# Pan retinal photocoagulation for proliferative diabetic retinopathy: pattern scan laser versus argon laser

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**Purpose of review**
Diabetic retinopathy is the leading cause of visual impairment in working-age adults worldwide. Pan retinal photocoagulation (PRP) has provided an effective treatment to decrease the risk of severe vision loss in patients with proliferative diabetic retinopathy for the past four decades. Pattern scan laser (PASCAL) was developed to minimize the side effects of PRP. The purpose of this review is to discuss the differences between the traditional argon laser and the PASCAL.

**Recent findings**
PASCAL can achieve comparable results with the conventional argon PRP in the treatment of patients with diabetic retinopathy. The PASCAL delivery system creates well aligned arrays of retinal lesions in a shorter period. PASCAL provides amore comfortable profile when compared to the argon laser.

**Summary**
The PASCAL is now being substituted for the conventional argon laser for PRP in many clinics. Ophthalmologists should keep in mind that adjusting the PASCAL settings (including the duration, number, and size of laser burns) might become necessary to maintain regression and eliminate recurrence of neovascularization in patients with proliferative diabetic retinopathy. Further studies are needed to determine the parameters for optimal safety and efficacy on the PASCAL.

**Keywords**
pan retinal photocoagulation, pattern scan laser photocoagulation, proliferative diabetic retinopathy

## INTRODUCTION

Diabetic retinopathy is the leading cause of visual impairment in working-age adults worldwide [1,2]. The disease is characterized by capillary nonperfusion and ischemia within the retina, which ultimately leads to macular edema and retinal neovascularization with the potential to severely damage visual function [3]. Diabetic retinopathy is clinically classified into two types: nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Pan retinal photocoagulation (PRP) was introduced in the Diabetic Retinopathy Study in 1976 as an effective treatment to decrease the risk of severe vision loss in patients with PDR [4].

Several studies have demonstrated a reduction in health-related quality of life in persons with diabetic retinopathy [5]. Moreover, vision loss due to PDR has a significant cost to society at large in terms of services needed and productivity lost. If treatments are delivered as recommended in the clinical trials, cost-modeling predicts a cost of US$966 per person-year of vision saved from PDR. These costs are less than the cost of a year of social security disability payments for those disabled by vision loss and do not take into account the indirect costs in lost productivity secondary to vision loss. Therefore, treatment yields a substantial savings compared with the direct cost to society of the care of an untreated proliferative diabetic patient [6]. However, treatment with PRP is not without side effects either, and may result in loss of central vision from macular edema, peripheral visual field constriction with poor dark adaptation and a loss of

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## KEY POINTS

- Pan retinal photocoagulation has provided an effective treatment to decrease the risk of severe vision loss in patients with proliferative diabetic retinopathy.
- Pattern scan laser can achieve comparable results to the conventional argon pan retinal photocoagulation in the treatment of patients with diabetic retinopathy.
- Pattern scan laser provides a better side effect profile when compared with the conventional argon laser.
- Adjusting the pattern scan laser settings might become necessary to maintain regression and eliminate recurrence of neovascularization in patients with high-risk diabetic retinopathy.

accommodation. Therefore, there have been attempts, both in laser development as well as in treatment protocol development, to try to minimize these side effects as much as possible. It is postulated that the pattern scan laser (PASCAL) may help minimize the side effects of PRP laser. This, together with the development of antivascular endothelial growth factor therapy, is increasingly being used as treatment for PDR.

## EVOLUTION OF PAN RETINAL PHOTOCOAGULATION

Pan retinal photocoagulation was historically performed with a xenon arc or argon blue-green (488 nm) laser of 100 ms duration by administering 800–1600 discrete gray-white 500-micron lesions outside the vascular arcades [4]. Consequent studies established comparable efficacy with the tunable dye (560–640 nm) [7], diode (810 nm) [8], and krypton red (647 nm) [9] lasers. However, the diode and krypton lasers resulted in more patient discomfort because of their higher wavelength and deeper penetration. Therefore, the argon green laser (514 nm) has, until very recently, become the delivery mechanism of choice for PRP. It has been reported that 57–77% of high-risk PDR eyes treated with traditional Diabetic Retinopathy Study-style PRP experience some regression of neovascularization within 6 months of treatment [9–11]. Figure 1 demonstrates retinal montage images of PDR treated with traditional PRP.

