

## Pneumatic Displacement of a Dense Submacular Hemorrhage with or without Tissue Plasminogen Activator

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**Background:** To evaluate the efficacy of treating a dense submacular hemorrhage with pneumatic displacement with or without tissue plasminogen activator (tPA).

**Methods:** Twenty-four patients with a dense submacular hemorrhage were treated with intravitreal expansile gas, with or without an intravitreal injection of tPA, in order to displace the submacular blood. The main outcome measurements include preoperative and postoperative visual acuity, postoperative fluorescein angiography (FAG) results and additional postoperative treatments.

**Results:** Total or subtotal subfoveal blood displacement was achieved in all 24 eyes. After a mean follow-up of 15.5 months (range 6-50 months), final visual acuity had improved two or more lines in 11 (45.8%) of the 24 eyes, and measured 20/100 or better in 10 (41.7%) of the 11 eyes. Based on the FAG results for 14 cases, nine eyes (64.3%) received additional postoperative laser treatment. Final visual acuity of 20/100 or better was achieved in four (40%) of the 10 eyes, with a choroidal neovascular membrane (CNVM) detected on FAG, and dye leakage not detected in three (75%) of the four eyes.

**Conclusions:** Pneumatic displacement, with or without intravitreal injection of tPA, seems useful in displacing dense submacular hemorrhage and facilitating visual improvement, although the visual result is often limited by the progression of the underlying macular disease. In patients with age-related macular degeneration, more treatable CNVM may be detected on postoperative FAG.  
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**Key words:** submacular hemorrhage, age-related macular degeneration, choroidal neovascularization, intravitreal gas, tissue plasminogen activator.

Submacular hemorrhage can occur due to a variety of conditions, including age-related macular degeneration (ARMD), presumed ocular histoplasmosis syndrome, retinal arteriolar macroaneurysm, trauma, myopia, or other conditions associated with choroidal neovascularization (CNV).<sup>(1-3)</sup> It is also a complication of ocular surgery, including vitrectomy

and scleral buckling procedure.<sup>(4)</sup>

The prognosis of untreated submacular hemorrhage is generally poor, although some cases may show spontaneous improvement in visual acuity.<sup>(5)</sup> A variety of therapeutic approaches have been developed, all with the common goal of clearing the submacular blood in order to minimize permanent dam-

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age to the photoreceptors and retinal pigment epithelium.<sup>(6)</sup> Heriot first described the management of submacular hemorrhage with intravitreal tissue plasminogen activator (tPA) injection and pneumatic displacement of blood from under the fovea.<sup>(7)</sup> His initial experience suggested a high anatomic success rate with few complications. However, other investigators had successfully displaced submacular hemorrhage using an intravitreal gas injection alone.<sup>(8,9)</sup>

The objective of our study was to evaluate the efficacy and safety of treating dense submacular hemorrhage with pneumatic displacement with or without tPA, and to identify any characteristics that may affect outcome after treatment.

## METHODS

From February 2, 2000 to August 6, 2004, the medical records of 24 patients who had undergone intravitreal injection of expansile gas, with or without adjunctive commercial tPA solution, for dense submacular hemorrhage were reviewed. A total of 24 eyes from 24 patients, who were seen at our institute with dense submacular hemorrhage, were enrolled. Chart review included the following data: age; gender; preoperative Snellen visual acuity; final Snellen visual acuity; duration and size of hemorrhage; type of expansile gas; dose of tPA injected; intra- and postoperative complications; postoperative fluorescein angiography findings and diagnosis; follow-up period, and other postoperative treatments.

A dense submacular hemorrhage was defined as one causing obvious foveal elevation with an ill-defined macular area detectable on stereo fundus photographs. The size of the hemorrhage needed to be at least three disc areas, and the period between symptoms and therapy one month but almost all were within 14 days. Individuals with a bleeding disorder, undergoing anticoagulant therapy or with a history of inflammatory eye disease were excluded from the study. Patients were also excluded if vitreous hemorrhage was present at the initial examination.

