Intraocular pressure fluctuation during microincision vitrectomy with Constellation(R) Vision System

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（新しい硝子体手術装置における小切開硝子体手術中の眼内圧動態）

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博 士 （ 医 学 ） 学 位 論 文

Intraocular pressure fluctuation during microincision vitrectomy with Constellation® Vision System

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Short title: Intraocular pressure fluctuations during vitrectomy

【Introduction】

Intraocular surgery induces substantial fluctuations in intraocular pressure (IOP).[1-5] Such IOP fluctuations can increase the risk of intraoperative and/or postoperative complications, including expulsive choroidal hemorrhage, vitreous hemorrhage, choroidal detachment, retinal ischemia, and optic nerve ischemia.[6-12] Expulsive choroidal hemorrhage, which is one of the most serious complications of intraocular surgery with reported incidence of 0.41% during vitrectomy, is more likely to occur after a sudden drop in IOP.[12] These IOP fluctuations may also adversely affect recovery of visual function after surgery. Especially, eyes with compromised retinal and/or optic nerve blood flow, such as those with proliferative diabetic retinopathy and cystoid macular edema due to retinal vein occlusion, are more susceptible to IOP fluctuation. Thus, recognizing intraoperative IOP fluctuations could improve safety of vitrectomy.

Several reports have assessed IOP fluctuations during vitrectomy in an animal model and human eyes.[1,13-15] In an animal model, major IOP fluctuations up to 40 mmHg during vitrectomy were demonstrated.[13] Studies in human eyes have shown that IOP during vitrectomy ranged from 0 to 120 mmHg.[1,14] In these studies, either of the two infusion systems were used ; the one dependent on the force of gravity or the Vented Gas Forced Infusion (Alcon Accurus® vitrectomy system, Fort Worth, TX, USA) system which uses pressurized air.

Recently, the new vitrectomy system (Alcon Constellation® Vision System, Fort Worth, TX, USA) has been developed. This device is equipped with a pressure control system and can maintain IOP at constant, independent of aspiration flow rates during vitrectomy. The intraoperative IOP fluctuations with this system, however, have not been assessed in detail. In addition, no studies have investigated the measurement of intraoperative IOP fluctuations under this IOP control system in eyeball. The purpose of this study was to measure changes in intraoperative IOP during vitrectomy with Constellation® Vision System, and to investigate IOP fluctuations during various maneuvers of vitrectomy.

【Methods】

Intraocular pressure monitoring system during vitrectomy in porcine eyes

This is a preclinical study, and no patients or no living animals were involved. Two fresh porcine eyes were obtained from a slaughterhous less than 1 day after death. We performed three-port vitrectomy in one eye with 23-gauge and the other eye with 25-gauge. After core vitrectomy, vitreous gel around the irrigation cannula was removed with a vitrectomy cutter. Then, a 22-gauge cannula was inserted into the vitreous cavity via a scleral stab wound 4 mm posterior to the limbus, and was connected to a pressure transducer (MLT0670, ADInstruments, USA). After the pressure transducer was filled with balanced saline solution, it was connected via conditioning modules to a chart recorder (PowerLab, ADInstruments, USA) for continuous monitoring of intraoperative IOP. The transducer was held at the level of the porcine eye and the liquid level of the bottle of balanced saline solution, and zeroed to atmospheric pressure. The set-up for this experiment is illustrated in Figure 1.

Intraocular pressure monitoring during surgical maneuvers

Three surgical maneuvers were assessed in terms of IOP fluctuations during the procedures. All procedures were conducted with the 23- and 25-gauge systems.

First, IOP monitored during vitreous cutting with the following settings: the vented gas forced infusion system-applied pressure was set at 30 mmHg, cutting rate at 5000 cuts per minute (cpm), and the aspiration pressure at 650 mmHg. The duty cycle, or the percentage of the time the cutter port was open relative to the complete cutting cycle, was set at ‘core mode’ (actually 51%). Measurements were performed in these settings with the IOP control setting turned on or off. We inserted plugs to unused ports, confirming that balanced saline solution was not leaking from those ports. The foot pedal was quickly pressed to the floor, and the time necessary for IOP to reach a plateau and its IOP value were measured.

Second, IOP was monitored in the aspiration mode without cutting with the following settings: applied pressure was set at 30 mmHg, and the aspiration pressure at 650 mmHg. Similar to the experiments in the vitreous cutting mode, measurements were performed with the IOP control setting turned on or off.

Third, IOP was monitored while was applied. To measure IOP fluctuations during scleral compression for observation and shaving of the peripheral vitreous, we conducted the following experiments: applied pressure was set at 30 mmHg, and the sclera 10 mm posterior to the corneal limbus was compressed with a scleral depressor. First, IOP fluctuations were recorded under rapid compression and release without aspiration. Next, IOP was recorded under gentle scleral compression for about 5 seconds with mild aspiration (approximately 100 mmHg), and under gentle release for about 3 seconds without aspiration. Like the above experiments,

measurements were performed either IOP control setting was turned on or off.

IOP measurements during cutting mode, aspiration mode and scleral compression were repeated 10 times respectively, and the mean was calculated. The time needed for IOP to reach ± 10% of the Vented Gas Forced Infusion-applied pressure was defined as “ the time necessary for IOP change ”. The mean and standard deviation were calculated for each variable. To assess reproducibility of measurements, we calculated coefficient of variation (CV) of the mean values of IOP at the point of 10 seconds after starting each maneuver of vitrectomy.

A paired t-test was performed to investigate the relationship between the reached IOP with the IOP control setting turned on and off, during three surgical maneuvers. An unpaired t-test was performed to investigate the relationship between 23-gauge and 25-gauge in the period of time during which IOP returned to system-applied pressure. The analyses were carried out using Stat View (version 5.0, SAS Inc., Cary, NC).

【Results】

Monitoring intraocular pressure in vitreous cutting mode (Table 1)

Using the 23-gauge system with the IOP control setting turned on, IOP showed a rapid decrease from 30.0 ± 0.1 to 23.7 ± 0.8 mmHg after starting vitreous cutting under aspiration pressure of 650 mmHg, and then quickly returned to approximately 30 mmHg in 2.6 ± 0.4 seconds (Figure 2, Top left). When the IOP control setting was turned off, IOP decreased from 30.0 ± 0.1 to 19.1 ± 0.2 mmHg in 0.9 ± 0.1 seconds, and remained at that pressure (Figure 2, Top right). Releasing of the foot pedal caused an IOP surge, the degree of which was smaller without the IOP control system (34.6 mmHg) than with the IOP control system (50.2 mmHg).

Using the 25-gauge system with the IOP control setting turned on, IOP exhibited a rapid depression from 30.0 ± 0.1 to 22.9 ± 0.2 mmHg, and then quickly returned to approximately 30 mmHg in 2.3 ± 0.3 seconds (Figure 2, Bottom left). When the IOP control setting was turned off, IOP decreased from 30.0 ± 0.1 to 16.7 ± 0.3 mmHg in 1.7 ± 0.2 seconds, and stayed at that pressure level (Figure 2, Bottom right).

With the IOP control setting turned on, there was no significant difference in the period of time during which IOP returned to approximately 30.0 mmHg between the 23-gauge and 25-gauge system ($P = 0.05$).

Monitoring intraocular pressure in aspiration mode (Table 1)

Using the 23-gauge system with the IOP control setting turned on, IOP showed a sharp depression from 30.0 ± 0.1 to 12.2 ± 0.6 mmHg under aspiration of 650 mmHg, and then recovered to 30.6 ± 0.6 mmHg in 3.6 ± 0.3 seconds (Figure 3, Top left). When the IOP control setting was turned off, IOP decreased from 30.0 ± 0.1 to 2.2 ± 0.5 mmHg in 9.7 ± 1.1 seconds (Figure 3, Top right).