A relatively recent development by Blumenkranz *et al.* [12] is the PASCAL, which is a new frequency-doubled 532-nm wavelength neodymium-doped:yttrium aluminum garnet (Nd:YAG) laser with the capability to deliver arrays of up to 56 spots over the course of less than 0.6 s following a single foot pedal depression. The PASCAL provides

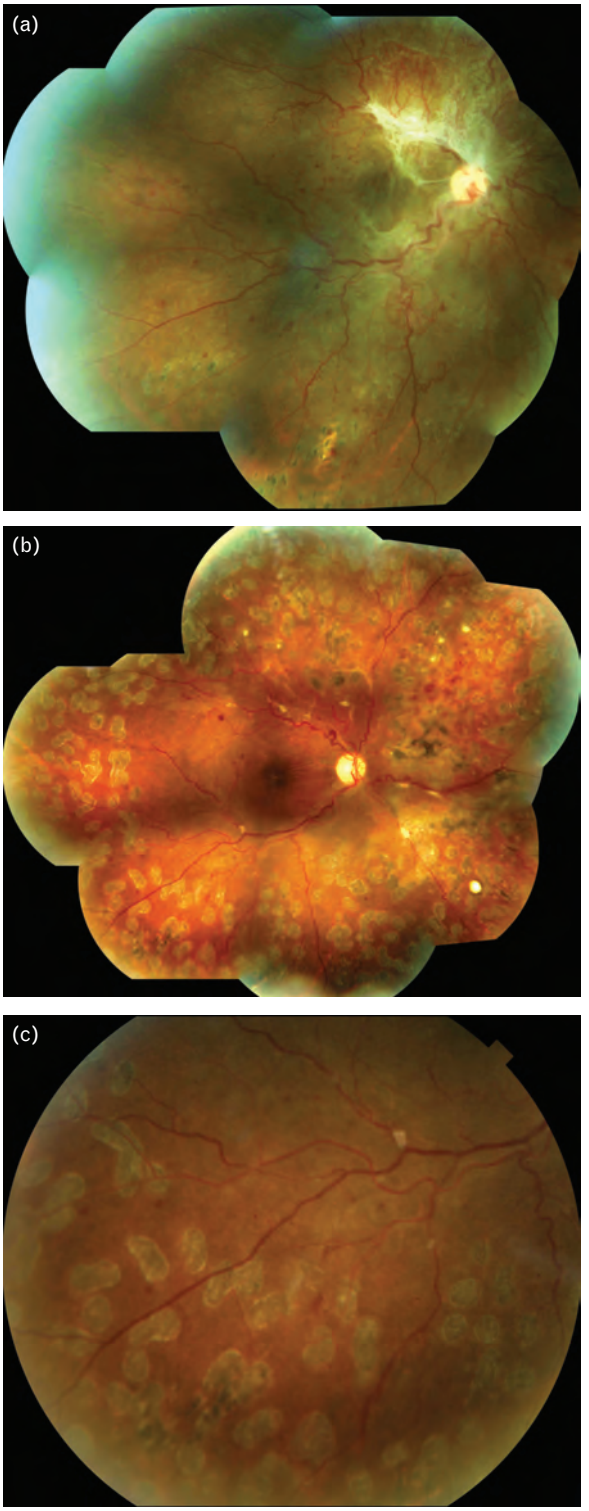


**FIGURE 1.** Montage retinal images of the right eye of a 29-year-old African-American woman with proliferative diabetic retinopathy who had received conventional 360 degree pan retinal photocoagulation using the argon laser (PRP); (a) before treatment with PRP, (b) after treatment with PRP; (c) color photograph of conventional argon laser scars. PRP, pan retinal photocoagulation.

the advantage of a quicker PRP procedure, by delivering nearly simultaneously a grid of short-duration laser pulses, each 1 magnitude shorter than the traditional argon laser pulse. The commercially available PASCAL (Pattern Scan Laser; Topcon Medical Laser Systems, Santa Clara, California, USA) was introduced as a safer and less painful alternative to the conventional argon laser for both macular photocoagulation and PRP. Figs. 2–4 demonstrate the well aligned arrays of retinal lesions created by the PASCAL.

