Utilisation of electrical impedance spectroscopy (EIS) in the detection of dysplasia

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Declaration of interest:
John Tidy holds patents in EIS technology, is clinical founder and consultant to Zilico Ltd.

There has been interest for many years in the use of electrical impedance to identify and image biological tissues; however, identifying a reliable method to detect changes has been challenging and hence has restricted this technique from wider application. Underpinning the technology is the observation that all biological tissues have electrical impedance, which is a function of frequency. The reason for this dependence is that tissues contain components that have both resistive and capacitive properties. Both the size of the impedance, as well as the dependence of impedance on frequency, are related to tissue composition [1,2].

Figure 1: ZedScan hand-held unit with single-use sensor.

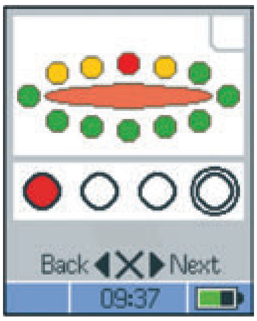

Figure 2: Results screen from ZedScan hand-held unit. Red and amber dots indicate high probability for HG-CIN.

Different tissues have different frequency bands within an impedance spectrum. At high frequencies (>1 GHz) molecular structure is the determining factor whereas at low frequencies (<100 Hz) charge accumulation at large membrane interfaces dominate. At frequencies of a few kHz to 1 MHz, sometimes referred to as the β dispersion region, cell structures are the main determinant of tissue impedance.

Within the β dispersion region, low frequency current can be considered as passing through the extracellular space; the current has to pass around the cells and the resistance to flow will depend upon cell spacing and arrangement. However, at higher frequencies current can penetrate the cell membranes and hence passes through both intracellular and extracellular spaces. Current will pass through the cells and will be determined by intracellular volume and, possibly, the size of the nucleus. The diameter of the electrodes and the distance between the electrodes will determine the depth of tissue measured by EIS. If the diameter of the electrodes and the distance between the electrodes is too large the current will flow into the stroma. This will have an adverse effect on the ability of EIS to detect any changes within the epithelium.

EIS in the detection of dysplasia

The alterations in architecture of an epithelial surface associated with the development of dysplasia can be measured by EIS. Dysplastic epithelia have increased extracellular space, lowering resistance to the flow of an electrical current at low frequency. Increase in the ratio between nucleus and cytoplasm may influence revistivity at higher frequencies. EIS technology has been used on epithelia to assess whether it can detect changes associated with dysplasia.

Detection of skin melanoma and basal cell carcinoma

Åberg et al. [3] used a multiple electrode device to take skin impedance measurements over the range 1-1000 kHz in 252 patients that had a spectrum of skin lesions [3]. There were significant differences between normal skin, benign pigmented nevi, dysplastic nevi and basal cell cancers, with the biggest being between normal skin and basal cell carcinoma. A range of parameters were used to describe the impedance spectra, which showed that the mean was higher in the basal cell carcinoma group than normal skin, and the changes with frequency were also reduced. Malignant melanoma could be distinguished from benign nevi. Nevisense, the product developed by Scibase, has recently been evaluated in a multicentre trial to assess if malignant melanoma can be separated from benign lesions; this device had a sensitivity of 97% for detection of melanoma and a specificity of 34% with lesions thought to be melanomas [4].

Detection of cervical intra-epithelial neoplasia

Cervical epithelium is a highly structured, stratified tissue. Preceding the development of cervical cancer the epithelia surface under goes dysplastic change usually as a consequence of infection by high risk human papillomavirus types. This dysplastic change is known as cervical intra-epithelial neoplasia (CIN). Cervical screening programmes use exfoliative cytology to detect the changes associated with the development of CIN and women with abnormal cytology are referred for colposcopy to examine the cervix and detect the presence of any CIN. Colposcopy involves examining the cervix with high power magnification, a colposcope, and the application of 3-5% acetic acid and iodine. The colposcopist assesses the development of any white lesions after the application of the acetic acid to the surface of the cervix. Utilising their clinical expertise the colposcopist will then assess if CIN is present and try to grade the CIN – low grade or high grade. A directed biopsy of the lesion or excision of the entire lesion may also be part of the examination. High grade CIN (HG-CIN) can be successfully treated and reduce the risk of the woman subsequently developing cervical cancer.