Using the 25-gauge system with the IOP control setting turned on, IOP similarly declined from 30.0 ± 0.1 to 14.7 ± 0.7 mmHg, which returned to 34.5 ± 0.3 mmHg in 4.1 ± 0.2 seconds (Figure 3, Bottom left). When the IOP control setting was turned off, it decreased from 30.0 ± 0.1 to 2.2 ± 0.2 mmHg in 9.1 ± 0.9 seconds (Figure 3, Bottom right).

With the IOP control setting turned on, there was significant difference in the period of time during which IOP returned to approximately 30 mmHg between the 23-gauge and 25-gauge system ($P < 0.001$).

Monitoring intraocular pressure with scleral compression (Table 1)

Using the 23-gauge system with the IOP control setting turned on, scleral compression without aspiration increased IOP rapidly from 30.0 ± 0.1 to 75.8 ± 9.2 mmHg, and it took 3.5 ± 0.4 seconds for IOP to return to the preset level of 30.0 mmHg. Then, by quick release, IOP

decreased to 0.0 mmHg in 0.2 ± 0.1 seconds (Figure 4, Top left). When the IOP control setting was turned off, IOP rose sharply to 79.5 ± 3.5 mmHg and returned to around 30 mmHg in 3.7 ± 0.3 seconds. At the release of compression, it decreased to 0.0 mmHg in 0.3 ± 0.1 seconds (Figure 4, Top right).

Using the 25-gauge system with the IOP control setting turned on, IOP rapidly increased to 109.0 ± 12.3 mmHg by scleral compression, and it took 4.0 ± 0.3 seconds to return to the preset level of 30.0 mmHg. Then, by quick release, IOP decreased to 0.0 mmHg in 0.5 ± 0.2 seconds (Figure 4, Bottom left). Similar results were observed when the IOP control setting was turned off (Figure 4, Bottom middle). When the sclera was gently compressed for about 5 seconds with mild aspiration and was released slowly for about 3 seconds, IOP fluctuated between 25.2 and 39.4 mmHg (regardless of the use of the 23- or 25-gauge system, and the IOP control setting was turned on or off) (Figure 4, Bottom right).

With the IOP control setting turned on, there was significant difference in the period of time during which IOP returned to approximately 30 mmHg between the 23-gauge and 25-gauge system ($P < 0.001$).

Table 2 summarized the reproducibility of measurements in each maneuver of vitrectomy. CV in 10 measurements was also shown.

【Discussion】

As shown in these results, the IOP control system can attenuate IOP fluctuations significantly during microincision vitrectomy. This surgical procedure with relatively smaller IOP fluctuations could be less invasive than the conventional vitrectomy.

In vitreous cutting mode, IOP decreased to15 - 20 mmHg when the IOP control setting was turned off, whereas the pressure remained around 30 mmHg with the IOP control setting turned on. In the aspiration mode, the difference became more conspicuous: while IOP declined to nearly 0 mmHg with the IOP control setting turned off, the pressure was kept around 30 mmHg with the control setting turned on. Some of the intraoperative complications during closed eye surgery are associated with significant fluctuations in IOP. Expulsive choroidal hemorrhage, vitreous hemorrhage, and choroidal detachment can occur after a sudden drop in IOP.[6-12] Therefore, minimally invasive surgery with relatively smaller IOP fluctuations would be preferred for vitrectomy.

We recorded IOP fluctuations during 23- and 25-gauge vitreous cutting under aspiration. When the IOP control system setting was turned on, IOP demonstrated spike depression after the start of vitreous cutting, but recovered and reached a plateau in approximately 3 seconds (Figure 2, Top left and Bottoom left). We observed similar IOP spikes in aspiration mode (Figure 3, Top left and Bottoom left). The reason that IOP spike depression occurred in the early phase of vitreous cutting may lie in the mechanism of the IOP control system. It incorporates an infusion system which controls the IOP at constant, independent of aspiration flow rates during vitrectomy surgery. The infusion flow rate is ultrasonically measured with a sensor in the machine and through the Non Invasive Flow Sensor in the infusion pathway located in the cassette. The measured flow rate is multiplied by the calibrated cannula resistance to determine the pressure drop across the cannula. The infusion pressure at the console is increased to match and cancel the pressure drop across the cannula in order to maintain a constant IOP. When the foot pedal is pressed down rapidly, aspiration begins simultaneously due to an electronic signal. But it takes a short period of time for the ultrasonical sensor in the infusion pathway to detect the flow rate of fluid inside the infusion tube. It also takes a little time before active pressure is applied on the infusion pathway and the fluid comes out into the eye. During the time lag, IOP decreased in a spike fashion. The degree of IOP depression was approximately 10 mmHg, however, and it took only about 3 seconds for IOP to get back to 30 mmHg. So there was no clinical problem.[16] The IOP spike elevation observed at a quick release of the foot pedal can be explained in the same manner. Although the degree of IOP spike elevation (10-20 mmHg) was relatively large, the duration was only 0.2 seconds. Kim JE et al. have investigated the changes in IOP following intravitreal injections of anti-vascular endothelial growth factor agents. They reported that the mean IOP was 44 mmHg immediately

after injections. But elevations in IOP were transient, and multiple intravitreal injections were not a significant risk factor for IOP elevation.[17,18] Shin HJ et al. have also reported that transient IOP elevations and multiple intravitreal injections did not appear to adversely affect retinal nerve fiber layer thickness.[19] So that the IOP spike elevation in our study could not cause any problem clinically.

In this experiment, while we did not observe significant difference in IOP fluctuations in vitreous cutting mode, there were significant difference in IOP fluctuations in the aspiration mode and scleral compression between 23-gauge and 25-gauge vitrectomies. The difference in the sclerotomy size is associated with differences in the inner diameters of the vitreous cutter and infusion cannula, resulting in lower flow rates in 25-gauge vitrectomy. Since IOP fluctuations in the aspiration mode and scleral compression are larger than that in the cutting mode, longer time might be necessary for IOP to return to system-applied pressure.

When we compressed the sclera without aspiration, IOP rapidly increased to approximately 100 mmHg, and then slowly decreased to the level of the vented gas forced infusion system pressure setting (30 mmHg), regardless of the sclerotomy size, and with or without the use of IOP control system. When we released compression suddenly, IOP rapidly decreased to around 0 mmHg. We consider that this system cannot control it because the amount of fluid flowed back from the vitreous cavity into the infusion cannula is too much under scleral compression. When we conducted intraoperative laser photocoagulation to the peripheral retina under scleral compression during vitrectomy, the condition was regarded the same as these experiments. Therefore, extra attention is required for the start of scleral compression and the start of release. When we gently compressed the sclera for about 5 seconds with mild aspiration and released it for about 3 seconds, IOP fluctuated between 30 ± 10 mmHg. Scleral compression with such a technique could diminish IOP fluctuations, resulting in improved safety of the operation.

We also confirmed the reproducibility of IOP measurements in each maneuver of vitrectomy by repeating the measurements 10 times in porcine eyes, where the coefficient of variation was sufficiently small except for the aspiration mode with IOP control setting turned off. Because IOP at the point of 10 seconds after starting aspiration was on the way of decreasing and did not reach a plateau in the aspiration mode.