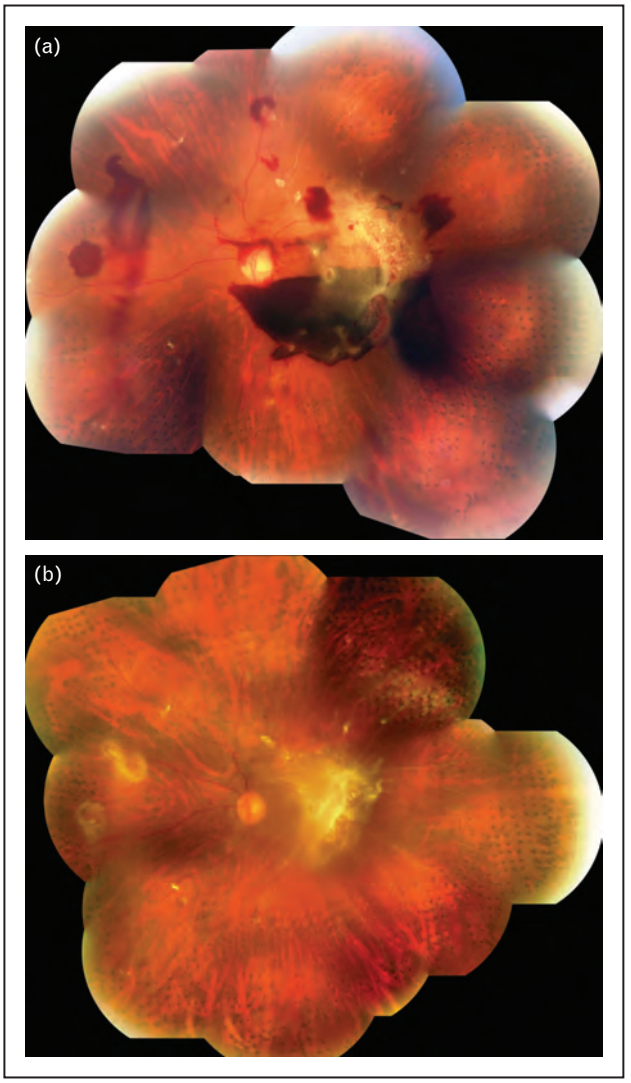


**FIGURE 2.** Montage retinal images of the left eye of a 43-year-old Caucasian man with proliferative diabetic retinopathy who had received treatment with pattern scan laser (PASCAL) photocoagulation. (a) There is neovascularization temporal to the macula which is causing preretinal hemorrhages. The PASCAL delivery system creates well aligned arrays of retinal lesions. (b) Regression of the neovascularization and resolution of the hemorrhage after more PASCAL treatments were applied.

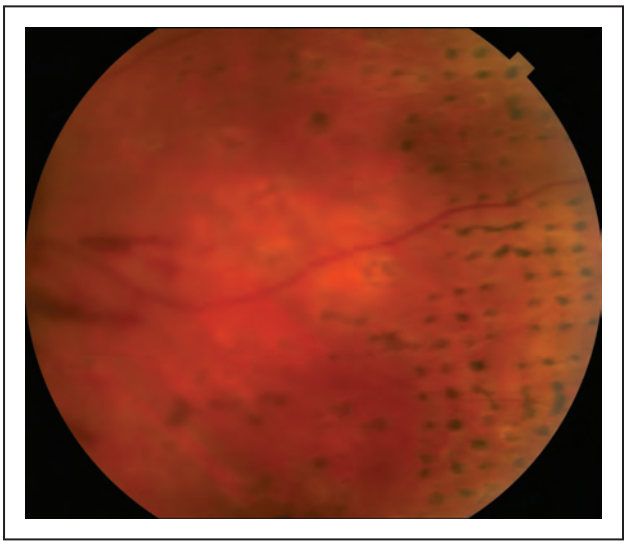

**FIGURE 3.** Retinal image of the right eye of a 50-year-old Caucasian man with proliferative diabetic retinopathy who had received treatment with pattern scan laser (PASCAL) photocoagulation. The PASCAL delivery system creates well aligned arrays of retinal lesions.

