

# Treatment of refractory open-angle glaucoma using ultrasonic circular cyclocoagulation: a prospective case series

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UNIVERSITE JOSEPH FOURIER  
FACULTE DE MEDECINE DE GRENOBLE

Année : 2014

N°

**TREATMENT OF REFRACTORY OPEN-ANGLE GLAUCOMA USING  
ULTRASONIC CIRCULAR CYCLOCOAGULATION: A PROSPECTIVE CASE  
SERIES**

**THESE**  
PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE  
DIPLOME D'ETAT

**Caroline DUPUY**

Née le 25 novembre 1985

A TOULON, France

THESE SOUTENUE PUBLIQUEMENT A LA FACULTE DE MEDECINE DE GRENOBLE

Le jeudi 16 octobre 2014

DEVANT LE JURY COMPOSE DE

Président du jury : Monsieur le Professeur Jean-Paul ROMANET

Directeur de thèse : Monsieur le Professeur Florent APTEL

Membres : Monsieur le Professeur Christophe CHIQUET

Monsieur le Docteur Fabrice ROMANO



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**Treatment of Refractory Open-Angle Glaucoma using Ultrasonic  
Circular Cyclocoagulation: a Prospective Case Series**

## **ABSTRACT**

**Objective:** To evaluate the efficacy and safety of the Ultrasonic Circular Cyclo Coagulation (UC<sup>3</sup>) procedure in patients with refractory primary open-angle glaucoma.

**Research design and methods:** Prospective non-comparative interventional case series performed in 2 French glaucoma centers. 28 eyes of 28 patients with primary open-angle glaucoma, intraocular pressure (IOP) > 21 mmHg, an average of 1.4 failed previous surgeries and an average of 3.8 hypotensive medications were insonified with a therapy probe comprising 6 piezoelectric transducers. The 6 transducers were activated and all patients were treated with a 6 seconds exposure time. Complete ophthalmic examinations were performed before the procedure, and at 1 day, 1 week, 1, 2, 3, 6 and 12 months after.

**Main outcome measures:** Primary outcomes were surgical success (defined as IOP reduction from baseline  $\geq 20\%$  and IOP > 5mmHg) at the last follow-up visit, and vision-threatening complications. Secondary outcomes were mean IOP at each follow-up visit compared to baseline, medication use, complications, and re-interventions.

**Results:** IOP was significantly reduced ( $p < 0.05$ ), from a mean preoperative value of  $29.0 \pm 7.2$  mmHg ( $n = 3.8$  hypotensive medications) to a mean value of  $21.6 \pm 9.4$  mmHg at last follow-up ( $n = 3.8$  hypotensive medications and  $n = 1.29$  procedures) (mean IOP reduction of 26%). Complete success (IOP reduction >20% without re-intervention and without hypotensive medications adjunction) was achieved in 50% of eyes at last follow-up (mean IOP reduction of 45% in these same eyes) and qualified success (IOP reduction >20% with possible re-interventions) was achieved in 68% of eyes at last follow-up. No major intra- or post-operative complications occurred.

**Conclusions:** UC<sup>3</sup> procedure seems to be an effective and well-tolerated method to reduce intraocular pressure in patients with primary open-angle glaucoma.



## INTRODUCTION

Many methods and energy sources for destroying the ciliary processes have been investigated, resulting in coagulation necrosis of the ciliary body following heating (laser, microwave) or freezing (cryotherapy)<sup>1-8</sup>. All these methods have two major drawbacks which limit their clinical use. Firstly, they are non-selective of the organ to be treated, often resulting in damage to the adjacent structures and ocular inflammation. Laser energy is mainly absorbed by the pigmented tissues, and therefore can also damage the iris and the choroid. Cryotherapy and cyclodiathermy also result in a large area of treatment having unpredictable dimensions. Secondly, 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 one year after the procedure<sup>1-8</sup>.

To overcome the drawbacks of the 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, the aim being to achieve a selective and precise destruction of the ciliary body, and sparing the adjacent ocular structures<sup>9-12</sup>. In the first human pilot study designed to evaluate the feasibility and safety of the method, conducted in patients with refractory and very advanced secondary glaucoma (neovascular, congenital, uveitic, aphakic), twelve patients were enrolled and followed during at least one year<sup>12</sup>. No complications occurred during the treatment. Intraocular pressure (IOP) was significantly reduced from a mean preoperative value of  $37.9 \pm 10.7$  mmHg to a mean postoperative value of  $27.3 \pm 12.4$ ,  $25.2 \pm 11.3$ ,  $25.2 \pm 7.7$ ,  $24.8 \pm 9.8$ , and  $26.3 \pm 5.1$  mmHg

at 1 day, 1 week, 1, 3 and 6 months respectively, and to a mean value of  $24.7 \pm 8.5$  at the last follow-up visit. An IOP reduction of 33.9% was obtained at the last follow-up visit. No major intra- or post-operative complications occurred.