It is said that many surgeons routinely set the vented gas forced infusion system pressure at approximately 30 mmHg, but this level may be considered too high for patients with highly ischemic vascular diseases, including proliferative diabetic retinopathy and advanced glaucoma. Normal IOP was generally defined as 10 – 21 mmHg.[20] We previously reported that ophthalmodynamometric pressure (the minimum IOP at which the first central retinal artery collapse occurs) was important to assess blood perfusion of the eye. In this study, the minimum

value of ophthalmodynamometric pressure in patients with proliferative diabetic retinopathy was 15.5 mmHg.[21] Therefore, for those high-risk patients, it seems better to set the pressure at 15 - 20 mmHg with this system.

This study has certain limitations. Since the experiments were conducted with porcine eyes, the results may not be exactly applicable to human eyes. Scleral rigidity is considered to be similar between porcine and human eyes.[22] However, the volumes of their vitreous cavities are different. The vitreous cavity of the human eye is approximately 4 ml, which is significantly smaller than that of the porcine eye. As our method is comparable to the direct cannulation technique in principle, precise and reproducible measurements of IOP seem to be possible.[15] However, this method cannot be easily used in living human eyes ethically, because extra sclerotomy to cannulate the pressure transducer is necessary. It is thus desirable to conduct detailed experiments in living human eyes.

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【**Table 1**】 The results of intraocular pressure fluctuations during various maneuvers of vitrectomy

Vitreous cutting mode; VGFI 30 mmHg, aspiration pressure 650 mmHg, cutting rate 5000 cpm				
	IOP control	Reached IOP (mmHg)	Change IOP from baseline (mmHg)	P value
23G	on	23.7 ± 0.8	-6.3 ± 0.8	< 0.001
	off	19.1 ± 0.2	-8.9 ± 0.2	
25G	on	22.9 ± 0.2	-7.1 ± 0.2	< 0.001
	off	16.7 ± 0.3	-13.3 ± 0.3	
Aspiration mode; VGFI 30 mmHg, aspiration pressure 650 mmHg				
	IOP control	Reached IOP (mmHg)	Change IOP from baseline (mmHg)	P value
23G	on	12.2 ± 0.6	-17.8 ± 0.6	< 0.001
	off	2.2 ± 0.3	-20.3 ± 0.3	
25G	on	14.7 ± 0.7	-15.4 ± 0.7	< 0.001
	off	2.2 ± 0.2	-27.9 ± 0.2	
Scleral compression; VGFI 30 mmHg, without aspiration				
	IOP control	Peak IOP (mmHg)	P value	IOP at release of compression (mmHg)
23G	on	75.8 ± 9.2	0.29	0.0
	off	79.5 ± 5.7		0.0
25G	on	109.0 ± 8.5	< 0.05	0.0
	off	128.3 ± 21.1		0.0

VGFI, Vented Gas Forced Infusion; cpm, cuts per minute; IOP, intraocular pressure; 23G, 23-gauge; 25G, 25-gauge.

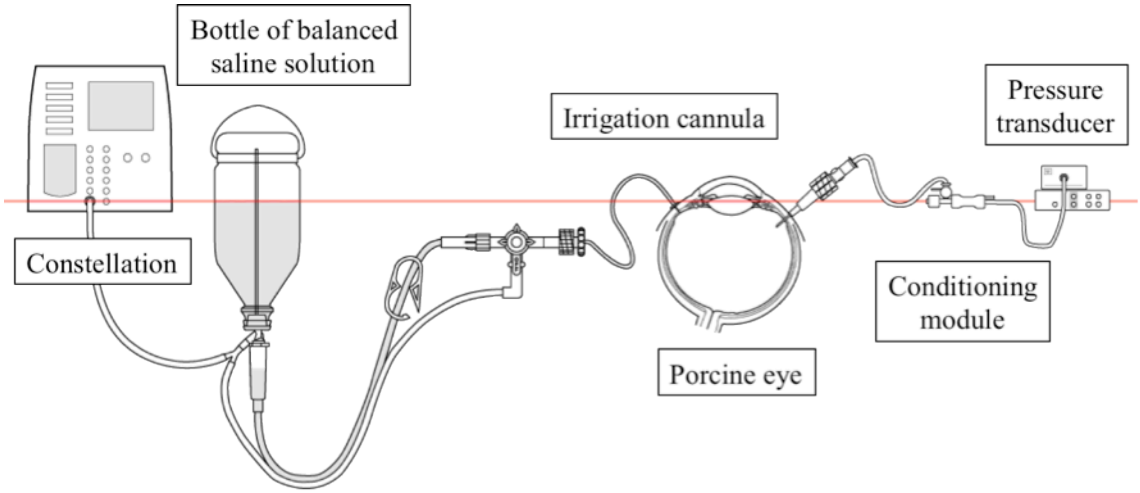
【**Table 2**】 Reproducibility of measurements in each maneuver of vitrectomy

Vitreous cutting mode; VGFI 30 mmHg, aspiration pressure 650 mmHg, cutting rate 5000 cpm			
	IOP control	IOP at the point of 10 seconds after starting procedure (mmHg)	Coefficient of Variation
23G	on	31.0 ± 0.3	0.010
	off	19.0 ± 0.3	0.014
25G	on	32.6 ± 0.7	0.022
	off	16.6 ± 0.3	0.016
Aspiration mode; VGFI 30 mmHg, aspiration pressure 650 mmHg			
	IOP control	IOP at the point of 10 seconds after starting procedure (mmHg)	Coefficient of Variation
23G	on	30.7 ± 0.7	0.023
	off	2.3 ± 0.4	0.168
25G	on	34.7 ± 0.7	0.022
	off	2.2 ± 0.7	0.335
Scleral compression; VGFI 30 mmHg, without aspiration			
	IOP control	IOP at the point of 10 seconds after starting procedure (mmHg)	Coefficient of Variation
23G	on	31.9 ± 1.3	0.042
	off	30.8 ± 1.0	0.031
25G	on	30.5 ± 1.6	0.051
	off	30.6 ± 1.4	0.045

VGFI, Vented Gas Forced Infusion; cpm, cuts per minute; IOP, intraocular pressure; 23G, 23-gauge; 25G, 25-gauge.

