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Our experience of the peri-ocular injection of Bevacizumab (Avastin) to the patient with malignant hypertension and grade III retinopathy in Taiwan

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Abstract

Purpose: To report a patient with malignant hypertension (200/160 mmHg) , ocular hypertension (30mmHg) and grade III hypertensive retinopathy induced from long-term near-distance working (12 hours/ day) without adequate relaxation for at least 3 months.

Case Report: A 22 female girl came to our hospital because of headache, periocular pain and blurred vision for 2 weeks since October 2015. To our surprise, her BP revealed 200/160 mmHg in stable condition. She is a slender official lady and denied any family and taking special medication history. Her intraocular pressure (IOP) was within 28-30 mmHg and the best-corrected visual acuity (BCVA) was only 6/30 because of hypertensive retinopathy (Grade III) in both eyes. Immediately, she received two doses of avastin injection and focal laser treatment to decrease the edema and enhance the absorption of retinal hemorrhage within one month. Six weeks later, her BCVA returned to 6/6 without complication. According to our previous studies, IOP may reach 3 mmHg/hour without enough rest. Moreover, the summative effects is significant that when the working distance is less than 30 cm for 8 hours without relaxation. Hence, the increasing 24 mmHg would be created. In

other word, when you got off day after 8 hours, you would possibly have the IOP above 44 mmHg (20mmHg baseline + added 24 mmHg). Similarly, you used the smartphone over time, and the troublesome disaster may come. It's evidence that associated higher IOP may damage the ocular structure and further result in glaucoma, various stages of hypertension, and even stroke.
Conclusion: Long-term short-distance reading or playing smartphone may block aqueous humor outflow and create higher IOP. Hence, further induced the advanced hypertension and hypertension retinopathy may impact the vision and even life. Therefore, we strongly suggested that you had better close your eyes and message the periocular region combined with hot compression may be benefit for ocular strain. It is an interesting that the case is the first one repot about playing smartphone resulting in hypertensive crisis and grade III hypertensive retinopathy in the world,

Key words: hypertension crisis, avastin, smartphone

Introduction

Hypertension affects from 20% to 30% of the world population. Blood pressure (BP) is the most consistent and power predictor of stroke. Hypertension results in a myriad of pathologic changes renal, neurologic, and ocular systems, in addition to the vascular system[1,2,3,4]. Hypertension is considered as a chronic disease; however, it may impact the life quality and even human life. For example, severe elevations in blood pressure within a short time are known to result in left ventricular hypertrophy[5], congestive heart failure, cerebrovascular disorders (i.e., ischemic heart disease, congestive heart failure), stroke [6,7,8,9,10,11], peripheral arterial disease, obesity, metabolic syndrome (BMI > 30) and acute neurologic symptoms (i.e. hypertensive encephalopathy, spinal cord edema, cerebral edema, renal failure, uremic process, and even posterior reversible leukoencephalopathy syndrome)[12,13,14]. The anti-hypertensive and well-planned strategies are available to achieve the gold of mental health and lifestyle modification[15]. At present, systemic hypertension affects approximately 78 million adults in the United States, with only 53% of those carrying this diagnosis. The ocular manifestations of systemic hypertension are very common and easily result in vascular compromise at the level of the retina, the choroid, or the nerve[1]. Hypertension crisis are divided into hypertensive urgencies and emergencies. Together they form a heterogeneous group of acute hypertensive disorders depending on the presence of type of target organs involved. Despite better treatment options for hypertension, hypertensive crisis and its associated complications (e.g. renal failure) remain relatively common[1]. For example, the Beaver Dam Eye Study (a large base of hypertensive studies) estimated that 10.7% of hypertensive patients over the age of 40 have hypertensive retinopathy and over a 5-year follow-up period 6% of those who had normal examinations developed hypertensive retinopathy[2].

Hypertensive retinopathy is the most common ocular sign of hypertension and is a result of the breakdown of the blood-retinal barrier. It is characterized by retinal arteriolar attenuation and is a result of the breakdown of the inner blood-retinal border. Oxidative stress and free radicals theory may be the pathogenesis of the hypertension[61]. