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● *Original Contribution*

SHORT- AND LONG-TERM EFFECTS ON THE CILIARY BODY AND THE AQUEOUS OUTFLOW PATHWAYS OF HIGH-INTENSITY FOCUSED ULTRASOUND CYCLOCOAGULATION

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Abstract—Several physical methods can be used to coagulate the ciliary body and decrease intra-ocular pressure in patients with glaucoma. The study described here investigated the short- and long-term effects of high-intensity focused ultrasound (HIFU) cyclocoagulation on the aqueous humor production structures and outflow pathways. Thirty-four rabbit eyes were sonicated with a ring-shaped probe containing six miniaturized HIFU transducers. Light, scanning electron and transmission electron microscopy and corrosion casts were performed. In the affected regions, the epithelium of the ciliary processes was degenerated or necrotic and sloughed off. Examinations performed several months afterward revealed involution of the ciliary processes. Vascular corrosion cast revealed focal interruption of the ciliary body microvasculature. In most animals, a sustained fluid space was seen between the sclera, the ciliary body and the choroid, likely indicating an increase in the aqueous outflow by the uveoscleral pathway. These results suggest that HIFU cyclocoagulation has a dual effect on aqueous humor dynamics. (E-mail: faptel@chu-grenoble.fr)

Key Words: **High-intensity focused ultrasound, Ciliary body, Aqueous outflow, Glaucoma, Histopathology, Scanning electron microscopy, Corrosion cast, Intravascular latex injection.**

INTRODUCTION

Many methods and energy sources for destroying ciliary processes that result in coagulation necrosis of the ciliary body after heating (laser, microwave) or freezing (cryotherapy) have been investigated (Al-Ghamdi et al. 1993; De Roetth 1965; Hamard et al. 1997; Kosoko et al. 1996; Maus and Katz 1990; Sabri and Vernon 1999; Uram 1992; Vernon et al. 2006). All these methods have two major drawbacks that limit their clinical use. First, they are non-selective of the organ to be treated, often resulting in damage to adjacent structures and ocular inflammation. Laser energy is absorbed mainly by pigmented tissues and, therefore, can also damage the iris and the choroid. Cryotherapy and cyclodiathermy also result in a large area of treatment with unpredictable dimensions. Second, these methods have an unpredictable dose–effect relationship, which prevents accurate prediction of the treatment effect. Published studies report a 6% to 64.3% risk of visual acuity decrease, 0.5% to 37.5% risk of ocular phthisis, 12.4% to 27% risk of chronic inflammation, 2% to 6% risk of corneal dystrophy, 10% to 35% risk of cataract formation and 12.9% to 80% risk of failure 1 y after the procedure (Al-Ghamdi et al. 1993; De Roetth 1965; Hamard et al. 1997; Kosoko et al. 1996; Maus and Katz 1990; Sabri and Vernon 1999; Uram 1992; Vernon et al. 2006).

To overcome the drawbacks of current and past methods of cyclodestruction, and taking advantage of recent breakthroughs in the field of high-intensity focused ultrasound (HIFU) technology, a new device was recently developed with the aim of achieving selective and precise destruction of the ciliary body and sparing the adjacent ocular structures (Aptel and Lafon 2012; Aptel et al. 2010, 2011; Charrel et al. 2011). In the first animal study designed to evaluate the feasibility and safety of the method, we treated rabbits using this device and then performed histologic examinations of the anterior

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segment focused on the ciliary body and ciliary processes (Aptel et al. 2010). We observed selective and circumferentially distributed coagulation necrosis of the ciliary processes and ciliary body. The bilayered epithelium was degenerated or necrotic and sloughed off in the distal parts of the most affected areas. The sclera from all treated areas appeared normal with no signs of thinning or necrosis. We therefore hypothesized that the decrease in intra-ocular pressure (IOP) after ultrasound cyclocoagulation is due mainly to a reduction in aqueous humor production by the ciliary body. Clinical studies were then started in patients with refractory glaucoma (Aptel et al. 2011; Aptel and Lafon 2012), with ultrasound biomicroscopy examinations of the treated eyes before and after treatment. In the pilot human study, cystic involution of the ciliary body was observed in 9 of the 12 eyes, with multiple hypo-echoic ovoid cystic cavities. Hyporeflective suprachoroidal fluid space was observed in 8 of the 12 eyes. Patients with hypo-reflective suprachoroidal space had significantly lower IOP than those without visible suprachoroidal space. We supposed that this may indicate increased uveoscleral outflow through the supraciliary and suprachoroidal space.