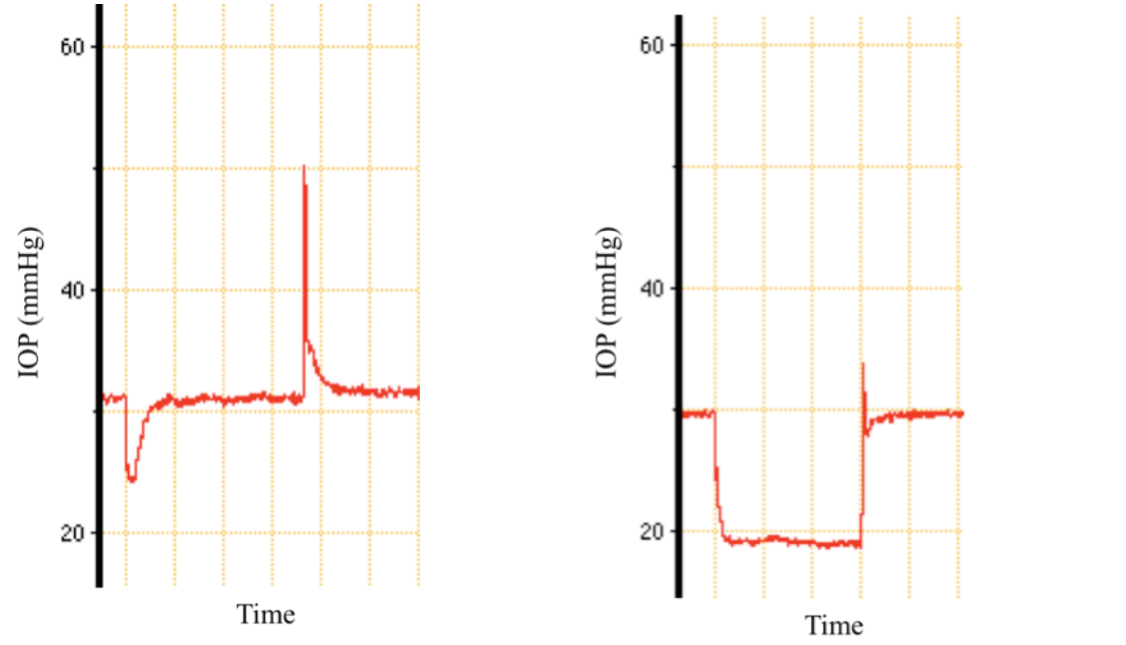
【Figure】

Figure 1



The illustration of experiment settings to measure intraocular pressure fluctuation during microincision vitrectomy with Constellation® Vision System. The vented-gas forced-infusion system in the Constellation® system controls the perfusion pressure by delivering the pressurized air into the bottle of balanced saline solution. At another side, a 22-gauge cannula was inserted into the vitreous cavity, and was connected to a pressure transducer. The transducer was held at the level of the porcine eye and the liquid level of the bottle of balanced saline solution.

Figure



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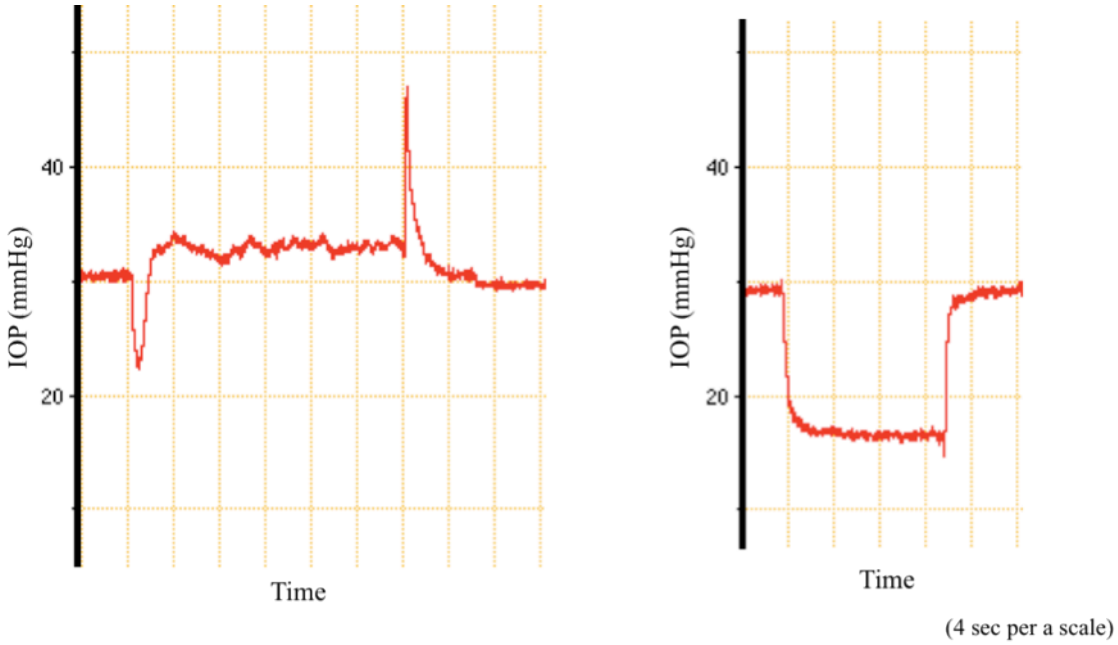
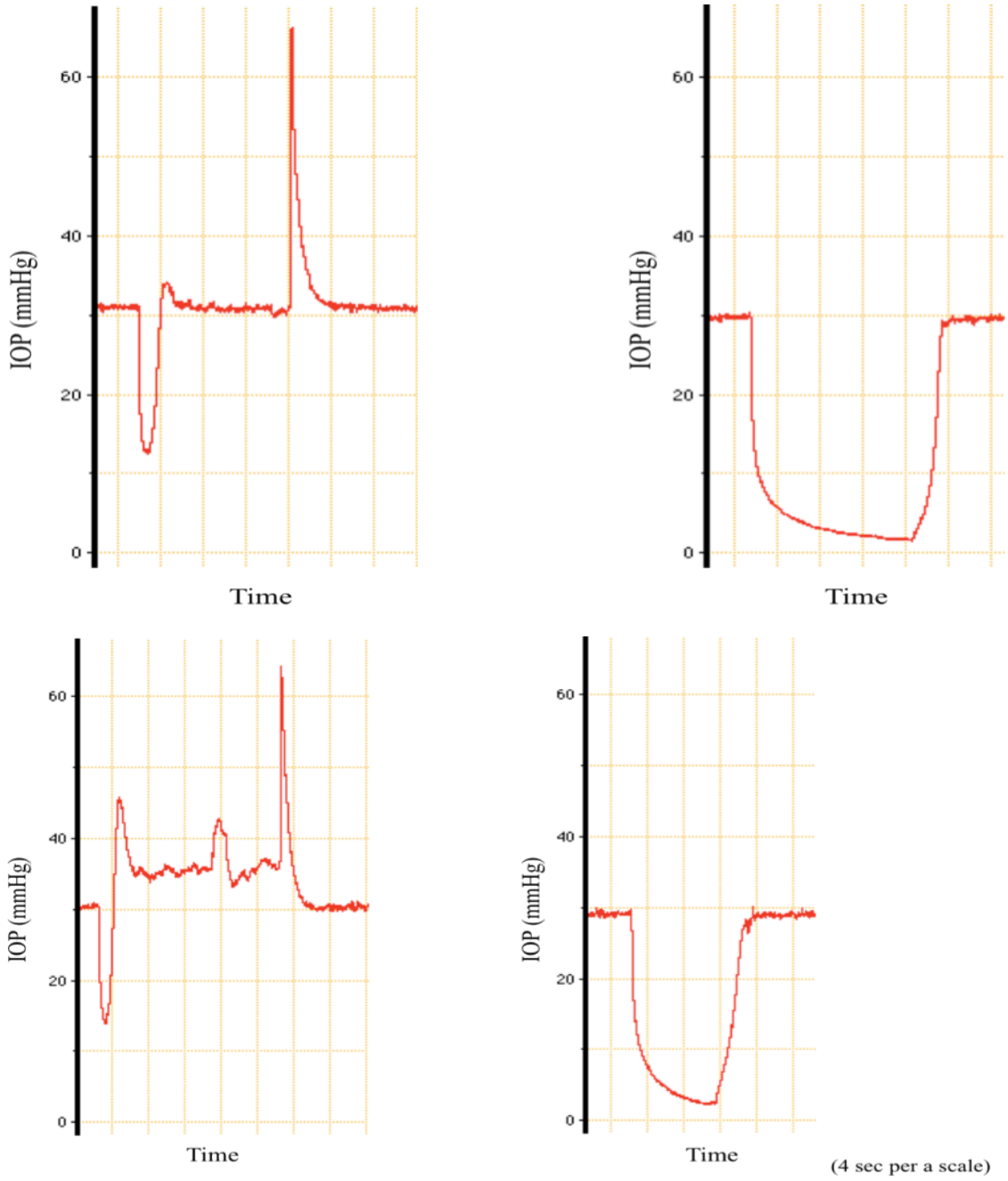


