Medical Engineering & Physics 34 (2012) 195–201

Contents lists available at ScienceDirect

Medical Engineering & Physics

journal homepage: www.elsevier.com/locate/medengphy

Measurement of corneal endothelial impedance with non-invasive external electrodes – A theoretical study

Yossi Mandel*, Shlomi Laufer, Boris Rubinsky

Center for Bioengineering in the Service of Humanity and Society, The Selim and Rachel Benin School of Computer Science and Engineering, Edmond J. Safra Campus, Givat Ram, Jerusalem 91904, Israel

ARTICLE INFO

Article history:
Received 21 October 2010
Received in revised form 11 July 2011
Accepted 13 July 2011

Keywords:
Eye
Cornea
Endothel
Bio-electricity
Corneal transplant
Finite elements

ABSTRACT

The corneal endothelial cell layer function is critical for the maintenance of hydration and transparency of the cornea. Recent advances in corneal lamellar transplantation point to the need for reliable, non-invasive and rapid endothelial function assessment. Findings using an invasive electrode in an experimental animal model have suggested an association between bioimpedance parameters and endothelial cell function. Currently, however there is no clinical device that allows for non-invasive measurements of endothelial layer electrical impedance. This report is a finite element simulation study that models the human eye. It evaluates the feasibility of using external non-invasive electrodes to detect changes in endothelial layer electrical properties as a function of electrode location and measurement frequencies. The findings show that the ratio between the potential recorded at low and high frequencies is sensitive to changes in endothelial resistivity as well as endothelial capacitance. Moreover, the optimal electrode configuration yielding the highest sensitivity is one where the current injecting electrodes are oppose to each other and the voltage recording electrodes are adjacent to the current injecting electrodes. This first-order theoretical study suggests that a non-invasive device which measures electrical properties of the endothelial layer from the exterior of the eye could be developed. Clearly further animal and human studies are required to develop a reliable clinical tool.

1. Introduction

The cornea is the outer transparent layer of the eyeball. The optical interface between the air and the tear film layer covering the cornea forms the major refractive component of the optical system of the eye and accounts for about 70% of its total refractive power. The outermost layers of the cornea are formed by the epithelium, below which is the stroma, composed of type 4 collagen organized in a lamellar structure. The innermost layer is composed of endothelial cells with an average cell density of about 2500 cells per mm^2; it is responsible for maintaining the correct hydration of the stroma. The transparency of the cornea is crucial for its function and is dependent on the organization of the corneal lamellae and the status of corneal hydration [1–3].

The endothelial cell monolayer plays a dual role in the maintenance of the hydration and transparency of the cornea. First, it acts as a barrier which only partially restricts movement of water from the anterior chamber into the stroma. This allows for a constant slow flow of fluid (aqueous humor) into the corneal stroma across the endothelial monolayer. Second, the corneal endothelial cells have a unique function which enables them to pump fluids from the stroma back to the interior of the eye. Thus the maintenance of corneal thickness and transparency depends on the balance between fluid leakage and pump activity [4–6]. This leak-pump mechanism is related to the electrical current and potential across the endothelial cell membrane. Fischbarg and Maurice [5] suggested that there is a local recirculating electric current that causes fluid flow via the paracellular route.

Most of the currently available endothelial function evaluation methods were designed mainly for research and are not available for routine daily clinical use because they are time-consuming and cause patients discomfort. In one method, for instance, a contact lens is applied to the eye to induce hypoxemic corneal edema. The endothelial pump function is assessed in terms of the rate of corneal thickness recovery as measured by a pachometer (corneal thickness meter) [4]. The barrier function of the endothelial layer is estimated by evaluating the endothelial permeability. This is done by applying fluorescein dye to the cornea and measuring fluorescence in the aqueous humor [4]. This technique has several drawbacks and sources for measurement error such as the variability in epithelial layer permeability to fluorescein [7], or the effect of stromal pH [8,9]. Further, when endothelial permeability was measured there have been contradicting results when permeability was unexpectedly found to be high in older normal [10] and low in transplanted

* Corresponding author. Tel.: +972 578133986; fax: +972 37376852.
E-mail address: yossimandel@bezeqint.net (Y. Mandel).

1350-4533/$ – see front matter © 2011 IPEM. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.medengphy.2011.07.010