## MECHANISM OF ACTION OF PAN RETINAL PHOTOCOAGULATION

In human eyes, approximately 60% of the light that reaches the retina is absorbed within the retinal

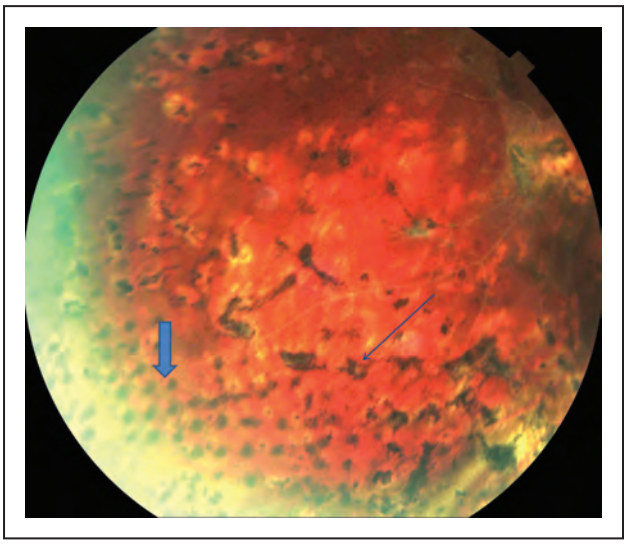

**FIGURE 4.** Retinal image of the left eye of a 26-year-old Caucasian man with proliferative diabetic retinopathy who had received treatment with conventional argon laser in the past and was recently treated with pattern scan laser (PASCAL) photocoagulation. The PASCAL delivery system creates well aligned arrays of retinal lesions (seen in the periphery of the color photo) (thick arrow), whereas the conventional argon laser scars are irregular with greater spread of the scar (seen in the center of the color photograph) (thin arrow).

pigment epithelium (RPE) [13,14]. The ellipsoidal, approximately 1-micron-sized melanosomes within the RPE cells are the strongest absorbent for visible light in the retina [15].

The primary stimulus for neovascularization in PDR is retinal ischemia and the consequent increase in local production of vasoproliferative factors [16]. PRP causes regression of neovascularization in PDR. However, the exact mechanism of this regression remains unknown. Theories have suggested that PRP causes improvement in retinal oxygenation by elimination of a portion of the hypoxic retina (reducing demand for oxygen), and by facilitating oxygen diffusion from the choroid, thereby decreasing the concentration of the vasoproliferative factors produced by the hypoxic retina. Since PRP targets the RPE, it might induce changes in the RPE production of the matrix metalloproteinase and tissue inhibitors of metalloproteinase production [17].

The RPE damage is caused by intracellular microbubble formation around the strongly absorbent melanosomes within the RPE cell, when the laser exposure time ranges between microseconds and nanoseconds [18–21]. The microbubble formation results in RPE cell structure disintegration and membrane disruption. However, when the laser exposure is within the sub-nanosecond range, nonlinear damage mechanisms unleash, including shock waves and laser-induced breakdown [20].

The Diabetic Retinopathy Study-based argon laser PRP burns were delivered with spot size ranging from 100 to 500 microns and pulse duration from 100 to 200 ms. This conventional PRP was performed over several sessions, because of the patient fatigue and discomfort encountered while completing at least a total of 1500 PRP burns [4]. When laser pulse durations are decreased below 50 ms, such as with the PASCAL, the laser-induced damage becomes limited to the RPE and photoreceptors, sparing both the inner retina and the choroid. This can be explained by the transition of cellular injury from thermal energy to mechanical rupture caused by the transient vapor taking place around the melanosomes [22].