Intraocular pressure (IOP) fluctuation with vitreous cutting mode during microincision vitrectomy with Constellation® Vision System. With the 23-gauge, the pressure was set at 30 mmHg, cutting rate at 5000 cuts per minute, and the aspiration pressure at 650 mmHg with the IOP control system (Top left), and without the IOP control system (Top right). With the 25-gauge, the pressure was set at 30 mmHg, cutting rate 5000 cuts per minute, and the aspiration pressure 650 mmHg with the IOP control system (Bottom left), and without the IOP

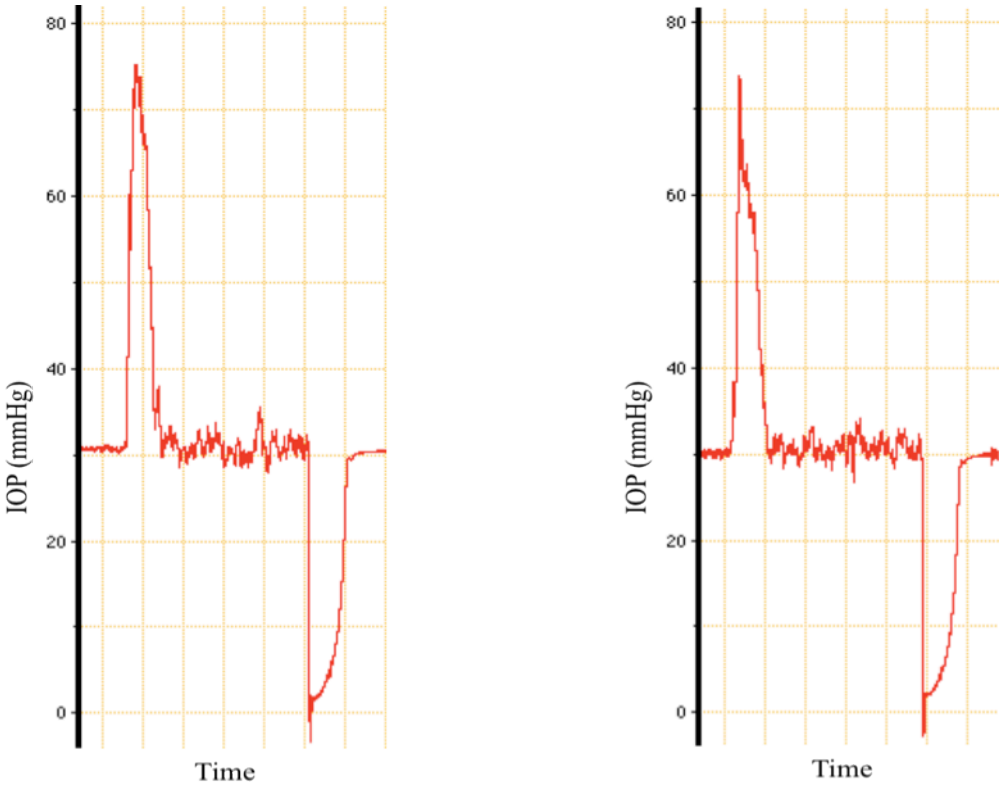
control system (Bottom right).

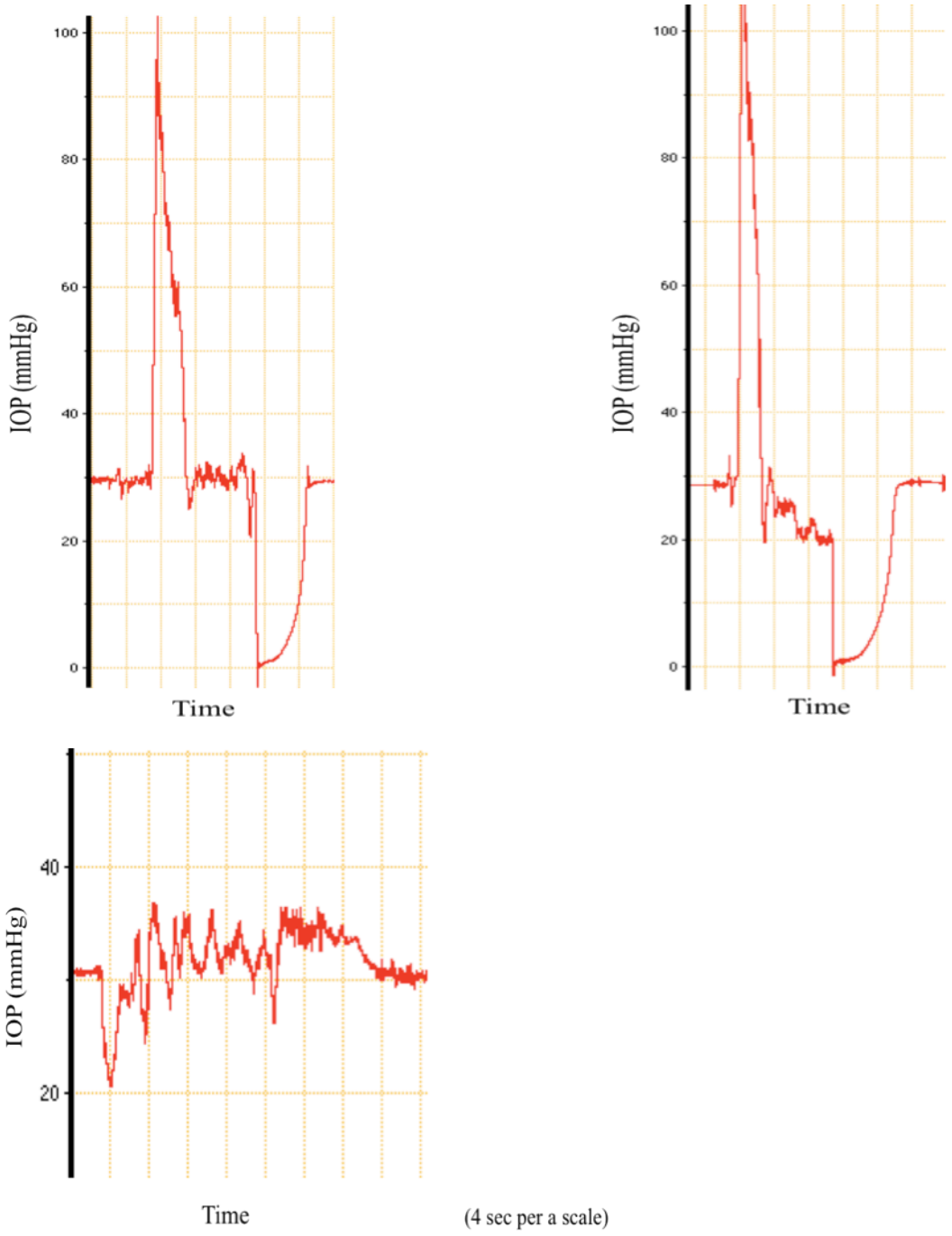
Figure 3



Intraocular pressure (IOP) fluctuation with aspiration mode during microincision vitrectomy with Constellation® Vision System. With the 23-gauge, the pressure was set at 30 mmHg and the aspiration pressure at 650 mmHg with the IOP control system (Top left), and without the IOP control system (Top right). With the 25-gauge, the pressure was set at 30 mmHg and the aspiration pressure 650 mmHg with the IOP control system (Bottom left), and without the IOP control system (Bottom right).