Each patient underwent a complete preoperative ophthalmological examination including visual acuity, slit-lamp biomicroscopy, indirect ophthalmoscopy and fundus photography to evaluate the size of the hemorrhage. Visual acuity was measured using a Snellen chart. The surgical procedure was

performed by one of four surgeons (HKK, MLK, YJC, HHT) at our institute between February 22, 2000 and October 15, 2003.

The procedure was performed in an outpatient setting, with the patient treated with topical anesthesia. After the bulbar conjunctiva was prepared with 5% Betadine solution, 25 to 33 µg of commercial tPA diluted with balanced salt solution up to a volume of 0.1 ml was injected into the midvitreal cavity, through a 30-gauge needle introduced 3-4 mm superotemporally posterior to the limbus; this was carried out on eight eyes. After an aqueous tap was used to reduce intraocular pressure, 0.3 to 0.4 ml of perfluoropropane (C<sub>3</sub>F<sub>8</sub>) or sulfur hexafluoride (SF<sub>6</sub>) gas was injected into the vitreous cavity, in a similar fashion, in all 24 patients. The patients were instructed to lie in a prone position within three hours of the procedure, and to maintain this position for 24 hours or as directed by the treating ophthalmologist.

Patients were typically examined one day and one week after surgery. Most patients underwent fluorescein angiography (FAG) to measure the adequate displacement of blood from the fovea, or once the vitreous hemorrhage had been resolved, within the first two months after surgery. In all cases, follow-up data was obtained over a minimum period of six months (mean 15.5 months; range 6-50 months).

## RESULTS

Table 1 summarizes the data collected. Of the 24 patients, 19 were male and five were female. Patients' ages ranged from 23 to 80 years (mean 61 years). The mean submacular hemorrhage duration was 9.8 days (range 1-30 days). The size of the subretinal hemorrhage ranged from three to 28 disc areas. The causes of the hemorrhages were ARMD (n = 18), traumatic choroidal rupture (n = 2), arterial macroaneurysm (n = 2), idiopathic polypoid choroidal vasculopathy (IPCV) (n = 1) and proliferative diabetic retinopathy (PDR) (n = 1).

All patients were followed up for a minimum of six months. Total or subtotal subfoveal blood displacement was achieved in all 24 eyes. Preoperative visual acuities varied from 20/60 to counting fingers. Final visual acuity, when compared with preoperative visual acuity, was improved by two or more lines in 11 out of 24 eyes (45.8%), was stable (within