Subsequent to the first human pilot study, the device obtained CE approval to treat refractory glaucoma (at least one previous failed filtering surgery). The present study was designed and conducted to evaluate the efficacy and safety of ultrasonic circular cyclocoagulation in patients with primary open-angle glaucoma and less advanced disease than those treated in the pilot study.

## **PATIENTS AND METHODS**

This study was designed, conducted, and reported according to the World Glaucoma Association guidelines on the design and reporting of glaucoma surgical trials.<sup>13</sup>

### **HIFU device**

The HIFU device has been previously described in detail.<sup>9-12</sup> A coupling cone made of polymer is placed in direct contact with the eye, which allows good placement of the transducers in terms of centration and distance. At the base of the coupling cone, a suction ring allows the application of a low-level vacuum and enables the cone to maintain contact with the eye. A 30-mm diameter, 15-mm high ring containing six active piezoelectric elements is inserted in the upper part of the coupling cone. The cavity created between the eye, the cone, and the probe (4 mL) is filled with room temperature saline solution (BSS,

Alcon Inc., Fort Worth, TX). Three device models with different ring diameters, equipped with the six transducers, are available. Depending on the diameter, the six elliptical cylinder-shaped impacts were centered on an 11 mm, 12 mm, or 13 mm diameter circle and spread over the circumference of the eye while avoiding the nasal-temporal meridian. In each patient, the ring model whose focal zones actually matched the ciliary body was determined by ultrasound biomicroscopy (UBM) imaging of the anterior segment performed at baseline. The location of the focal zones was simulated using the UBM images, and the model that best targeted the ciliary body was chosen.<sup>11</sup>

## **Patients**

We conducted this prospective pilot investigation in two university-affiliated glaucoma centers. The clinical trial protocol was submitted to an institutional review board (IRB #5891). As all patients were treated and followed as done in routine clinical practice with this device, the institutional review board stated that ethical approval was not required. The study followed the tenets of the Declaration of Helsinki and was conducted in conformity with the standards of ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects). All patients provided both verbal and written informed consent. Inclusion criteria were men or women aged 18 years or older; diagnosis of refractory primary open-angle glaucoma with at least one previous incisional glaucoma surgery or poor candidates to glaucoma filtering surgery; average baseline IOP of 21 mm Hg or more while on maximally tolerated medical treatment. Exclusion criteria were pregnancy; concomitant systemic medications that could affect IOP; diagnosis of normal tension glaucoma; history of refractive surgery, retinal detachment or ocular tumor; intraocular surgery or laser within the past month; and ocular infection in the past 2 weeks.

## **Procedures and Follow-up**

Baseline evaluation included best-corrected visual acuity; slit lamp biomicroscopy with gonioscopy and mydriatic fundus examination, Goldmann applanation tonometry with three measurements, ultrasound pachymetry, visual field when applicable, and UBM. Visual field was performed using an automated diagnostic system (Humphrey Field Analyzer; 24–2 SITA-standard program; Carl Zeiss Meditec, Dublin, CA), and UBM with a 50-MHz probe (Aviso; Quantel Medical, Clermont-Ferrand, France). For UBM, radial and transverse scans were obtained at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315° meridians.<sup>11</sup>

All HIFU procedures were performed by two authors (FA, JFR) under topical (n = 3), peribulbar (n = 14), or general (n = 11) anesthesia, depending on patient and physician preferences. The following parameters were used: aspiration (external), 150 mm Hg; operating frequency, 21 MHz; number of sectors activated, 6; acoustic power, 2.45 W; duration of each of the six shots, 6 seconds and time between each shot, 20 seconds. Postoperatively, patients were treated topically with tobramycin and dexamethasone (Tobradex; Alcon Inc., Fort Worth, TX), four times a day for 4 weeks. Preoperative hypotensive medications were maintained unchanged throughout the course of the study, without any washout period before the baseline IOP measurements.

Best-corrected visual acuity, slit lamp biomicroscopy with mydriatic fundus examination, and Goldmann applanation tonometry were performed postoperatively at 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months. Ultrasound biomicroscopy was performed postoperatively at 1 week, 1 month, and 3 months. All IOP measurements were taken at the same time of day as the preoperative IOPs.