Figure 4





Changes in intraocular pressure (IOP) with scleral compression during microincision vitrectomy with Constellation® Vision System. With the 23-gauge, without aspiration, the sclera was rapidly compressed and then released with the IOP control system (Top left), and without the IOP control system (Top right). With the 25-gauge, the same procedure was done with the IOP control system (Middle left), and without the IOP control system (Middle Right). Under mild aspiration, the sclera was gently compressed and then released with the IOP control system with the 23-gauge system (Bottom).

参　考　論　文

Ophthalmodynamometric pressure in eyes with proliferative diabetic retinopathy measured during pars plana vitrectomy

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Short title: Ophthalmodynamometric pressure in eyes with PDR

【Introduction】

Diabetic retinopathy is one of the most common causes of vision loss in industrialized countries.[1] Visual impairment due to diabetic retinopathy is caused by macular edema and retinal neovascularization. Disturbance of retinal circulation exists even in the early-stage of diabetic retinopathy.[2-5] Changes in retinal blood flow are responsible for the development of nonperfusion area and retinal ischemia, eventually resulting in the development of proliferative diabetic retinopathy (PDR).

Ophthalmodynamometric pressure (ODP) means the minimum intraocular pressure (IOP) at which the first central retinal artery collapse occurs, and this collapse is intermittent, that is, pulsating. Measurement of ODP is important in the assessment of blood perfusion into and out of the eye.[6-12] In patients with retinal vascular occlusion diseases, such as central retinal artery occlusion,[13] giant-cell arteritis-induced anterior ischemic optic neuropathy,[14] and unilateral ischemic ophthalmopathy,[7] ODP is known to decrease. Thus, measurement of ODP is of clinical relevance in patients with retinal circulation problems.

Ophthalmodynamometry is an ODP measurement method in which IOP is elevated while observing the central retinal artery. Several methods have been used to raise and measure the IOP, such as external calibrated compression and direct cannulation.[9-12,15-18] However, external calibrated compression cannot measure precise ODP because IOP is added to the external pressure applied to the eye. Repeated pressure application to the eye may change IOP. Moreover, the method of pressure application and fundus observation are not sophisticated. In contrast, the direct cannulation method can measure ODP directly,[18] but it is not easily applicable to living human eyes due to its invasiveness. We developed a new method to measure ODP using Vented Gas Forced Infusion (VGFI; Alcon Accurus vitrectomy system, Fort Worth, TX, USA) system during pars plana vitrectomy. This technique directly applies pressure into the vitreous cavity with VGFI system. As our new method is comparable to the direct cannulation technique in principle, it seems that ODP can be measured with precision. The purpose of the present study is to measure ODP in patients with PDR using VGFI system during vitrectomy, and to investigate factors related to ODP.

【Methods】

Patients

We analyzed 75 eyes of 75 patients with PDR who were undergoing pars plana vitrectomy at Tsukuba University Hospital from July 2007 through December 2008. The current study was a prospective, interventional, consecutive case series, and was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Committee of Tsukuba University Hospital. Prior to inclusion in the study, all patients provided written informed consent after the nature of the study was explained to them. Exclusion criteria included preoperative IOP above 22 mmHg or previously diagnosed glaucoma, age less than 18 years, and previous history of vitreous surgery. The indications for vitrectomy included recurrent or persistent nonclearing vitreous hemorrhage, traction or combined traction/rhegmatogenous retinal detachment, and adherent posterior hyaloid causing excessive macular traction.

The following preoperative information was obtained for each patient: age, gender, body mass index, presence of hypertension (HT), serum hemoglobin A1c (HbA1c), fasting plasma glucose and presence of rubeosis iridis. By means of preoperative retinal photographs, fluorescein angiography and intraoperative retinal findings, the severity of PDR was graded by Early Treatment Diabetic Retinopathy Study (ETDRS) final retinopathy severity scale.[19] Data on the patients' characteristics are presented in Table 1.

Surgical procedures

All surgeries were performed by two experienced surgeons under sub-Tenon local anesthesia. The crystalline lens was removed with phacoemulsification and intraocular lens implantation when required, followed by 20-gauge three-port pars plana vitrectomy. We used a bottle of balanced saline solution injected in 0.5mg of epinephrine during surgery as an infusion fluid. Using contact lenses, posterior hyaloid separation and removal of the posterior vitreous membrane were performed, and then bimanual delamination, en bloc dissection, and segmentation techniques were used to remove proliferative tissues. Membrane dissection and segmentation were performed when necessary to eliminate all tangential tractions. Peripheral vitrectomy and panretinal endophotocoagulation were routinely performed. Air-fluid exchange was conducted when an iatrogenic retinal tear and/or rhegmatogenous retinal detachment were identified intraoperatively.

Measurement of ophthalmodynamometric pressure

We measured ODP during vitrectomy using Vented Gas Forced Infusion System (VGFI; Alcon Accurus vitrectomy system, Fort Worth, TX, USA). This system controls the perfusion pressure by delivering the pressurized air (0 ~ 120 mmHg) into the bottle of balanced saline solution, instead of changing the height of the irrigation bottle. After core vitrectomy, we confirmed that balanced saline solution was not leaking from each sclerotomy. And then, intraocular pressure was gradually raised using VGFI, and the optic nerve head was continuously monitored through a planoconvex contact lens. When the central retinal artery or its first branches on the optic nerve head showed pulsations, the pressure was recorded as ODP. The measurements were repeated three times, and their mean values were used for data analyses.

Systemic blood pressure was measured at the same time of ODP measurements. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded with a indirect blood pressure measurement (oscillometric methods). Mean arterial blood pressure (MBP) was defined as DBP plus one third of the difference between SBP and DBP.

Statistical analysis

The mean and standard deviation were calculated for each variable. The relationship between ODP and systemic blood pressures were examined with the Pearson's correlation coefficient. Mann-Whitney U test was performed to compare ODP between patients with and without rubeosis iridis. Multiple regression analysis was performed to investigate the relationship between ODP and various explanatory variables. Variables tested were DBP, SBP, age, body mass index, presence of HT, serum HbA1c, presence of rubeosis iridis, and the severity of PDR. All tests of association were considered statistically significant if $p < 0.05$. The analyses were carried out using Stat View (version 5.0, SAS Inc., Cary, NC).

【Results】

ODP measured during vitrectomy was 63.6 ± 11.5 mmHg (range 15.5 - 84.4 mmHg). DBP, SBP, and MBP measured at the same time were 75.8 ± 9.7 mmHg (range 50.0 - 98.0 mmHg), 149.6 ± 18.4 mmHg (range 102.0 - 187.0 mmHg), and 125.6 ± 12.0 mmHg (range 94.0 - 149.7 mmHg), respectively (Figure 1). ODP was significantly correlated with DBP ($r = 0.570$, $p < 0.0001$) and MBP ($r = 0.522$, $p < 0.0001$), but there was no significant correlation between ODP and SBP ($r = 0.121$, $p = 0.303$) (Figure 2). ODP was significantly lower in patients with rubeosis iridis than those without rubeosis iridis ($p < 0.005$, Figure 3). Multiple regression analysis showed that DBP ($p < 0.0001$), presence of rubeosis iridis ($p < 0.0001$) and the severity of PDR ($p = 0.046$) had a significant positive correlation with ODP, whereas other explanatory variables showed no relationship with ODP (Table 2).