**Table 1.** Summary of Collected Data

No.	Age/ Gender/ Eye	SMH		IVA	Gas Type	tPA Dose (µg)	Compli- cation	Post-op Angio.	Diagnosis	Post-op Laser Tx	F/U (month)	FVA
		D (day)	Area (DA)									
1	52/M/OD	7	11	20/100	C3F8	33	No	No leakage	ARMD	No	12	20/30
2	73/M/OD	3	3	20/1000	SF6	25	Rebleeding	Juxtafoveal CNV	ARMD	LPH x 1	16	20/400
3	51/M/OS	3	8	20/100	C3F8	33	No	Occult CNV	ARMD	TTT x 2	17	20/400
4	52/M/OD	1	28	CF	C3F8	33	No	Occult CNV	ARMD	TTT x 1	19	20/60
5	50/F/OS	4	5	CF	SF6	25	No	ND	ARMD	No	32	20/1000
6	23/M/OD	3	10	20/100	C3F8	33	No	Choroidal rupture	Traumatic choroidal rupture	No	13	20/30
7	41/M/OS	3	> 10	20/1000	C3F8	33	No	Choroidal rupture	Traumatic choroidal rupture	No	6	20/60
8	76/M/OD	14	10	20/100	SF6	25	No	MA	MA	No	16	CF
9	50/M/OS	30	24	CF	C3F8	—	VH	No leakage	ARMD	No	19	20/50
10	50/M/OS	30	> 10	CF	SF6	—	No	No leakage	ARMD	No	6	20/40
11	80/F/OS	7	> 10	CF	C3F8	—	No	No leakage	ARMD	No	16	CF
12	80/F/OD	30	11	CF	C3F8	—	No	Extrafoveal CNV	ARMD	LPH x 1	19	20/1000
13	78/M/OD	9	> 15	20/200	C3F8	—	VH	Extrafoveal CNV	ARMD	LPH x 1	8	20/400
14	70/M/OD	20	3	20/60	C3F8	—	No	Extrafoveal CNV	ARMD	LPH x 1	16	20/40
15	62/M/OS	10	10	20/400	C3F8	—	VH	Extrafoveal CNV	ARMD	LPH x 1	11	20/60
16	74/M/OD	4	12	20/400	C3F8	—	No	Juxtafoveal CNV	ARMD	LPH x 1	6	20/200
17	57/M/OS	7	5	20/60	C3F8	—	No	Occult CNV	ARMD	No	10	20/50
18	73/M/OD	3	16	20/1000	C3F8	—	VH	Occult CNV	ARMD	TTT x 1	10	20/400
19	66/M/OS	9	20	20/200	C3F8	—	VH	ND	ARMD	No	12	20/100
20	55/M/OD	3	> 20	20/1000	SF6	—	VH	ND	ARMD	No	12	20/400
21	66/M/OS	13	> 20	CF	C3F8	—	VH	ND	ARMD	No	27	20/1000*
22	54/F/OD	3	11	20/1000	C3F8	—	Rebleeding	IPCV	IPCV	LPH x 3	50	CF†
23	74/F/OS	12	> 10	20/400	C3F8	—	No	MA	MA	LPH x 1	6	20/200
24	56/M/OS	7	> 10	20/1000	C3F8	—	No	ND	PDR	No	13	20/400‡

**Abbreviations:** Angio.: angiography; ARMD: age-related macular degeneration; CF: counting fingers; CNV: choroidal neovascularization; D: duration; DA: disc area; F: female; F/U: follow-up; FVA: final visual acuity; IPCV: idiopathic polypoid choroidal vasculopathy; IVA: initial visual acuity; LPH: laser photocoagulation; M: male; MA: arterial macroaneurysm; ND: not done; Post-op: postoperative; SMH: submacular hemorrhage; TTT: transpupillary thermotherapy; Tx: treatment; VH: vitreous hemorrhage.

\* Additional trans pars plana vitrectomy + scleral buckling were performed two weeks after primary surgery for massive vitreous hemorrhage.

† Additional phacoemulsification + scleral buckling + trans pars plana vitrectomy + silicone oil tamponade were performed 28 months after primary surgery for recurrent massive bleeding.

‡ s/p trans pars plana vitrectomy before pneumatic displacement.

less than two lines from baseline) in 11 eyes (45.8%), and decreased two or more lines in two eyes (8.3%). Ten eyes (41.7%) attained a final visual acuity of 20/100 or better, of which four eyes (40%) had initial visual acuity of 20/100 or better. In the remaining 14 eyes with final visual acuity under 20/100, two eyes (14.3%) had initial visual acuity of 20/100 or better.

Of the 18 ARMD eyes, with an average follow-up period of 14.9 months, five eyes received surgery using tPA. Two of the five eyes (40%) that underwent pneumatic displacement with tPA had a final

visual acuity of 20/100 or better, whereas six of the 13 eyes (46.2%) that underwent pneumatic displacement alone, had the same result. Furthermore, three of the five eyes (60%) that underwent pneumatic displacement with tPA had improved two or more Snellen lines of visual acuity, whereas six of the 13 eyes (46.2%) that underwent pneumatic displacement alone showed a comparable result.

In the non-ARMD group, two eyes with choroidal rupture without foveal involvement had improved visual outcomes of 20/30 and 20/60. Of the two eyes with macroaneurysm, the final visual

acuties were counting fingers and 20/200. The visual outcome of the eye with IPCV was poor and complicated by massive subretinal rebleeding during the follow-up period. The remaining case with PDR had a final visual acuity of 20/400.