Many mechanisms have been advanced to explain IOP reduction after cyclodestruction or cyclophotocoagulation in previously published studies, including destruction of the pigmented and non-pigmented epithelium resulting in reduced aqueous production, vascular depletion of the ciliary body, ciliary body inflammation, enhanced uveoscleral outflow caused by changes in the ciliary body stroma and damage to the pars plana (Aptel and Lafon 2012; Blasini et al. 1990; Ferry et al. 1995; Liu et al. 1994; Schubert and Federman 1989). The present study was therefore conceived to qualitatively investigate by histologic studies the possible short- and long-term effects of high-intensity focused ultrasound cyclocoagulation on the aqueous humor production structures and aqueous outflow pathways.

METHODS

High-intensity focused ultrasound device, procedures and follow-up

The HIFU device was previously described in detail (Aptel et al. 2010; Charrel et al. 2011). A coupling cone made of polymer was placed in direct contact with the eye, which allowed good placement of the transducers in terms of centering and distance. At the base of the coupling cone, a suction ring allowed the application of a low-level vacuum and enabled the cone to maintain contact with the eye. A 30-mm-diameter, 15-mm-high ring containing six active piezoelectric elements was inserted in the upper part of the coupling cone (Fig. 1). The cavity created between the eye, the cone and the probe (5 mL) was filled through the central aperture of the device with room temperature saline solution. Each of the six transducers was a segment of a 10.2-mm-radius cylinder with a 4.5-mm width and a 7-mm length. The focal volume of each transducer had approximately an elliptic cylinder shape. The six transducers were placed at regular intervals on the upper and inferior circumference of the ring, avoiding the nasal and temporal meridians, and were oriented to create a focal zone consisting of six regularly distributed elliptical cylinder-shaped volumes. The six elliptical cylinder-shaped volumes were centered on a 12-mm-diameter circle, adapted to the anatomy of the rabbit ciliary body. The transducers were operated at the frequency of 21 MHz. The ring was connected to a control module, which allowed each sector to be sequentially activated according to a program defined by the operator.

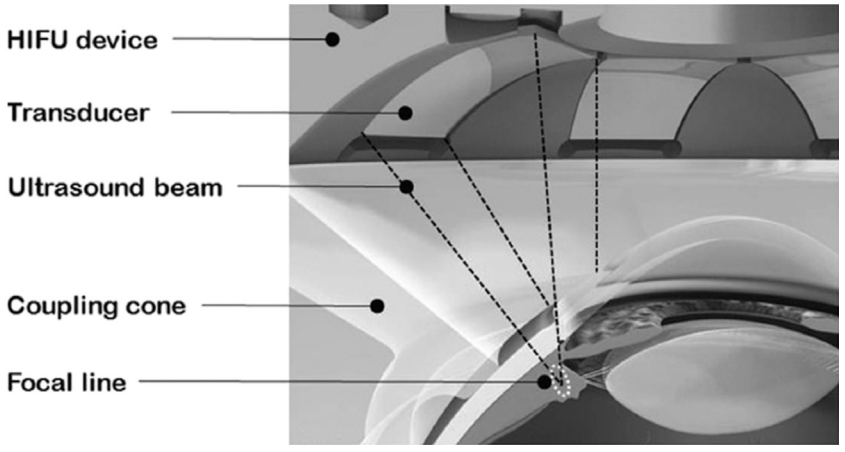

Fig. 1. Schematic cross section of the device and the coupling cone. HIFU = high-intensity focused ultrasound.