson, 2000; Zou and Guo, 2003; Süselbeck et al., 2005; Xiao and Luong, 2003; Lind et al., 1991; Kyle et al., 1999; Wegener et al., 1996; Giaever and Keese, 1991, 1993; Lo et al., 1995; Tiruppathi et al., 1992). This is possible because cells and tissues have resistive and capacitive properties that can be measured using a variety of techniques. Cell membranes, because of their structure, are both resistive and capacitive in nature. Extracellular matrix and cell contents are largely resistive due to their ion content although proteins and lipids can be capacitive. Hence cells and tissues are frequently represented as a combination of resistors and capacitors. One important use for impedance methods *in vivo* in patients has been for the detection of cancer (Beetner et al., 2003; Scholz and Anderson, 2000; Zou and Guo, 2003). Malignant, benign and normal tissue have different impedance properties (Fricke and Morse, 1926; Surowiec et al., 1988; Jossinet, 1996), due to changes in cell content,

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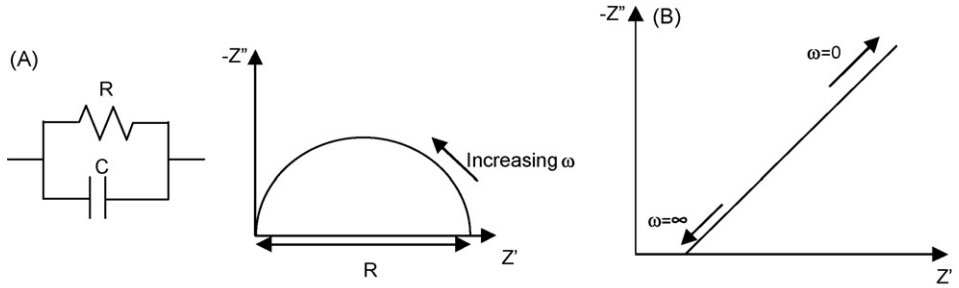

Fig. 1. Typical impedance measurements made in the complex plane. (A) Complex plane representation of the impedance of a resistor and capacitor in parallel. A semi-circle of diameter *R* and centre on the real axis is traced out as frequency increases. (B) Complex plane representation of the Warburg impedance. A straight line is produced, with gradient 45°, impedance increases as frequency decreases.

membrane properties and intracellular relationships, and this allows areas of malignant tissue to be identified. Most work in this area has been carried out with respect to detection of breast cancer and basal (skin) cancer. Süselbeck et al. (2005) have used microelectrodes mounted on a catheter to measure the impedance of neointimal tissue associated with stent implanted in rabbit iliac arteries. Impedance techniques have also been used *in vitro*, to monitor cell growth and cytotoxicity (Xiao and Luong, 2003) and mobility and adhesion of single cells (Lind et al., 1991). It has also been used to characterise tissue cultures (Kyle et al., 1999) and can be used to differentiate between cell types (Wegener et al., 1996), and monitor cell micromotion, (Giaever and Keese, 1991, 1993). Impedance of a confluent cell layer is related to the different paths through the cell layer. Electric cell–substrate impedance sensing techniques have been used to characterise these pathways (Lo et al., 1995) and impedance methods are also used to assess the barrier function of a cell layer (Tiruppathi et al., 1992).

This study aimed to investigate the possibility of using measurement of electrical impedance to monitor in-stent restenosis in an *in vitro* organ culture model. This model is based on the models of Carere et al. (1992) and Voisard et al. (1995), which used pig coronary artery organ culture models to study the effects of the injury caused by angioplasty and Guérin et al. (2004), who investigated neointimal hyperplasia in stented human mammary arteries grown in culture.

The various electrochemical processes related to electrodes and biological tissues in the experiment described above can be translated into the electrical component values, in order that they can be defined in terms of their electrical impedance (Bard and Faulkner, 1980). Non-faradaic electrode processes (the charging and discharging of the electrical double layer) can be represented by a capacitive element. Faradaic electrode processes can be represented most simply by a resistive element, which defines the resistance to charge transfer across the electrode/electrolyte interface and through the cell culture media. The complex permittivity and conductivity of lossy dielectric materials, such as biological tissues can also be represented by a combination of resistors and capacitors (Rigaud et al., 1996). Theoretically, the impedance of the stent, the biological tissue of the artery and the counter electrode may all be represented as a parallel combination of resistor and capacitor (Fig. 1), and the impedance of the cell culture media by a resistor alone. The impedance of the parallel combination of a resistor and capacitor describes a semi-circle in the complex impedance plane (Fig. 1A) as the frequency of applied AC voltage increases, according to the Cole equation (Rigaud et al., 1996) and known as a biological Cole plot. If the electrochemical reactions are limited by diffusion processes a straight line rather than a semi-circle may be produced in the complex plane, which can be represented using a Warburg impedance element (Fig. 1B). These 'equivalent circuits' will be used in Section 4 of this paper to illustrate how clinically relevant measurements may be made by the stent.

2. Methods and materials

In order to measure the time-dependent impedance of the stent interface, special apparatus was designed, as shown in Fig. 2. This experimental arrangement establishes an electrical circuit with a stent acting as one electrode, and a silver chloride-coated silver wire as the other. This circuit can be used to measure the electrical impedance of the path between the electrodes, which includes the stent, counter electrode, cell culture media, the artery mounted on the stent, and any neointimal tissue that may grow on the stent surface during the period of the experiment.

The left anterior descending coronary artery was dissected from a pig heart obtained from a local abattoir. Under sterile conditions a stent was expanded according to manufacturer's instructions (Cordis BX SONIC™ balloon-expandable bare metal stents, made of medical grade 316L stainless steel, were used) into a 10 mm section of artery, with the artery positioned at one end of the stent as shown in Fig. 2.

The stent was then connected to the circuit as shown in Fig. 2 and placed in the bottle, which contained 50 ml smooth muscle cell media (50:50 mix of Waymouth's MB752/1 + L-Glutamine and

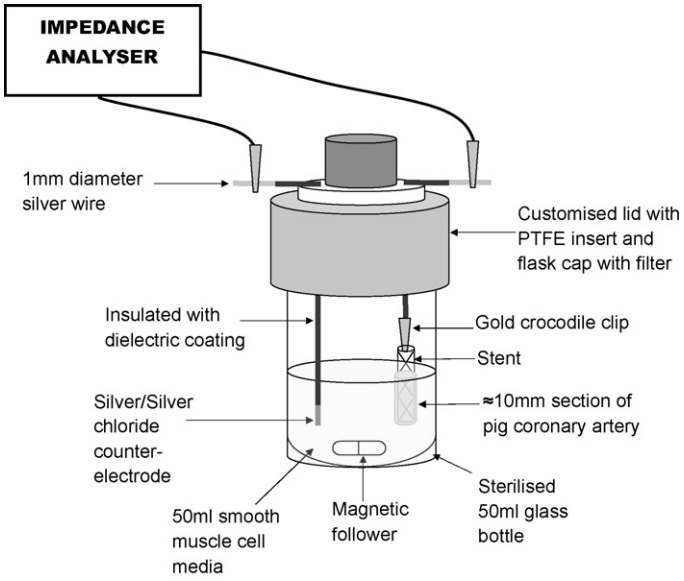

Fig. 2. Experimental apparatus for *in vitro* coronary artery model of in-stent restenosis. Stent is used as one electrode, and silver–silver chloride wire as the other.