## SIDE EFFECTS AND SAFETY PROFILE OF PAN RETINAL PHOTOCOAGULATION

The conventional argon laser mechanism of action relies on thermal-induced damage to the RPE, which can diffuse to the sensory neuron-rich choroid causing pain and discomfort. Because of the decreased pulse durations with the PASCAL, the mechanism of cellular injury shifts from thermal energy to mechanical rupture, and theoretically can spare the choroid and cause less pain. However, in the setting of PASCAL, the laser pulse duration and associated duration of hyperthermia decrease. Therefore, the temperature required to achieve the same amount of retinal coagulation increases, and subsequently higher laser power is needed. Once the temperature exceeds the vaporization threshold, vapor bubbles result in retinal rupture [23]. Therefore, the ophthalmologist has a smaller safety margin when titrating the power of the PASCAL, because the difference between the power resulting in therapeutic burn and the power that can cause rupture of the Bruch's membrane becomes smaller.

The Manchester Pascal Study evaluated 40 eyes of 24 patients with treatment-naive PDR and reported significantly lower levels of anxiety, headache, pain and photophobia by using multispot 20 ms PRP when compared to 100 ms single-spot PRP. These findings were related to the shorter-pulse duration, lower fluence, and spatial summation of laser nociception with multispot Pascal technique [24].

Mirshahi *et al.* [25▪] studied patients with symmetrical severe NPDR or PDR, in which one eye of each patient was randomized to receive conventional (100 ms) PRP and the other eye to undergo single-spot short-duration (20 ms) PRP. Pain scores were compared between the two treatments. Single-spot PRP was significantly less painful but just as effective when compared to conventional laser. Short-term single-spot PRP was well tolerated and highly accepted among patients. Al-Hussainy *et al.* [26] described decreased pain responses in patients with PDR treated with 20 ms PRP.

## PATTERN SCAN LASER VERSUS ARGON LASER

The Manchester PASCAL Study established favorable PDR regression rates and minimal laser burn expansion over 18 months follow-up after applying multiple 20-ms PASCAL treatments. However, this study reported significant increase in the average number of laser spots, retinal ablation areas and laser dosimetry necessary to achieve complete regression with worsening PDR [27]. The application of PASCAL 20-ms PRP burns also decreases the risk of overlapping laser burns, because the PASCAL laser burns show healing responses over time [27,28].

It is crucial to understand the differences between the PASCAL and the traditional argon laser in order to make the PASCAL treatment more effective for patients with PDR. Muqit *et al.* [29] compared the effects of PASCAL multispot PRP given in a

single session (SS-PRP) versus single-spot multiple-session PRP (MS-PRP) in 40 eyes with PDR. The mean treatment time for SS-PRP group was significantly shorter than the MS-PRP group (5.04 versus 59.3 min). There were no significantly increased adverse outcomes from using PASCAL versus single-spot MS-PRP at 12 weeks after laser, when looking at central retinal thickness, visual acuity, and visual field. PASCAL was as effective as MS-PRP in the treatment of PDR when looking at visual acuity and visual field improvements at 12 weeks after treatment.

Recently, Chappelow *et al.* [30▪▪] studied a total of 82 eyes with newly diagnosed high-risk PDR and found that the PASCAL was less effective than the traditional argon green laser PRP both in inducing regression and in preventing recurrence of retinal neovascularization within 6 months of initial treatment. Both lasers were applied with a similar number and size of laser spots in similar patients with high-risk PDR. The difference in the properties of the PASCAL and argon lasers limits the efficacy of the PASCAL when used in the context of traditional argon laser treatment parameters. Ophthalmologists may need to change treatment parameters when using PASCAL pattern laser therapy in high-risk PDR.

## TARGETED PATTERN SCAN LASER

Conventional PRP techniques involve laser application to all areas of the retina in patients with PDR, including normally perfused retina, nonperfused areas of the retina, as well as ischemic and angiographic areas of capillary dropout. Therefore, the idea of targeted PRP in PDR emerged with the goal of targeting only the areas of retina with ischemia and neovascularization using a wide-field fluorescein angiography system. Targeting those specific areas with laser treatment reduces long-term functional loss associated with burn expansion and makes the treatment less invasive and more comfortable. Muqit *et al.* [31▪▪] investigated the clinical effects and safety of targeted PASCAL in 28 eyes with treatment-naive PDR. Guided by wide-field fluorescein angiography using the Optos system, they applied single-session 20-ms-PASCAL 1500 burns to areas of retinal capillary nonperfusion and intermediate retinal ischemia. Wide-field Optos angiography at 24 weeks revealed complete disease regression in 37% and partial regression in 33% of treated patients. Additional PRP was planned for active PDR in 30%. There was a statistically significant increase in visual acuity by three letters at 24 weeks. However, there is no long-term follow-up on these patients.

