

# Combine intravitreal bevacizumab with Nd: YAG laser hyaloidotomy for valsalva pre-macular haemorrhage and observe the internal limiting membrane changes: a spectralis study

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## Abstract

• **Valsalva retinopathy was described as a particular form of retinopathy, pre-retinal and subinternal limiting membrane haemorrhages in nature that rarely may break through and become subhyloid or intravitreal, secondary to a sudden increase in intrathoracic pressure. We reported a new way that Nd:YAG laser for ILM hyaloidotomy in order to drain the sub-ILM blood into vitreous cavity combined with intravitreal bevacizumab to improve the absorption of blood. Therapeutic alliance make significant outcome, protecting vision in time. We used spectralis OCT to observe sub-ILM mix cells and special ILM structure in this lesion for the first time, as the spectralis OCT can reach histology level imagination.**

• **KEYWORDS:** valsalva retinopathy; spectralis OCT; internal limiting membrane; bevacizumab

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## INTRODUCTION

Valsalva retinopathy was first described in 1972 by Thomas Duane as a particular form of retinopathy, pre-retinal and haemorrhagic in nature, secondary to a sudden increase in intrathoracic pressure. Incompetent or no valves in the venous system of head and neck allow direct transmission of intrathoracic or intra-abdominal pressure into the head and neck. Sudden elevation of venous pressure may cause a decompensation in the retinal capillary bed, with

subinternal limiting membrane haemorrhages that rarely may break through and become subhyloid or intravitreal<sup>[1]</sup>. We reported a new way to cure this lesion and observed the ILM changes by spectralis OCT.

## MATERIALS AND METHODS

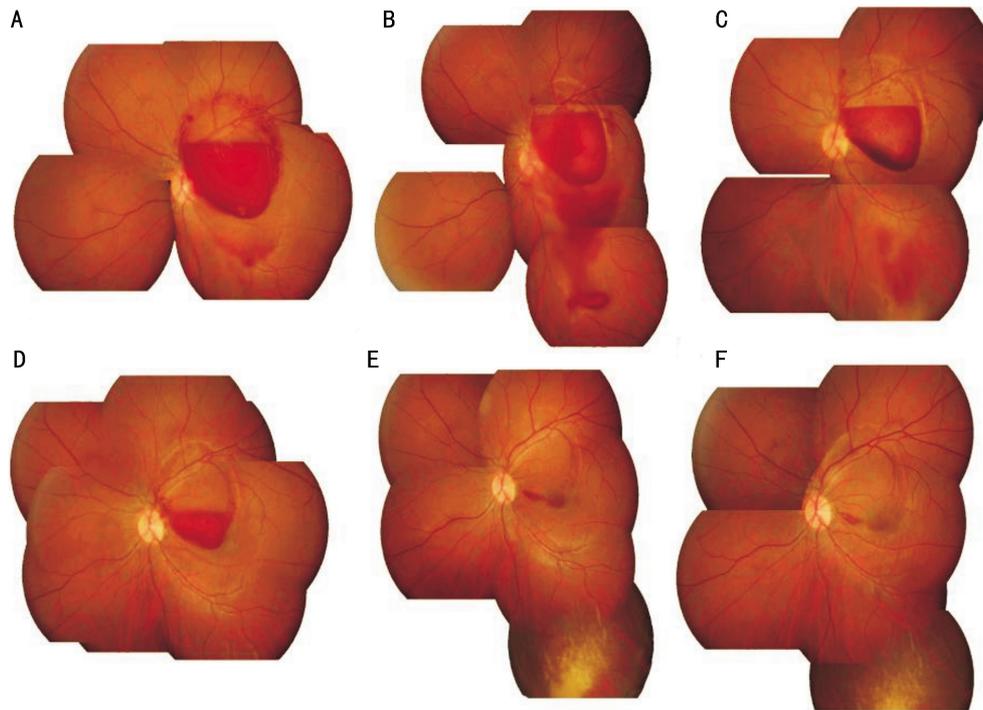
A 21-year-old male sportsman was referred to fundus disease clinic unit with a spontaneous and sudden loss of vision with black shadow in front of left eye after exercise 1 week ago without any history of trauma, hypertension or diabetes.