## **End points and Statistical analysis**

Primary outcomes were surgical success at the last follow-up visit, and vision-threatening complications. Complete success was defined as IOP reduction from baseline  $\geq 20\%$  and IOP  $> 5\text{mmHg}$  without re-intervention and without hypotensive medications adjunction. Qualified success was defined as IOP reduction from baseline  $\geq 20\%$  and IOP  $> 5\text{mmHg}$  with possible re-intervention. Vision-threatening complications were the number of standardized severe complications defined in the World Glaucoma Association guidelines on the design and reporting of glaucoma surgical trials.<sup>13</sup> Secondary outcomes were mean IOP at each follow-up visit compared to baseline, medication use, complications, and re-interventions.

Student's t-test was used to compare means and percentages, and  $X^2$  tests were used for the analysis of dichotomous variables. Statistical significance was set at  $P < 0.05$ . Statistical software (SPSS version 17.0; SPSS, Inc., Chicago, IL) was used for data analysis.

## **RESULTS**

### **Patients characteristics**

Patients characteristics are summarized in Table 1. Twenty-eight patients were enrolled, treated and followed at least up to the 6-month visit. Mean follow-up time was  $9.3 \pm 3.1$  months [Range: 6 – 12 months].

### **Efficacy**

Mean and relative intraocular pressure reductions from baseline of each follow-up are shown in Table 2. Complete surgical success was achieved in 14 of 28 (50%) patients at the last

follow-up visit. Qualified surgical success was achieved in 19 of 28 (68%) patients at the last follow-up visit. Graphs showing IOP reduction in all patients and responders patients (qualified success) over time are displayed in Figure 1. Scattergrams of postoperative versus preoperative IOP in all patients at 6 months and at the last follow-up are shown in Figure 2.

## **Safety**

No complications occurred during any of the procedures. One patient presented a serious choroidal detachment which did not reach the posterior pole seven days after treatment, with complete resolution at two months. No other major intraoperative or postoperative complications occurred. None of the patients encountered IOP spikes or major IOP increases in the early follow-up (IOP > baseline IOP + 10 mm Hg in the first 7 days). Clinical examinations showed little or no signs of intraocular inflammation, particularly with no cases of hypopyon or anterior or posterior synechia.

Mean visual acuity remained statistically unchanged (best-corrected visual acuity logMAR  $0.84 \pm 1.09$  before surgery and logMAR  $1.09 \pm 1.20$  at last follow-up;  $P = 0.42$ ). Visual acuity loss of 3 lines or more was observed in four patients (15.4%).

Superficial punctate keratitis occurred in 13 of 28 patients (46.4%) and central superficial corneal ulceration in 3 of 28 patients (10.7%). Other minor postoperative complications are listed in Table 3.

## DISCUSSION

The initial pilot study conducted with the device for ultrasound circular cyclocoagulation was performed in patients with refractory primary or secondary glaucoma (at least one previous incisional glaucoma surgery) and a limited residual visual acuity and visual field (best-corrected visual acuity less than 20/60; and visual field defect with a minimum of one location in the paracentral region exhibiting repeatable abnormality at the  $P < 0.5\%$  level).<sup>11</sup> Patients included had primary open-angle glaucoma, neovascular glaucoma, congenital glaucoma, primary angle-closure glaucoma and iridocorneal endothelial glaucoma. IOP was reduced from a mean preoperative value of  $37.9 \pm 10.7$  mmHg to a mean postoperative value of  $26.3 \pm 5.1$  mmHg at 6 months and  $24.7 \pm 8.5$  mmHg at the last follow-up visit, respectively. An IOP reduction of 33.9% was obtained at the last follow-up visit. Surgical success (defined by an IOP reduction greater than or equal to 20% and an IOP more than 5 mmHg) was obtained in 10 of 12 patients (83.3%) at the last visit.

In the present case-series, twenty-eight patients with primary open-angle glaucoma and much less advanced disease were enrolled and followed during at least 6 months. Results between these two studies in terms of efficacy (mean IOP reduction and rate of responders) and safety were rather similar. IOP was reduced from a mean preoperative value of  $29.0 \pm 7.2$  mmHg to a mean value of  $21.6 \pm 9.4$  mmHg at last follow-up. Qualified success (IOP reduction  $>20\%$  and IOP  $> 5$  mmHg with possible re-treatment) was achieved in 68% of eyes, with an average IOP decrease of 45% in the same eyes. One reason explaining the slightly better results of the pilot study compared to the present study could be that one fourth of the patients of the pilot study had had diode laser cyclocoagulation procedures prior to having ultrasound cyclocoagulation, likely leading to a more significant IOP decrease, whereas only 1/28

patients of the present study had had diode laser cyclocoagulation before ultrasound treatment. One other reason could be the small number of patients included in the pilot study (n=12), making the observed results more sensitive to IOP variability. The tolerability was also good in the present study, as reported in the pilot study, with no IOP spikes or major IOP increases in the early follow-up and, in the long term no cases of severe hypotony or phthisis, which are some of the most serious adverse effects of the currently available cyclodestructive methods.<sup>1-8</sup> Clinical examinations showed little or no signs of intraocular inflammation and visual acuity remained statistically unchanged.