## EFFECTS OF PAN RETINAL PHOTOCOAGULATION ON MACULAR THICKNESS

Optical coherence tomography (OCT) use has become ubiquitous among retina specialists, because of its ability to diagnose and quantitatively follow diabetic macular edema more accurately than slit-lamp biomicroscopy [32]. Recently, many studies have utilized OCT to evaluate macular changes after PRP in patients with diabetic retinopathy. PRP has been reported to cause temporary worsening of macular edema in patients with high-risk PDR. Shimura *et al.* [33] studied 14 patients with bilateral high-risk PDR who required pars plana vitrectomy (PPV) and had not received treatment with PRP. Only one eye per patient received PRP prior to the PPV. The concentrations of various cytokines were measured in each vitreous sample obtained during the PPV. OCT was utilized to measure and monitor the macular thickness throughout the clinical course. The authors found that PRP-induced macular edema was mediated by pro-inflammatory cytokines including interleukin-6 (IL-6) and regulated upon activation normal T-cell expressed and secreted (RANTES), but not with vascular endothelial growth factor (VEGF) and stromal derived factor-1 (SDF-1) [30▪▪]. Lee *et al.* [34▪▪] reported significant increase in central subfield thickness in patients with diabetic retinopathy at 3, 6, 12, and 24 months after conventional argon green PRP.

The Manchester Pascal Study investigated the effects of PRP on Fourier Domain OCT-measured macular thickness in 40 eyes with PDR. Compared with 20-ms single-session PRP with the PASCAL, PDR eyes treated with conventional 100-ms single-spot delivered over multiple sessions demonstrated increased total macular thickness at 4 weeks after treatment [35]. Similarly, Mirshahi *et al.* [25▪] used traditional laser with shorter duration (20 ms) and reported significantly smaller changes in central macular thickness from baseline in the short-time laser group when compared with the traditional-time laser group.

## EFFECTS OF PAN RETINAL PHOTOCOAGULATION ON RETINAL NERVE FIBER LAYER THICKNESS

Retinal nerve fiber layer (RNFL) thinning has been reported in diabetes itself [36–38], diabetic retinopathy [39], and associated glaucoma [40,41]. Recently, studies have investigated PRP as an independent cause of RNFL thinning in patients with diabetic retinopathy [34▪▪]. Kim *et al.* [42▪▪] evaluated the long-term changes of peripapillary RNFL thickness before and after PRP in patients with

severe NPDR and PDR by using Stratus OCT 3000 (Carl Zeiss Meditec, Dublin, California, USA). They applied multiple-session conventional argon green laser in three sessions and reported that the average peripapillary RNFL thickness increased slightly during the initial 6 months after PRP, and subsequently decreased gradually, showing a statistically significant reduction at 2 years post-PRP.

The Manchester Pascal Study investigated the effects of PRP on Fourier Domain OCT-measured macular nerve fiber layer thickness in 40 eyes with PDR. PDR eyes treated with PASCAL 20-ms single-session PRP showed no significant change in macular nerve fiber layer thickness from baseline at 12 weeks after treatment. In contrast, PDR eyes treated with conventional 100-ms single-spot delivered over multiple sessions demonstrated thinning of macular nerve fiber layer at 12 weeks after treatment [35].

## CONCLUSION

Pattern scan laser can achieve comparable results to the conventional argon PRP in the treatment of patients with diabetic retinopathy when applied appropriately [27,29]. The PASCAL delivery system creates well aligned arrays of retinal lesions in a shorter period. It provides a better side-effect profile. However, ophthalmologists should keep in mind that adjusting the PASCAL settings (including the duration, number, and size of laser burns) might become necessary to maintain regression and eliminate recurrence of neovascularization in patients with high-risk diabetic retinopathy. With the combination of anti-VEGF agents and laser used in the clinical setting for treatment of PDR, these parameters may change further.

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### Conflicts of interest

*The authors report no conflict of interest in regard to the material provided in the manuscript.*

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