The cellular changes associated with CIN include an increase in the nuclear:cytoplasmic ratio, loss of the layer of flattened cells close to the surface, and an increase in extracellular space. Mucus has a relatively high electrical conductivity and can shunt electrical current away from the epithelium. These changes can be measured by EIS. Finite element analysis has been used to model the electrical properties of cervical epithelia characteristics typical of normal cervical tissue and CIN. The results were in good agreement with measurements taken from the cervix with a tetra-polar electrical device [5,6]. Over 490 women were studied using a pre-production EIS device, including 124 in the initial study [7-10]. The results of a European multi-centre study on 429 women using the hand-held device and a single-use sensor were published in 2013. ZedScan in conjunction with colposcopy showed a significant improvement in specificity, positive and negative predictive value, accuracy and positive likelihood ratio, with no loss of sensitivity. Sensitivity for colposcopy in the trial was high at 88% [11]. On the basis of the data, a CE-marked device called ZedScan (Zilico) is now commercially available.

ZedScan is a hand-held device with a single-use sensor used as an adjunct to the normal colposcopic examination. (Figure 1). ZedScan measures the electrical impedance from the cervix and compares the data with the finite element model of electrical impedance to create a probability of the presence or absence of high grade CIN. These results are immediately available to the colposcopists. The sensor is placed over the snout of the hand-held unit and the tip of the sensor placed on the cervical epithelium after acetic acid has been applied to the cervix. Up to 12 measurements are taken to scan the cervix and aceto-white areas. A traffic-light system is used to display measurement sites that are consistent with high grade CIN (Figure 2). Using a single-point mode, the optimal site for biopsy can be identified, or the ZedScan result can indicate if treatment of high grade CIN after first visit is appropriate. A recent single-site evaluation of 453 women showed that colposcopy with ZedScan had a sensitivity of 100% and negative predictive value of 100%. The detection of HG-CIN increased by 12.8% compared with colposcopy alone. At first visit, 55 women underwent treatment, of whom 100% had HG-CIN.

Detection of Barret's esophagitis

A tetra-polar device was developed by Gonzalez et al. [12] for the investigation of esophageal mucosa [12]. Four gold electrodes were incorporated into a 3 mm diameter device at the end of a catheter passed down the biopsy channel of an endoscope. Patients with Barrett's Esophagus were explored, in particular the impedance changes associated with dysplasia and inflammation. Significant changes were observed from normal controls, but they were not sufficiently different to allow the technique to be used clinically.

Detection of bladder dysplasia

Keshtkar et al. [13], using a tetra-polar device to investigate bladder pathology, studied 38 patients in which both impedance spectroscopy and biopsy measurements were made. A significant difference was found between malignant and benign tissues. Unlike the cervix, malignant tissues in the bladder had higher impedance than normal tissue, due to normal bladder urothelium having a lower impedance than cervical squamous epithelium. The urothelium has an impedance spectrum similar to that of columnar tissue of the uterine canal. Distinction of malignant from benign tissue in the bladder is not as clear as for cervical tissue. However, the technique may be a useful complement to cystoscopy and biopsy.

Detection of oral dysplasia

The epithelial structure of oral intra-epithelial neoplasia is similar to CIN; however, there are many different tissues types and structures within the oral cavity, posing more variation in EIS measurements. Using a tetra-polar device similar to that used in the CIN studies 51 controls and 47 patients were examined. EIS separated high grade lesions from normal and low grade changes with a sensitivity of 65.2%, specificity of 91.7%, and a positive likelihood ratio of 7.8 [14]. Assessment of a re-engineered oral EIS device is underway. EIS could be of use in screening and detecting oral neoplasia.

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