This study could help to define the optimal indications of this new method of treatment. The results, particularly the good intraoperative safety profile and postoperative tolerability, likely indicate that this new method of cyclocoagulation using ultrasound may be indicated in eyes refractory to one or several filtering surgeries, but with visual acuity and a visual field still relatively unaffected. In these eyes, where surgery may no longer be a valid option, physicians are sometimes prone to rule out the use of the current methods of cyclocoagulation, including diode laser, because of the possible side effects and the poor predictability of the IOP decrease.

Approximately one-third of patients of the present study do not respond to the treatment, with usually no IOP reduction. Several reasons can be advanced to explain the complete absence of IOP reduction in some cases. One explanation may be that the amount of ciliary body tissue coagulated was not sufficient or was offset by an increased secretion of the ciliary body remaining intact. One other reason could be that the ciliary body targeted was not actually reached by the ultrasound beam during the procedure due to, possibly, an incorrect preoperative calculation of the diameter of the probe to be used (e.g. UBM scans not passing



through the apex of the cornea or partially oblique scans instead of perfectly radial scans, leading to an underestimated size of the ciliary ring and thus the required probe), or due to suboptimal intraoperative centering or moving of the device (which is positioned and maintained manually by the operator), or because of excessive pressure exerted on the coupling cone on the eye during the procedure with consequent deformation of the sclera and the ciliary body below.

Some patients having an IOP response insufficient to reach the target IOP were retreated in the present study. The six transducers were activated and the probe was rotated with the intention of targeting different areas of the ciliary body. The diameter of the probe was generally unchanged for the second treatment (n = 6/8 eyes retreated without diameter change, 1/8 increased, 1/8 reduced). IOP decrease was frequently significant after the retreatment (n = 5/8 eyes retreated were complete successes). This finding could corroborate the hypothesis that the amount of ciliary body tissue treated during the first procedure was not sufficient and/or that the position of the device was not optimal.

A second large multicenter study evaluating the long-term efficacy and safety of this procedure on a larger number of patients having less advanced open-angle glaucoma is currently in progress (clinicaltrial.gov registration # NCT01338467).<sup>14</sup> As the tolerability and safety profile of this new method of cyclocoagulation is good, it also seems logical to compare it to filtering surgery as a second line treatment, after medical treatment. At the time of writing, a third clinical trial is ongoing in patients with primary open-angle glaucoma uncontrolled with medical treatment and naïve of any glaucoma filtering surgery (clinicaltrial.gov registration # NCT01791673). In the future, randomized controlled clinical

trials should also be conducted to directly compare the efficacy and safety of HIFU cyclocoagulation with that of trabeculectomy or diode laser.

## **CONCLUSIONS**

In summary, the present case-series study shows that ultrasonic coagulation of the ciliary body using high-intensity focused ultrasound delivered by miniaturized high-frequency transducers seems to be an effective method of reducing IOP in patients with open-angle glaucoma refractory to filtering surgeries but still having a good residual visual acuity and visual field . The procedure seems to be safer than other previous available cyclodestructive procedures.

THESE SOUTENUE PAR : DUPUY Caroline

**TITRE : Treatment of Refractory Open-Angle Glaucoma using Ultrasonic Circular  
Cyclocoagulation: a Prospective Case Series**

CONCLUSION

La cyclocoagulation par ultrasons focalisés de haute intensité semble être une méthode efficace et bien tolérée pour réduire la pression intraoculaire chez les patients présentant un glaucome primaire à angle ouvert réfractaire aux chirurgies filtrantes.

Cette méthode permet une réduction de la pression intraoculaire moyenne de 45% dans 68% des cas.

Une étude prospective est actuellement en cours, étudiant l'efficacité et la tolérance de cette méthode chez les patients présentant un glaucome primaire à angle ouvert non contrôlé par les traitements médicaux et naïfs de toute chirurgie filtrante.

VU ET PERMIS D'IMPRIMER  
Grenoble, le 18-08-2014 -

LE DOYEN



J.P. ROMANET

LE PRESIDENT DE LA THESE



PROFESSEUR J.P. ROMANET

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## FIGURE CAPTIONS

**Figure 1.** Graphs showing IOP reduction (mean  $\pm$  standard deviation) and the mean number of procedures performed in all patients (up) and responder patients (qualified success) (down) over time.