【Discussion】

In the 1960s and 1970s, ophthalmodynamometry was used to measure ODP, in which IOP was raised by exerting a standardized pressure on the globe and observe the optic nerve head through an ophthalmoscope.[10-12,16,17] It was found that ODP in patients with central retinal artery occlusion was lower than that of normal controls.[13] ODP in patients with giant-cell arteritis-induced anterior ischemic optic neuropathy was decreased compared with patients with non-arteritic anterior ischemic optic neuropathy.[14] Jonas et al reported a case in which ODP measurement was helpful to diagnose unilateral ischemic ophthalmopathy.[7] Another study demonstrated that ODP in patients with ischemic central retinal vein occlusion was significantly lower than that of patients with nonischemic central retinal vein occlusion.[20] These previous reports indicate the clinical relevance of ODP measurements in patients with retinal circulation problems. Ophthalmodynamometer developed by Jonas is a simple and well designed device to measure ODP, which has been evaluated so far in various ocular disorders.[21-24] However, due to the pressure exerted onto the globe by the ophthalmodynamometric contact lens, IOP would change in repeated measurements. Furthermore, since the target pressure is the sum of IOP and externally applied pressure, precise determination of IOP is difficult. In contrast, ODP measurement using the direct cannulation method can measure more precise ODP because it monitors the true pressure in the eye.[15,18] This method, however, cannot be easily used in living human eyes. We developed a new method to determine ODP using VGFI during vitrectomy. As our new method is comparable to the direct cannulation technique in principle, it seems that precise and reproducible measurements of ODP are possible. Okamoto et al has reported that the reproducibility and validity of the IOP measurement using VGFI.[25]

As shown in the results, ODP showed a significant correlation with DBP and MBP, but not with SBP. These results are not surprising because ODP represents the diastolic phase of the central retinal artery collapse pressure. These findings are in good agreement with previous reports which evaluated ODP with an ophthalmodynamometer and direct cannulation. [9,18]

In our study, ODP in PDR patients was not associated with SBP. Jonas measured ODP of patients with various eye diseases using ophthalmodynamometer, and reported that ODP of normal controls showed a significant association with both DBP and SBP, whereas ODP of patients with retinal occlusive disease did not show a significant association with SBP.[9] It has

been known that blood flow velocity of the central retinal artery of PDR patients is lower than that of normal subjects.[5] Disturbance of retinal blood flow seems to be the reason for lack of correlation between SBP and ODP in PDR patients, as in patients with retinal vascular occlusive disease.

ODP showed a highly significant correlation with MBP in our study. The result is consistent with the previous report which evaluated ODP using ophthalmodynamometer.[9] Blood pressure is characterized by its pulsatile and steady components. The steady component, estimated from MBP, refers to peripheral vascular resistance and hence to the wall-to-lumen ratio of small arteries. The elevation of MBP results reduction in the caliber or number of small arteries or arterioles.[26] MBP may be associated with peripheral vascular circulation such as a retinal perfusion. Meanwhile, MBP indicates a function of left ventricular contractility, heart rate, and vascular resistance and elasticity averaged over time.[27] Dyer et al. found that MBP was strongly associated with the risk of cardiovascular diseases in epidemiological studies.[28] Thus, ODP, which is associated with MBP, can be a marker that indicates the degree of systemic vascular resistance.

We found that ODP was lower in eyes with rubeosis iridis. Multiple regression analysis also revealed that ODP was significantly associated with the presence of rubeosis iridis. Fujioka et al. evaluated the retinal arterial flow using color Doppler imaging in patients with PDR, and demonstrated that both central retinal artery flow and short posterior ciliary artery flow were reduced in eyes with rubeosis iridis.[29] Decreases in the velocity of the central retinal artery and the short posterior ciliary artery can cause a drop of ocular perfusion pressure, i.e. a decrease in ODP. Thus, it is not surprising that eyes with lower ODP are more susceptible to developing rubeosis iridis when their PDR is already severe enough to be treated with vitrectomy.

Multiple regression analysis revealed that ODP was significantly associated with the severity of PDR. Decreases in retinal blood flow and retinal artery velocities are detected even in very early stage of diabetic retinopathy.[30,31] Mendivil measured blood flow velocity of the central retinal artery in PDR patients using color Doppler imaging, showing that the blood flow velocity in PDR patients was lower than that of normal controls.[5] Our and previous results suggest that severer PDR causes greater degree of retinal perfusion disturbances.

We acknowledge certain limitations of our study. First, ODP and systemic blood flow were measured in a supine position. However, in daily lives, patients spend longer hours in the sitting or standing position. Considering the relative position of

patient's eye and the brachium/heart, ODP should be lower in the sitting and standing positions than in the supine position. Second, systemic blood pressure tends to rise during surgery due to operative stress. As a result, patient's ODP can be elevated to some extent. Third, ODP may be influenced by surgical procedure. We measured ODP after we confirmed that infusion fluid was not leaking from each sclerotomy under surgical microscopy. However, slight leakage may exist around 20 gauge plugs or instruments. Increased leakage would falsely elevate the ODP. Therefore, ODP measured in our study might be slightly higher than an accurate ODP. In addition, we used the infusion fluid including epinephrine during surgery. Epinephrine may have effect on decrease in ODP.

Measurements of ODP and blood pressure under more physiological conditions will await for further refinement of technology and methodology.

In conclusion, we evaluated ODP using VGFI system during vitrectomy in patients with PDR. The patients' ODP was significantly associated with DBP, and was lower in eyes with rubeosis iridis and severe PDR.

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【Table】

Table 1. Clinical Characteristics of the Patients with Proliferative Diabetic Retinopathy

Number of eyes	75
Male / female	53 / 22
Age (years)	57.4 ± 11.8
Body mass index	23.6 ± 3.8
Hypertention (+) / (-)	47 / 28
Serum HbA1c (%)	7.2 ± 1.8
Fasting plasma glucose (mg/dl)	152 ± 67
Rubeosis iridis (+) / (-)	15 / 60
Severity of PDR	
Level 61	0
65	5
71	11
75	14
81	16
85	18

Values are presented as the mean ± standard deviation; PDR, proliferative diabetic retinopathy; Severity of PDR, refer to ETDRS final retinopathy severity scale.

Table 2. Correlations with Ophthalmodynamometric Pressure in Multiple Regression Analysis

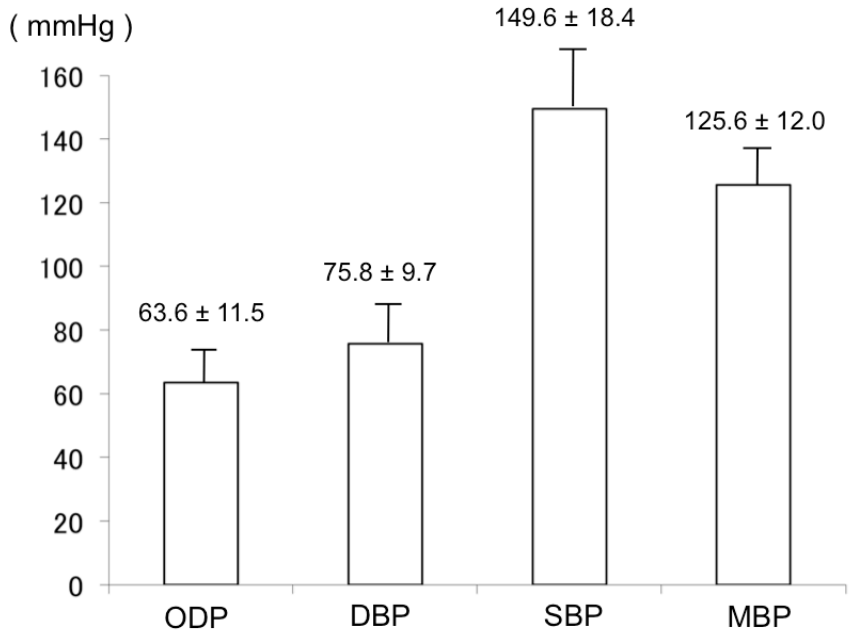
Ophthalmodynamometric pressure (objective variable)			
Explanatory variable	β	SE	p value
Diastolic blood pressure	0.870	0.119	< 0.0001*
Systolic blood pressure	0.090	0.063	0.161
Age	-0.041	0.100	0.683
Body mass index	-0.002	0.274	0.994
Presence of hypertention	1.974	2.719	0.473
Serum HbA1c	-0.133	0.627	0.834
Presence of rubeosis iridis	-13.68	3.092	< 0.0001*
Severity of PDR	-1.934	0.937	0.046*

β, standard regression coefficient; SE, standard error; PDR, proliferative diabetic retinopathy;

* Significant at $p < 0.05$.