Of the 18 eyes with ARMD, postoperative FAG was carried out on 14 eyes, of which positive postoperative angiographic findings were noted in 10 (71.4%). In 14 eyes subjected to postoperative FAG, four showed a classic extrafoveal choroidal neovascular membrane (CNVM) that was treated successfully by laser photocoagulation and this resulted in two having improved final visual acuities of 20/40 and 20/60. The angiograms of two eyes showed a predominantly classic juxtafoveal CNVM that was treated with laser photocoagulation, and they had final visual acuities of 20/400 and 20/200. Four eyes showed a predominantly occult CNVM, and transpupillary thermotherapy (TTT) was performed on three of them, resulting in two with improved final visual acuities of 20/50 and 20/60. Four postoperative angiograms did not show any leakage, and three of these eyes had 20/50 or better final visual acuities. Only one eye that showed no leakage on FAG but continued to have poor visual acuity (counting fingers), had a macular disciform scar. No postoperative angiogram was carried out on four eyes because the surgeons believed that the neovascular lesion was fibrotic and clinically inactive.

Surgery was accomplished without major intraoperative complications. No evidence of retinal toxicity, such as retinal detachment or pigment epithelial changes, was found with tPA usage. During the course of the follow-up, two of the 24 eyes (8.3%) in our study developed recurrent subretinal hemorrhage; one of these had undergone scleral buckling, pars plana vitrectomy and cataract surgery. Neither of them showed any improvement in visual acuity after surgery. Seven eyes (29.2%) had postoperative vitreous hemorrhage; one of these patients received scleral buckling and pars plana vitrectomy for a massive vitreous hemorrhage. Among the seven eyes suffering postoperative vitreous hemorrhage, six had a submacular hemorrhage that was larger than 15 disc areas. Further, none of the eyes with submacular hemorrhages smaller than 10 disc areas developed this complication. The vitreous hemorrhages had almost resolved by the final follow-up visit.

## DISCUSSION

Several mechanisms, including the toxic effects of iron, shearing damage to the photoreceptors by fibrin clots and a mechanical barrier between the retina and the choriocapillaris, may be the cause of dense subretinal hemorrhage, and have been postulated as explanations for retinal damage caused by thick subretinal blood.<sup>(5,6,10,11)</sup> The natural course of submacular hemorrhage is associated with a poor prognosis.<sup>(12)</sup> Avery et al. described the clinical course of eyes with subfoveal hemorrhage secondary to ARMD.<sup>(10)</sup> After a follow-up period of six months, a loss of three or more lines of visual acuity from the baseline level was observed in 48% of eyes. In a retrospective case series, Scupola et al. reviewed the clinical course of untreated eyes with submacular hemorrhage related to ARMD, and found that they showed a considerable decrease in visual acuity over time, with an average visual acuity of 20/1250 at the final follow-up visit (mean 24 months).<sup>(11)</sup> In the 18 eyes with ARMD and submacular hemorrhage in our study, the average final visual acuity was 20/200 after a follow-up period of 14.9 months, which is better than the untreated eyes reported by Bennett et al.<sup>(6)</sup> Therefore, it seems to be beneficial to treat patients with dense submacular hemorrhage by pneumatic displacement.

In a prospective case series, Hattenbach et al. investigated the efficacy of treating submacular hemorrhages secondary to ARMD with an intravitreal injection of tPA and gas. They reported that they were able to displace the blood from under the fovea in 81% of cases. Also, visual acuity was improved two or more lines in 30% of eyes, was stable in 61% of eyes, and two or more lines worse in 9% of eyes.<sup>(13)</sup> Hassan et al. reported on their experience of treating thick submacular hemorrhages with tPA and pneumatic displacement.<sup>(14)</sup> The final visual acuity for their patients with hemorrhage secondary to ARMD ranged from 20/30 to 2/200, with five of 13 (38.5%) having a visual acuity 20/80 or better after a mean follow-up of 10.8 months. In the 18 eyes with ARMD in our study, final visual acuity was improved in nine (50%), and eight (44.4%) had a final visual acuity of 20/100 or better after a mean follow-up of 14.9 months. The visual outcomes of our cases are thus similar to the study by Hassan et

al. In our cases, subjective visual improvement and total or subtotal subfoveal blood displacement were noted postoperatively. Since the blood displacement correlates to the duration of onset, size and thickness of blood, and patients' cooperation in maintaining a postoperative prone position etc., it is difficult to estimate and compare the speed of blood disappearance between the tPA and non-tPA group.