**Figure 2.** Scattergrams showing the IOP before ultrasonic circular cyclocoagulation *versus* at 6 months (top) and at last follow-up (bottom) for all patients. All points below the diagonal line represent eyes in which there was a decrease in IOP. All points below the dashed line represent eyes in which IOP reduction was reduced by at least 20% from the preoperative value.

**Figure 3.** UBM examinations taken at month 3 showing two ultrasound- induced lesions in the superior (A) and inferior (B) circumference of one patient with complete success. Note that the areas of treatment are located at the junction between the sclera and the base of the ciliary body.

## TABLES

**Table 1.** Demographic characteristics.

Age (yrs): Mean (SD) [Range]	65.1 ± 11.1 [31-85]
Gender (Male/Female)	17 / 11
Previous glaucoma surgery: total number of procedures	
- Trabeculectomy/ Deep sclerectomy	39 / 28
- Diode cyclo-photocoagulation	1 / 28
- Cataract with IOL	13 / 28
Preoperative hypotensive therapies: number of patients	
- Beta-blockers	27/28
- Prostaglandin analogues	25/28
- Topic carbonic anhydrase inhibitors	20/28
- Systemic carbonic anhydrase inhibitors	10/28
- Alpha-2-adrenergic agonists	14/28
- Myotics	1/28

Number of Preoperative hypotensive therapies: Mean (SD) [Range]	3.8 ± 1.6 [0-7]
Follow-up (months): Mean (SD) [Range]	9.3 ± 3.1 [6-12]*

SD, standard deviation. IOL, intraocular lens. MD, mean deviation.



**Table 2.** IOP at baseline and during follow-up with number of procedures and hypotensive medications.

	All patients			Responders patients (Qualified Success)		
	Mean IOP (no. patients) [Mean Glaucoma Medication]	Relative IOP Reduction (%)	Mean UC3 procedure	Mean IOP (no. patients) [Mean Glaucoma Medication]	Relative IOP Reduction (%)	Mean UC3 procedure
Baseline	29.0 ± 7.2 (28) [3.8]	NA	NA	29.0 ± 7.2 (28) [3.8]	NA	NA
Day 1	20.6 ± 6.6 (24) [3.9]	-29	1.00	18.6 ± 5.9 (19) [3.7]	-36	1.00
Day 7	16.9 ± 7.9 (28) [3.8]	-42	1.00	14.5 ± 4.0 (25) [4.1]	-50	1.00
Month 1	19.4 ± 9.2 (27) [4.0]	-33	1.00	16.4 ± 5.9 (23) [4.0]	-43	1.00
Month 3	21.3 ± 10.2 (28) [3.6]	-27	1.11	15.5 ± 4.6 (16) [3.7]	-47	1.11
Month 6	19.3 ± 7.2 (22)* [3.7]	-34	1.18	17.0 ± 4.1 (19) [3.8]	-41	1.18
Month 12	15.6 ± 4.9 (12)**	-46	1.29	15.6 ± 4.9 (12) [4.3]	-46	1.29

	[4.4]					
Last FU <sup>[x]</sup>	21.6 ± 9.4 (28)	-26	1.29	16.0 ± 4.3 (19)	-45	1.29
	[3.8]			[3.8]		

*NA = not applicable*

*\*6 patients withdrew from the study because of the glaucoma surgery (5 patients) and Diode Laser (1 patient) performed less than 6 months after the UC3 procedure*

*\*9 patients withdrew from the study because of the glaucoma surgery (7 patients) and Diode Laser (2 patients) performed less than 12 months after the UC3 procedure, 1 patient died, 6 patients not already controlled at 12 months.*

*[x] data at 6 or 12 months follow-up, or for patients withdrew from the study, last IOP measure.*

**Table 3.** Details of postoperative complications.

Description	Number of eyes
Conjunctival hyperhemia	19/28
Superficial punctate keratitis	13/28
Tyndall	5/28
Corneal edema	3/28
Chemosis	2/28
Scleral thinning	2/28
Sub-conjunctival hemorrhage	1/28
Corneal ulcer	1/28
Choroidal detachment	1/28

Figure 1a and 1b.