On examination, his vision was 6/6 and 6/60 the in right and left eyes, respectively. Anterior segment examination and IOP is normal. Dilated funduscopy revealed a dense 3 papilla disc (PD) diameter preretinal and subinternal limiting hemorrhage in the left eye and normal fundus appearance in the right eye.

Fundus fluorescein angiography (FFA) combined with indocyanine green fluorescein angiography (ICGA) demonstrated that vascular filling time was normal in the early phase and fluorescence in the posterior pole was covered by the hemorrhage, while the fluorescence of FFA and ICGA were visible on the upper part of sub-ILM hemorrhage in the left eye. SD-OCT combined with FFA showed sub-ILM hemorrhage with RBC sedimentation while plasma and WBC was above, forming a well-defined fluid level boat shape cavity. Highly reflective dots were visible on the upper part of the hemorrhage cavity. The other nine retinal layers were intact except the elevated ILM. A 1/4 PD diameter round blocked fluorescence just located above the optic nerve head and besides the retinal arteries on temporal upside. SD-OCT combined with FFA showed that it was preretinal hemorrhage beyond the ILM, without any leaking in the late phase of FFA. Ultrasound echography revealed there was none significant posterior vitreous detachment. Systemic examination was normal and Bp: 125/60mmHg. PT: 1.17s, APTT: 43.1s. A typical of Valsalva retinopathy was noted.

## RESULTS

Nd:YAG laser hyaloidotomy and intravitreal bevacizumab were employed to solve such problem and followed up by SD-OCT (Figures 1-2, Table 1). The treatment and outcome were listed as Table 2. About the ILM, there were two issues we should focus on (Figure 3).



**Figure 1 Fundus photograph demonstrates the nature history of valsalva retinopathy before and after therapy which is correspondence to table 2** A: Before therapy; B: 1 day after Nd:YAG hyaloidotomy; C: 10 days after Nd:YAG hyaloidotomy and 1 day after intravitreal bevacizumab; D: 2 months after Nd:YAG hyaloidotomy and 1 month and 19 days after intravitreal bevacizumab; E: 3 months and 5 days after Nd:YAG hyaloidotomy and 2 months and 24 days after intravitreal bevacizumab; F: 4 months after Nd:YAG hyaloidotomy and 3 months and 8 days after intravitreal bevacizumab.

**Table 1 The nature history of valsalva retinopathy before and after therapy which is correspondence to Figure 1**

Nd:YAG hyaloidotomy	Before therapy	1 day post-treatment	10 days post-treatment	2 months post-treatment	3 months and 5 days post-treatment	4 months post-treatment
Intravitreal bevacizumab			1 day post-treatment	1 month and 19 days post-treatment	2 months and 24 days post-treatment	3 months and 8 days post-treatment
Preretinal and sub-ILM	A dense 3 PD diameter haemorrhage with a clear fluid level		Blood reduced with dark red appearance, RBC sediment and intact retina was visible on the upper part of scaphoid shape hemorrhage cavity.	Blood kept on reducing with dark red appearance.		
Vitreous cavity	Vitreous floaters(below)	Sub-ILM blood inflow into vitreous cavity	Hemorrhage was absorbed significantly	The hemorrhage had been absorbed completely	The hemorrhage had been almost absorbed. There was white and yellow exudation in inferior of retina due to hemorrhage in the vitreous cavity degradation.	The hemorrhage had been almost absorbed. White and yellow exudation reduced gradually.