Though intravitreally injected tPA may facilitate the dissolution of subretinal blood clots,<sup>(15,16)</sup> the benefit of intravitreal tPA injection is controversial.<sup>(14,17)</sup> In an experimental study, Kamei et al. demonstrated that intravitreal tPA does not diffuse through the intact neuroretina either in healthy eyes or in eyes with an experimental created subretinal hemorrhage.<sup>(18)</sup> Furthermore, intravitreal gas, without tPA, can adequately displace submacular blood in most cases.<sup>(8)</sup> This is probably because fibrinolysis is a naturally occurring process and the displacement of hemorrhages seems to be as successful with SF<sub>6</sub> as it is with C<sub>3</sub>F<sub>8</sub>.<sup>(2,19)</sup>

Our sample size is small and without a control model so we could not conclude the benefit of tPA treatment. Further prospective studies are necessary in order to draw a conclusion as to whether intravitreal tPA has a beneficial effect on visual outcome. In light of the cost and potential complications of tPA, including retinal toxicity, vitreous hemorrhage and recurrent bleeding,<sup>(14,17)</sup> it would be desirable to use it as adjunctive therapy only in the subset of eyes that would fail to show displacement by gas alone.

The visual outcomes in patients with submacular hemorrhage appear to be closely related to the underlying cause of the hemorrhage.<sup>(6)</sup> Patients with submacular hemorrhage due to ARMD usually have a poor outcome,<sup>(5,6,10)</sup> whereas those with submacular hemorrhage due to traumatic choroidal rupture or as a complication of scleral buckling surgery, tend to do better.<sup>(6,20)</sup> In our study, we found that submacular hemorrhage associated with traumatic choroidal rupture with foveal sparing showed excellent results, as a previous study had shown.<sup>(6)</sup> Hemorrhages due to arterial macroaneurysm, IPCV and PDR showed poorer results.

Although Hattenbach et al. showed that visual results of ARMD cases tend to be worse with a larger size of hemorrhage and poor initial visual acuity,<sup>(13)</sup> we did not find the same link between poor prognosis and hemorrhage size. We believe that the thick-

ness of hemorrhage correlates with the prognosis but we did not measure the thickness of the blood clot because of technical difficulties. There is growing evidence that visual improvement in eyes with ARMD is limited by the underlying disease, namely, the presence and location of a CNVM.<sup>(5,9,14)</sup> Berrocal et al. demonstrated that eyes with submacular hemorrhage secondary to ARMD may show spontaneous visual improvement, and the best predictive factor for poor final visual acuity was the presence of a subretinal neovascular membrane.<sup>(5)</sup> In their retrospective series, Hassan et al. showed that among 13 patients with ARMD, 11 eyes underwent fluorescein and/or indocyanine green angiography after submacular blood displacement, and final visual acuities of 20/80 or better were seen in only three out of the four patients with quiescent fibrovascular pigment epithelium detachment (non-leaking) and in two out of the three patients without CNVM detected by FAG.<sup>(14)</sup> Laser treatment for CNV was performed in only two eyes. However, none of the four patients with active FAG leaks in the above-mentioned articles had a final visual acuity of 20/80 or better.

In our study, of the 18 eyes with ARMD, postoperative FAG results were obtained for 14 eyes; among these, further treatment was performed on nine (64.3%) based on the results of the FAG. A better visual outcome (final visual acuity of 20/100 or better) was associated with the findings of the postoperative FAG. In the subgroup with CNVM on FAG, four of the 10 eyes (40%) had a final visual acuity of 20/100 or better, whereas three of the four eyes (75%) without active leakage on FAG attained the same outcome. In those eyes with CNV that were treated with postoperative laser, four out of nine (44.4%) had a final visual acuity of 20/100 or better over a follow-up period of at least six months. Compared with the study by Hassan et al., our results demonstrated that displacement of blood may improve the chances of successful laser treatment of CNV for ARMD.