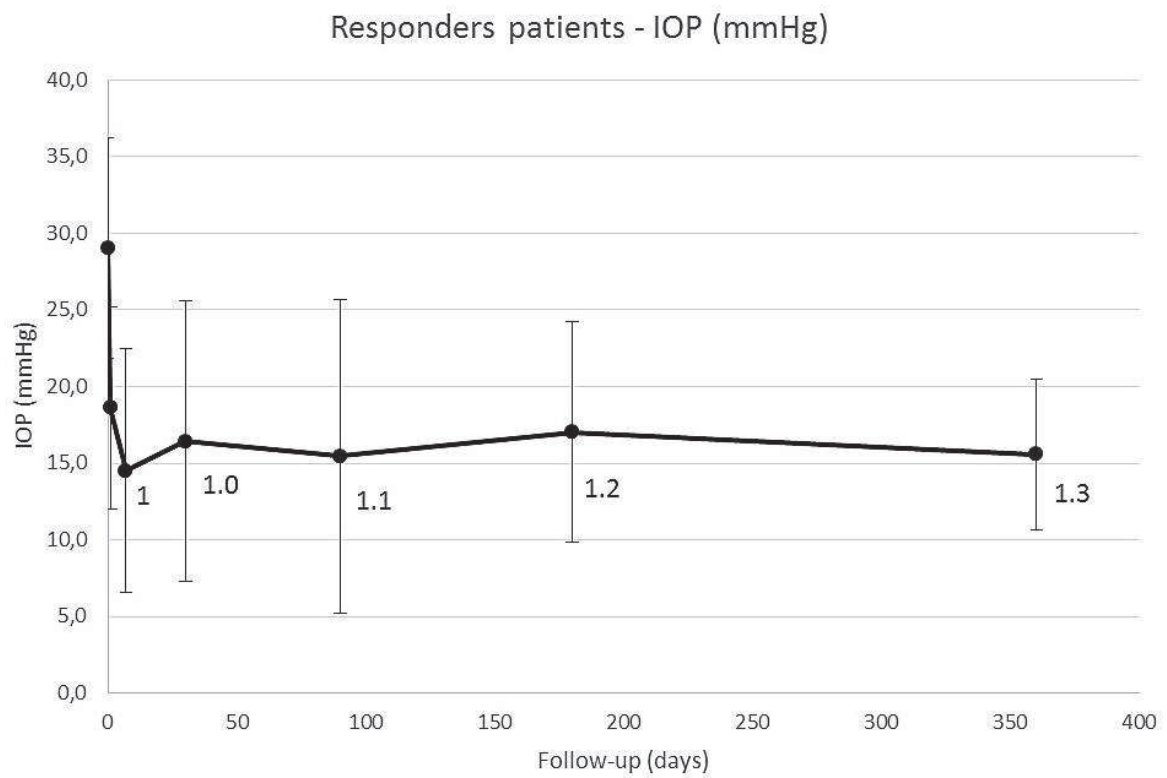
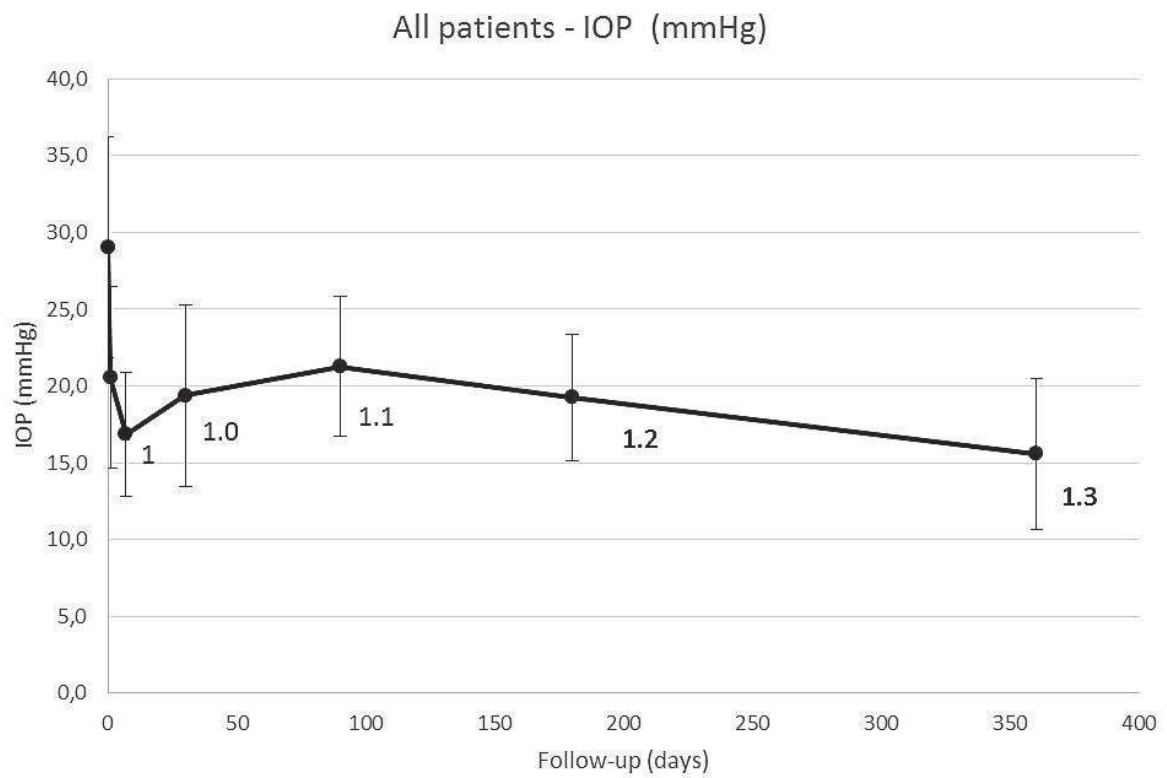