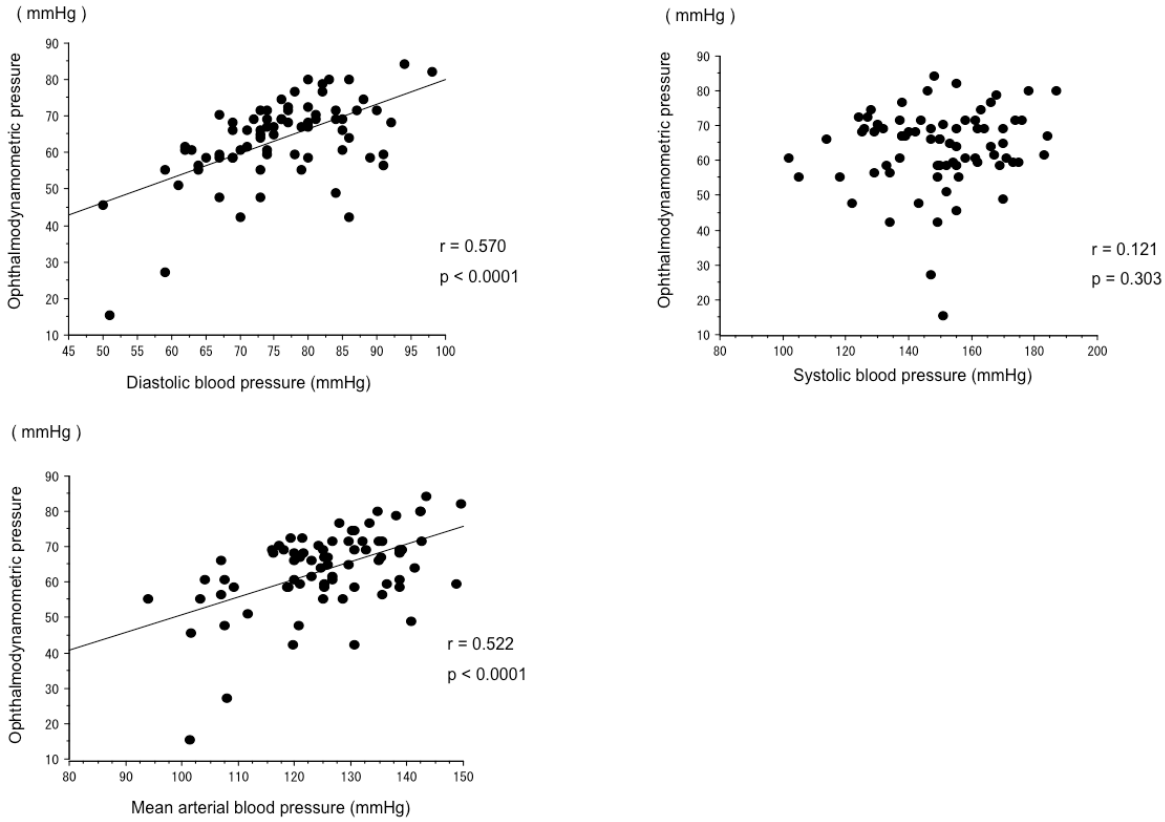
【**Figure**】

Figure 1



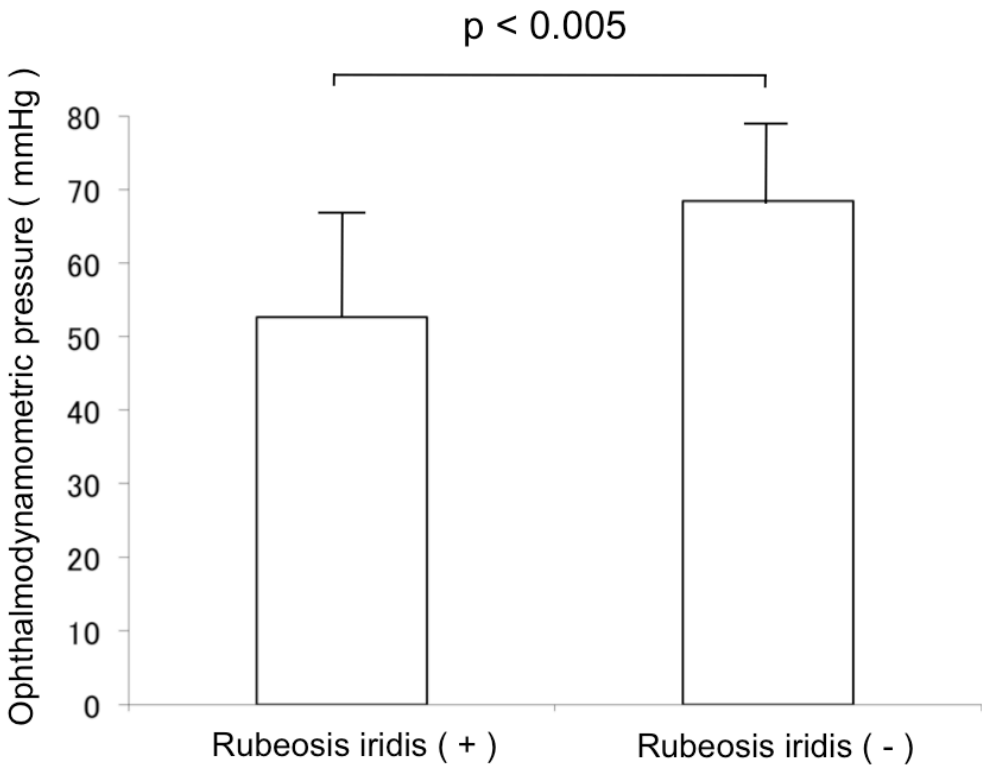
Ophthalmodynamometric pressure and systemic blood pressure measured during vitrectomy in patients with proliferative diabetic retinopathy. Values are presented as mean ± standard deviation. DBP, diastolic blood pressure; SBP, systolic blood pressure; MBP, mean arterial blood pressure. MBP was defined as DBP plus one third of the difference between SBP and DBP.

Figure 2



The relationship between ophthalmodynamometric pressure (ODP) and systemic blood pressure in patients with proliferative diabetic retinopathy.
(Upper left) ODP was significantly correlated with diastolic blood pressure: r = 0.570, p < 0.0001. (Upper right) There was no significant correlation between ODP and systolic blood pressure: r = 0.121, p = 0.303. (Bottom left) ODP was significantly correlated with mean arterial blood pressure: r = 0.522, p < 0.0001.

Figure 3



Ophthalmodynamometric pressure and presence of rubeosis iridis in patients with proliferative diabetic retinopathy. Ophthalmodynamometric pressure was significantly lower in eyes with rubeosis iridis (52.7 ± 16.2 mmHg) than in eyes without rubeosis iridis (68.5 ± 11.0 mmHg, $p < 0.005$).