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Non-invasive assessment of corneal endothelial permeability by means of electrical impedance measurements

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ABSTRACT

The permeability of the corneal endothelial layer has an important role in the correct function of the cornea. Since ionic permeability has a fundamental impact on the passive electrical properties of living tissues, here it is hypothesized that impedance methods can be employed for assessing the permeability of the endothelial layer in a minimally invasive fashion. Precisely, the main objective of the present study is to develop and to analyze a minimally invasive method for assessing the electrical properties of the corneal endothelium, as a possible diagnostic tool for the evaluation of patients with endothelial dysfunction. A bidimensional model consisting of the main corneal layers and a four-electrode impedance measurement setup placed on the epithelium has been implemented and analyzed by means of the finite elements method (FEM). In order to obtain a robust indicator of the permeability of the endothelium layer, the effect of the endothelium electrical properties on the measured impedance has been studied together with reasonable variations of the other model layers. Simulation results show that the impedance measurements by means of external electrodes are indeed sufficiently sensitive to the changes in the electrical properties of the endothelial layer. It is concluded that the method presented here can be employed as non-invasive method for assessing endothelial layer function.

1. Introduction

Although corneal surgery and disease are very common, there is a lack of proper non-invasive diagnostic methods for determining the suitability of a given patient for a corneal surgical procedure that may weaken the cornea or for assessing the suitability of a donor cornea for transplantation.The cornea (Fig. 1) is a transparent hemispherical structure located in front of the eye that allows the transmission of light. Basically, it consists of three layers: the epithelium, the stroma and the endothelium. To maintain transparency the cornea does not have capillaries for supplying nutrients, they are supplied by diffusion through the epithelium and endothelium. The transparency of the cornea depends on the level of hydration of the stroma, remaining in a constant state of dehydration. As shown in Fig. 2, the hydration level of the stroma depends mainly of three different ion fluxes. Two of those fluxes are due to diffusion: one between tear layer and stroma through the epithelium and another one between stroma and aqueous humor through the endothelium. Finally, an active flux is due to fluid pump through the endothelium cells. The endothelium is a monolayer of cells without regenerative capacity and plays the most important role for maintaining the low hydration rate of the stroma and consequently the transparency of the cornea [1,2].The corneal endothelium morphology and its physiopathological status can be evaluated in the clinical practice by several techniques. Indirect methods as endothelial fluorophotometry [3] and pachymetry [4] are unreliable for monitoring individual patient changes [5]. On the other hand, specular microscopy [6] and confocal microscopy are direct methods only suitable for the examination of corneal endothelium morphology [7]. The endothelial cell density is the most widely used parameter for assessing the suitability of a cornea to be transplanted. But, a recent study concludes that the preoperative value of this parameter is unrelated to graft failure due to endothelial decomposition, whereas there is a strong correlation of this parameter at 6 months [8]. The barrier effect of the cornea can be assessed by the study of their passive electrical properties. Transendothelial electric resistance (TER) method is consistently used in *in vitro* studies for assessing the permeability of the corneal endothelium [9,10]. Studies using TER measurements in *in vivo* setups [11,12] are out of consideration for clinical methods due to their invasiveness.Here is proposed that it is possible to assess corneal endothelium permeability by means of non-invasive impedance measurements

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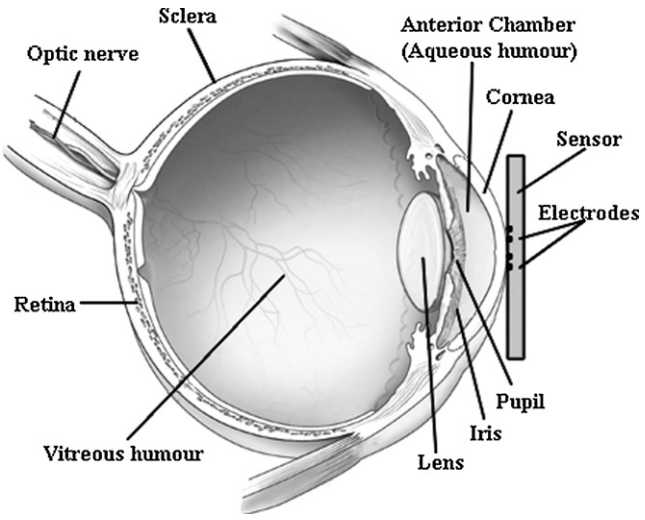

Fig. 1. Schematic representation of the ocular globe, which shows the location of the main parts and the position of the proposed sensor.

performed with electrodes placed on the surface of the cornea, as illustrated in Fig. 1. For analyzing the feasibility of the proposed method, and for finding which impedance parameters are better suited for such purpose, a numerical study has been carried out. This numerical study is based on simulations performed using the finite elements method (FEM); an electrical model of the main cornea layers was built and the corresponding electrical properties were selected from data reported in the literature. In particular, endothelial permeability was modeled as a variation of its conductivity. The simulated conductivity variations were based on experimental measurements made in a number of *in vitro* studies.