**Table 2 The treatment and outcome about Nd:YAG laser hyaloidotomy and intravitreal bevacizumab**

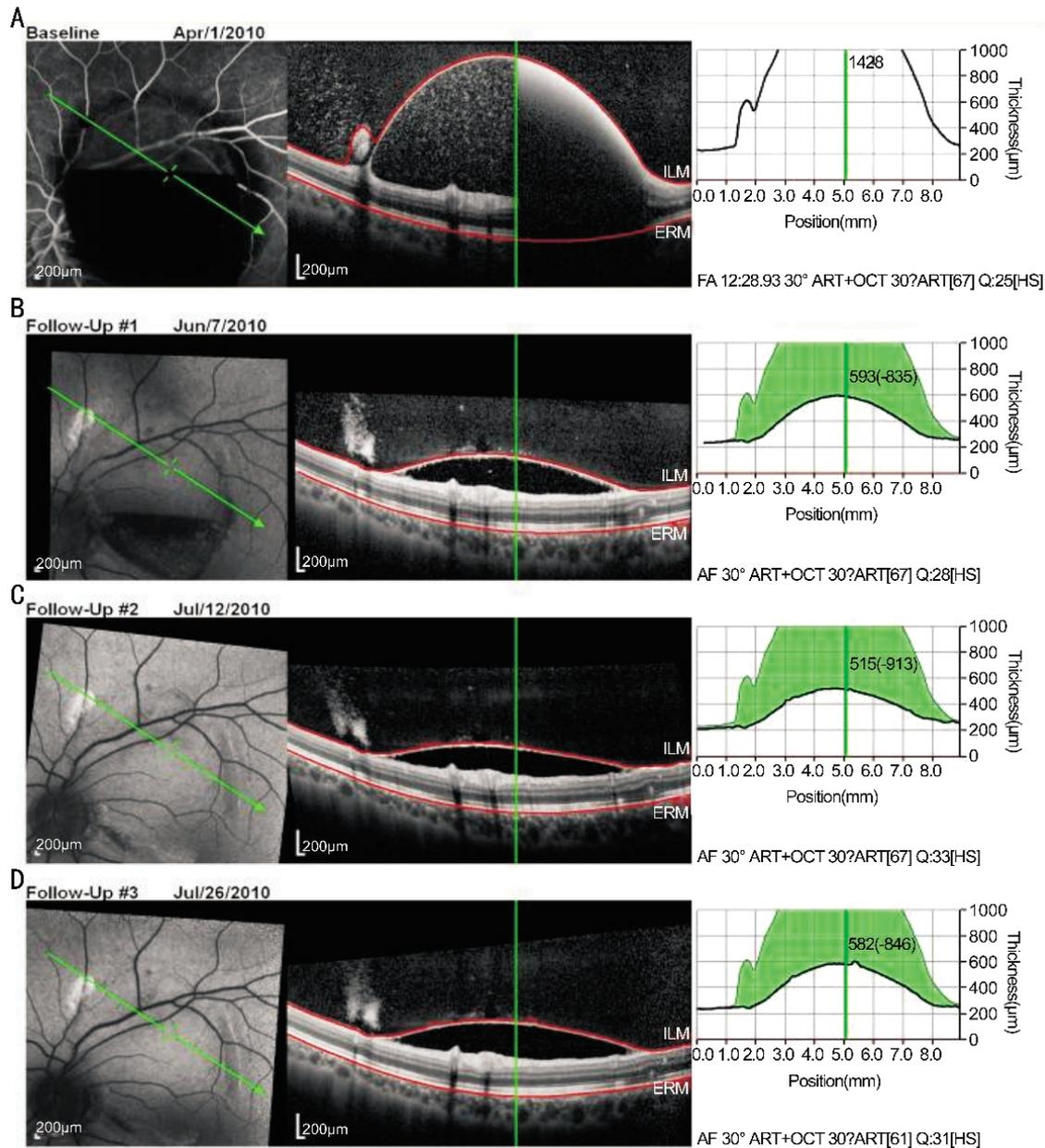
Schedule	Treatment	Outcome
For the first seven days	Sorbefacient conservative treatment	The condition not improved.
At the eighth day	Nd:YAG laser hyaloidotomy for valsalva pre-macular haemorrhage was performed (Nd:YAG laser energy: 2.5MJ, 4 point exploded)	The blood under the ILM enter into vitreous cavity partially and then the absorbing tendency was observed at a low rate. His vision was 7.2/60 in the left eye.
At the eleventh day after Nd:YAG laser therapy	Intravitreal bevacizumab 0.05mg	The patient felt better and the black shadow in front of left eye was shrinking gradually. There was great improvement in intravitreal hemorrhage absorption, and the sub-ILM hemorrhage was reducing significantly. But the left eye vision was still 7.2/60
After 1.5 months, 2.5 months and 3 months	Purely follow up	The preretinal hemorrhage above the optic nerve head scattered into vitreous cavity and was absorbed slowly. The sub-ILM hemorrhage was absorbed gradually and significantly making the fovea visible. Finally, his vision improved to 36/60 in the left eye.