We found no evidence of retinal toxicity using tPA in a dose of 25-33  $\mu$ g. This is consistent with the findings of Hassan et al., who used tPA of 25-100  $\mu$ g in their study.<sup>(14)</sup> However, intravitreal tPA should be used with caution because several experimental studies have demonstrated dose-dependent toxicity, and it could be harmful if the concentration is greater than 50  $\mu$ g.<sup>(21)</sup> Two eyes in our study developed recurrent

submacular hemorrhage, and both of them had poor visual outcomes. This could be attributed to the progression of their underlying macular disease. The major complication seen in this series was breakthrough vitreous hemorrhage, which occurred in seven eyes (29.2%). Interestingly, none of them had been treated with tPA. Among these seven eyes, six had a submacular hemorrhage larger than 15 disc areas. Further, none of the eyes with submacular hemorrhages smaller than 10 disc areas developed this complication. This is probably because the larger the submacular hemorrhage, the greater the risk of breakthrough vitreous hemorrhage.

The follow-up interval varied considerably, so our long-term data must be interpreted with caution. Since the rate of recurrent CNV was so high,<sup>(22,23)</sup> we recommend that treated patients be monitored carefully. Other limitations of this study include its retrospective and non-controlled nature, its relatively small sample size, and its lack of standardized visual acuity measurements. More research and controlled randomized trials are needed to determine the benefit of this therapeutic approach.

We conclude that pneumatic displacement, with or without intravitreal injection of tPA, is useful in displacing dense submacular hemorrhage and facilitating visual improvement. However, the visual result is often limited by the progression of the underlying macular disease. More treatable CNVM can be detected on postoperative FAG in ARMD patients, and 44.4% of those treated with laser ablation attained a visual acuity of 20/100 or better at the end of a follow-up period of at least six months. In the ARMD group, those without CNVM had a better visual outcome. Further controlled studies will be required to assess the efficacy of laser photocoagulation in the treatment of submacular hemorrhage complicated by choroidal neovascularization.

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# 以合併或不合併使用 tPA 的氣體移位術 來治療厚的黃斑部下出血

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**背景：** 評估以合併或不合併使用組織蛋白溶酶原活化劑 (tPA) 的氣體移位術來治療厚的黃斑部下出血的效果。

**方法：** 24 位有厚的黃斑部下出血的病人，以玻璃體內注射會膨脹的氣體合併或不合併使用 tPA，使黃斑部下出血移位。治療結果以術前及術後的視力，術後螢光血管攝影 (FAG) 的結果，及術後附加的治療作為評估的主要依據。

**結果：** 所有 24 隻眼睛都可達到視網膜中央凹出血完全或近乎完全移位。在平均追蹤 15.5 個月後，11 隻眼睛 (45.8%) 的最終視力進步兩行以上，10 隻眼睛 (41.7%) 的最終視力在 20/100 以上。在術後做 FAG 檢查的 14 個病人中，9 隻眼睛 (64.3%) 在術後接受雷射治療。在 FAG 上發現有脈絡膜新生血管 (CNVM) 的 10 隻眼睛中，4 隻眼睛 (40%) 的最終視力在 20/100 以上，其中 3 隻眼睛 (75%) 在 FAG 上沒有發現螢光染劑的滲漏。

**結論：** 合併或不合併使用玻璃體內注射 tPA 的氣體移位術對使厚的黃斑部下出血移位及改善患者視力似乎有所幫助，雖然視力的結果常受限於患者原本黃斑部病變的進一步惡化。在 ARMD 的病人，術後的 FAG 檢查能發現可做進一步治療的 CNVM。  
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**關鍵字：** 黃斑部下出血，老年性黃斑部病變，脈絡膜新生血管，玻璃體內氣體，組織蛋白溶酶原活化劑。

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