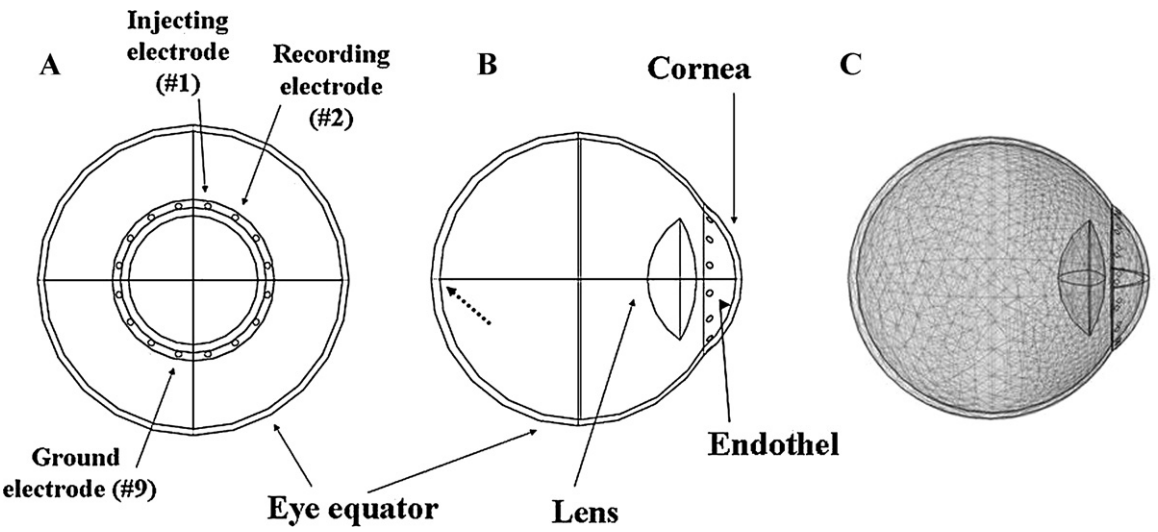

Fig. 1. (A) Anterior–posterior projection of the eye model with the sixteen electrodes located in the limbus (corneal–scleral junction) numbered sequentially. (B) Lateral view of the eye model. Arrow points to macular point. (C) Meshed model of the eye consisting of 20,928 elements.

corneas with low endothelial cells density [7]. A morphological evaluation of endothelial cells can be carried out under a specular microscope, which makes it possible to calculate cell density and cell size as well as other morphological features. Recent advances in endothelial cell surgery will increase the need for non-invasive measurement of endothelial function. Progress in corneal transplant now enables endothelial layer transplantation rather than transplantation of the full thickness of the cornea [11,12]. Moreover, there are reports of transplantation of corneal endothelial cells without the Descement's membrane [12].

One promising candidate for evaluating the endothelial function is bioimpedance. Bioimpedance analysis covers a family of methods in which an electrical field is applied to a tissue to determine its impedance. This non-invasive method can assess various changes in tissue structure or various physiological changes such as blood flow, ischemia, etc. Bioimpedance is used routinely to measure body fluids [13]. In particular, there are several reports of a correlation between bioimpedance parameters and endothelial cell function. DePaola et al. [14] found a change in the electrical resistivity and capacitance of cultured bovine aorta endothelial cells when they were exposed to shear stress of fluidic flow. Rutten et al. [15] found an association between various types of endothelial resistivity and their permeability. Other studies have reported an association between various types of endothelial layer electrical properties and morphological or functional characteristics [16–18]. Moreover, there are published data [19] that the electrical properties of the corneal endothelium are sensitive to biochemical changes which also affect its function. For example, when bicarbonate, which is essential to cell function, was removed from the medium, the resistivity was reduced. This effect was partially reversible upon bicarbonate replacement. The authors reasoned that intercellular width is affected by the functional state of the endothelial cells and thus alters the electrical resistivity [20].

Overall, these results suggest that bioimpedance measurements of the cornea have the potential to evaluate the function of the endothelium. However the insertion of an intraocular electrode into the cornea is unfeasible in routine clinical use. The theoretical analysis presented here was designed to evaluate whether externally applied electrodes can detect changes in the electrical properties of the corneal endothelial layer, and to determine the best electrode configuration to increase the sensitivity of the reading. Preliminary results of this work were first presented in ARVO 2008 [21].

2. Methods

2.1. Eye modeling and analysis

COMSOL version 3.3 (Stockholm, Sweden) was used to study the effects of electrical fields generated by electrodes in contact with a realistic model of the eye. A three-dimensional model of the eye was constructed according to ocular dimensions reported in the literature [22]. Corneal radius and thickness were 7.8 mm and 0.5 mm, respectively. Eyeball radius was 12 mm. Since endothelial layer thickness is significantly smaller (about 5–7 μm) than the corneal thickness, the endothelial layer was modeled as a surface resistance, without geometrical thickness.

The model incorporated sixteen electrodes evenly placed around the limbus (the junction between the cornea and the eyeball). Due to the symmetry of the electrode configuration one of the current injecting electrode (electrode #1) was placed in a fixed position (Fig. 1) while the other current injecting electrode was the opposing electrode #9. The recording electrodes were placed in various positions in each simulation to find the optimal electrode configuration yielding the highest sensitivity. The injecting electrodes were assumed to have no resistance and no capacitance while it was assumed that there was no current flow in the recording electrodes, i.e. ideal electrodes. The eye model was meshed into a model consisting 20,928 elements. Fig. 1A–C depict the geometrical properties of the eye model, the electrodes, and the meshed model. The electrical properties of the ocular structures were taken from an online database [23] based on the extensive work of Gabriel and Gabriel (Gabriel et al., 1996, 1983) [33,34]. The electrical properties of the endothelial layer were based on experimental work by Lim and Fischbarg [19] who developed an electrical model of the corneal endothelium of rabbit eyes. In this model, the endothelial electrical bioimpedance can be modeled into the lumped electrical circuit depicted in Fig. 2. The model assumes that the endothelial cell membranes behave like an electrical capacitor in parallel with a resistor. Another resistor represents the paracellular electrical conductivity and is probably dependent on endothelial function. We calculated the electrical conductivity and relative permittivity of the endothelial layer in 8 frequencies (10 Hz, 1 kHz, 3 kHz, 10 kHz, 30 kHz, 100 kHz, 300 kHz, 1 MHz) using the SPICE program based on this electrical model. The endothelial layer conductivity was modeled as a surface conductivity using the distributed impedance boundary condition. Table 1 [23] depicts the electrical conductivity