Figure 2a and 2b.

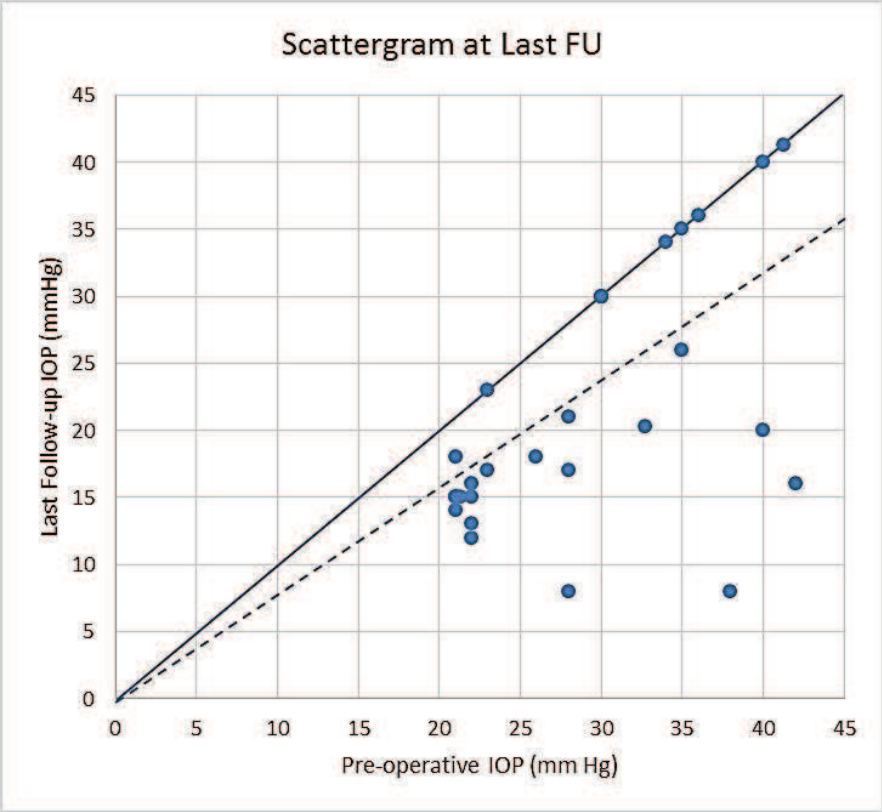
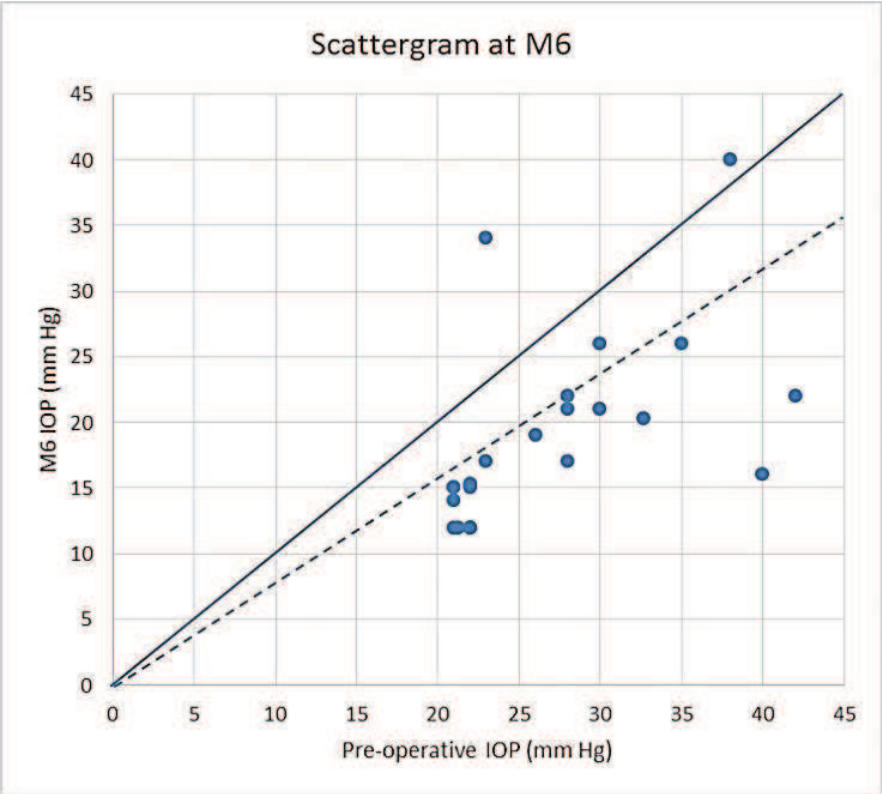
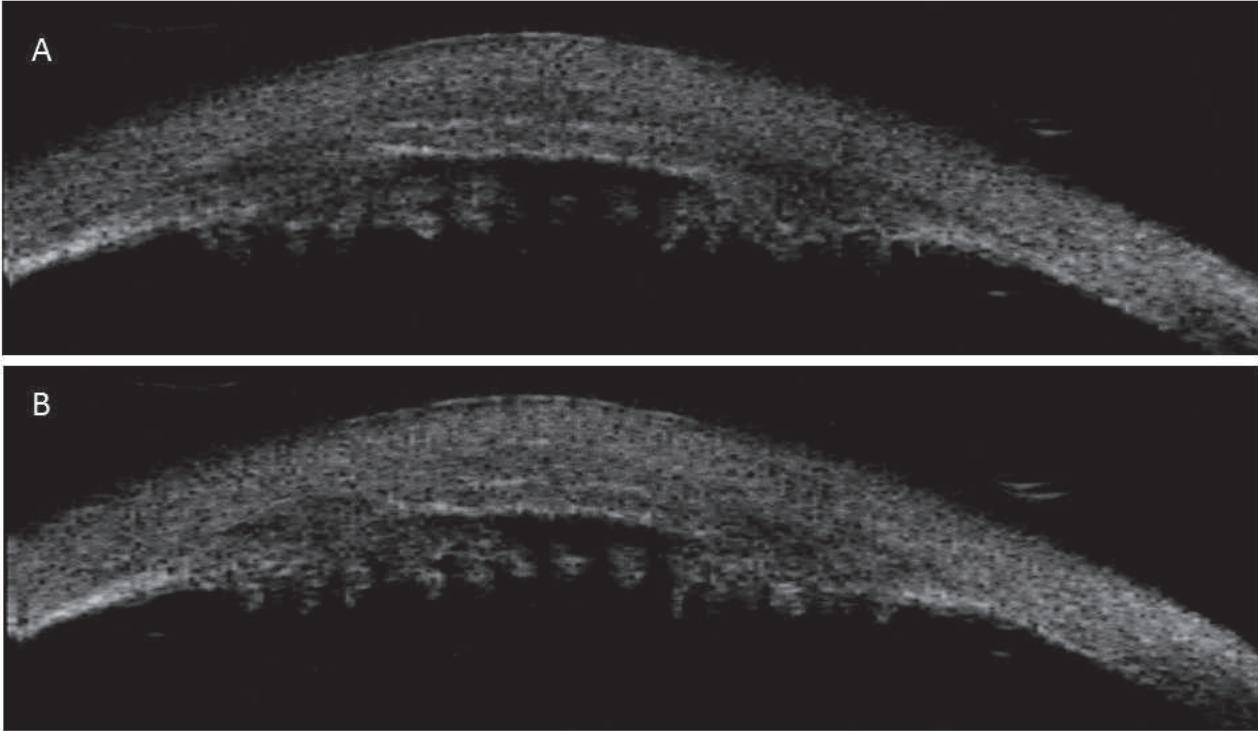
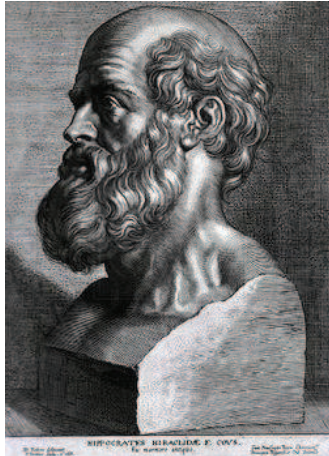


Figure 3.





## **SERMENT D'HIPPOCRATE**

*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,*

*Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*