First of all, a special reflective layer was observed in the SD-OCT, lying on the retinal nerve fiber layer (RNFL) tightly and just under the hemorrhage in the ILM elevated area. What was it? At the junction of elevated layer and the other retinal layers, we observed that the special layer mentioned above just derived from the intact ILM, in other words, only part of the ILM elevated. Further histopathology research is essential to confirm this structure. Secondly, we found that the retinal side of ILM became

rough with several high reflective spots attached to the (retinal) surface of the ILM. It was in accord with Gibran SK study that it was transdifferentiated retinal pigment epithelial (RPE) cells. It was the first time to observe such cell structure by spectralis OCT without histology technology *in vivo*

## DISCUSSION

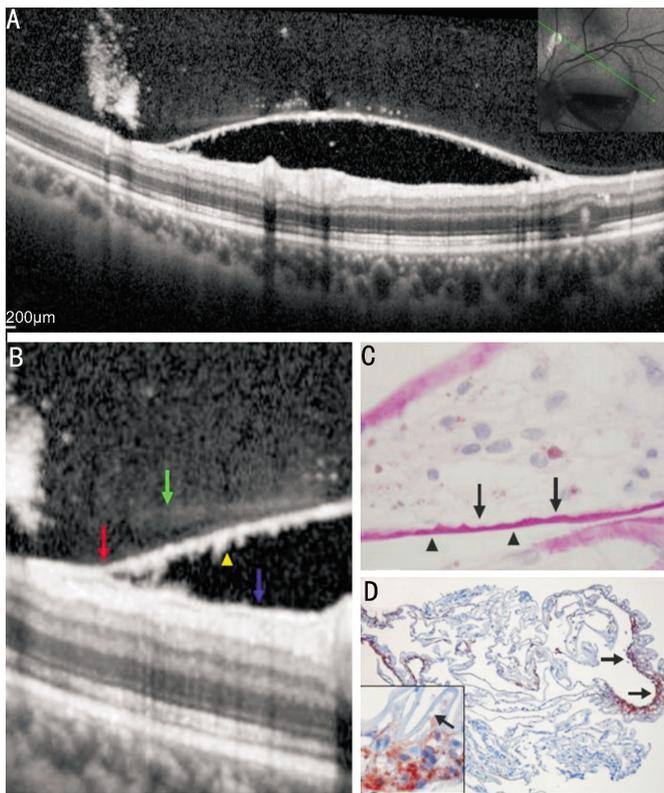
Valsalva retinopathy may occur due to intense physical exercise. Therapeutic options in Valsalva retinopathy include



**Figure 2** follow up by spectralis OCT in accord with Table 2 A: Before therapy; B: 2 months after Nd:YAG hyaloidotomy and 1 month and 19 days after intravitreal bevacizumab. The elevation of ILM decreased by 825 nm and the 1/4PD preretinal hemorrhage scattered into vitreous cavity; C: 3 months and 5 days after Nd:YAG hyaloidotomy and 2 months and 24 days after intravitreal bevacizumab. The elevation of ILM continued to decrease and the 1/4PD preretinal hemorrhage continued to scatter into vitreous cavity; D: 4 months after Nd:YAG hyaloidotomy and 3 months and 8 days after intravitreal bevacizumab.