2. Methods

2.1. Simulation model

FEM modeling has been used for investigating the current and the potential distributions in the cornea in the case of impedance measurements made with the four-electrode method. In particular, modeling has been carried out by employing the commercial FEM tool COMSOL Multiphysics 3.4 and its associated application mode "Quasi-statics, Electric" of the "AC/DC module".

The four-electrode method here considered, compared to the more common two-electrode method, offers the advantage of minimizing, and ideally cancelling, the parasitic effects of the electrode–electrolyte interface impedances [13]. The impedance has been calculated using Ohm's law, $Z = V/I$. In the simulations, a constant AC current has been injected through the outer electrodes ($I+$ and $I-$) and the inner electrodes ($V+$ and $V-$) have been used to sense the voltage drop. The electrodes have been modeled with a very high conductivity (6×10^7 S/m) so that the voltage in all points of the electrode is the same. The outer boundaries of the model have been defined as electric insulation, in other words, no current can flow through them. These boundaries have been placed far enough from the electrodes (5 mm) so that it can be considered that the current density in this zone is very low and, therefore, the effect of the tissues located near these boundaries in the impedance measurements is negligible.

Fig. 3 shows the model used that is formed by the three main layers of the cornea and the electrodes, and takes into account the surrounding fluids like tear and aqueous humor. Assuming that the length of the electrodes is much greater than their width, only a vertical cross-section of the layers needs to be modeled [14]. This fact simplifies the computational model because it can be reduced in one dimension, from 3D to 2D. Using this model, a 2D analysis within frequency range from 10 Hz to 1 MHz has been carried out. Two sets of electrodes have been tried in this study, in order to find the better configuration for detecting changes in the passive electrical properties of the endothelium layer. Fig. 3 shows the geometry of the used electrode sets. In both electrode sets, the ratio of the separation between the electrodes is the same; it is the total sensor width that is different between both sets (3 mm and 5 mm). In particular, the distance between inner electrodes is three times larger than the separation between the outer electrodes. This ratio of distances offers some advantages in terms of spatial resolution [15,16]. The sensor width is related to the "penetration" of the measurement; it is advantageous to maximize this parameter in order to ensure that much of current goes through the endothelium layer. On the other hand, the sensor width is limited by the dimensions

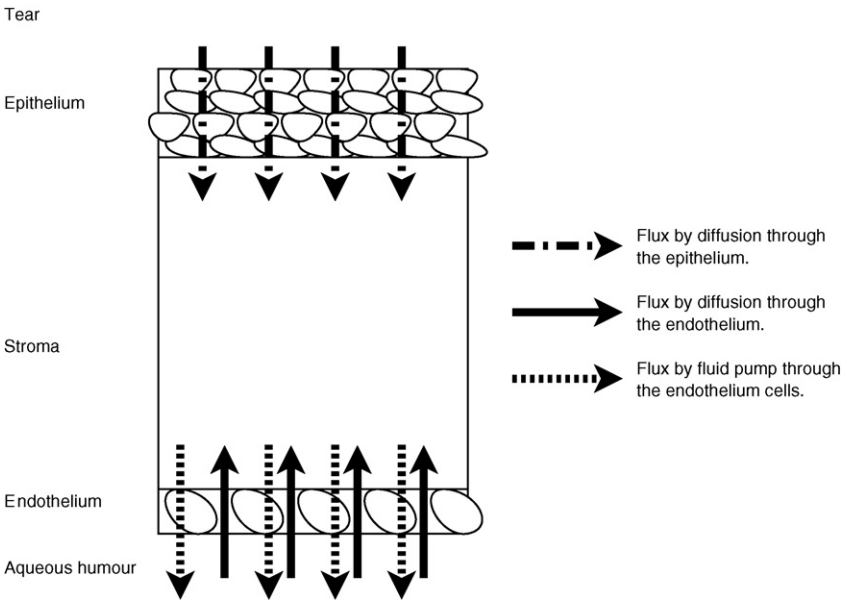

Fig. 2. Schematic representation of the main layers of the cornea and the main ion fluxes.