conservative management, surgery (vitrectomy) and laser membranotomy. Most patients have better prognosis and the hemorrhage can be absorbed within several months, while due to RPE changes in macula, some patients have poor vision outcome. Kirwan and Cahill<sup>[2]</sup> conclude that Nd:YAG laser posterior hyaloidotomy is a useful outpatient procedure for successful clearance of large pre-macular haemorrhages that offers patients rapid recovery of visual acuity and the avoidance of more invasive intraocular surgery. Mumcuoglu *et al*<sup>[3]</sup> has reported that twelve soldiers had Valsalva retinopathy related to military exercise received Nd:YAG laser membranotomy and were observed for an average of 12.6 months and all eyes had visual acuities of 20/20 at the

end of the first month of follow-up. Nd:YAG laser treatment for Valsalva retinopathy related to military exercise is an effective and safe procedure. On the other hand, bevacizumab are used to cure neovascularization and vitreous hemorrhage by the effect of anti-VEGF, which usually are used in proliferative diabetic retinopathy and age related macular degeneration. Intravitreal injection of bevacizumab (IVB) and triamcinolone acetonide (IVT) at the end of diabetic vitrectomy is a useful adjunctive therapy for reducing early postoperative VH. IVB injection does not have a risk of a temporary rise of IOP, which the IVT group has<sup>[4]</sup>. The main characters of this lesion included huge sub-ILM



**Figure 3 ILM changes** A: the same as image B in Figure 2; B: SD-OCT showed a special reflective layer on RNFL tightly (blue arrow) derived from the intact ILM (red arrow); the rough side of elevated ILM (yellow arrowheads); the posterior hyaloids (Green arrow); C: High-power view of section in staining with periodic acid schiff reagent and haematoxylin to show that the cells are on the undulated (retinal) surface of the ILM (arrows) whereas no cells are seen on the smooth (vitreous) surface (arrowheads); D: Stained with the immunoperoxidase technique for cytokeratin 7 (red-brown chromogen) and counterstained with haematoxylin: layers of transdifferentiated retinal pigment epithelial (RPE) cells are observed (arrows). Inset: higher magnification demonstrates that the RPE cells are adjacent to the undulated (retinal) surface of the ILM (arrow). (C,D were cited from Gibran SK study: Changes in the retinal inner limiting membrane associated with Valsalva retinopathy).

hemorrhage, so that conservative management did not work. We used Nd:YAG laser for ILM hyaloidotomy in order to drain the sub-ILM blood into vitreous cavity, and combining with intravitreal bevacizumab to improve the absorption of blood. Therapeutic alliance make significant outcome, protecting vision in time. It is the first time to combine intravitreal bevacizumab with Nd:YAG laser hyaloidotomy for valsalva pre-macular haemorrhage all over the world, which provide a new way to cure such disease.

Epiretinal membrane (ERM) formation with ILM wrinkling

has been reported 10 months after ND-YAG membranotomy of Valsalva haemorrhage [5]. Histological examination of surgically removed ILM revealed the presence of haemosiderin within macrophages on the retinal side of the ILM and a fine glial ERM, resembling glial proliferation on the vitreous surface of the ILM [5]. Instead of an ERM, Gibran *et al* [6] reported there was a mixed-cell-type proliferation on the retinal surface of the ILM. The sub-ILM cells included trans-differentiated RPE cells, and hence the proliferation had the histological appearances of a proliferative vitreoretinopathy (PVR)-type membrane 'beneath' the ILM. Our study confirmed Gibran SK research about sub-ILM mix cells, while as we mentioned above, there was a special reflective layer observed in the SD-OCT, lying on the retinal nerve fiber layer (RNFL) tightly and just under the hemorrhage in the ILM elevated area which derived from the intact ILM. Further histopathology research is essential to confirm this structure.

Sabella *et al* [7] concluded that SD-OCT evaluation of Nd:YAG laser treatment for Valsalva retinopathy confirmed the cleavage plane of the pre-macular hemorrhage. In addition, it revealed the exact location of the ILM disruptions caused by the laser spots, and the safety of the procedure, with no involvement of the underlying retinal layers.

It is the first time to use spectralis OCT to observe sub-ILM mix cells and special ILM structure in valsalva retinopathy, as the spectralis OCT can reach histology level imagination.

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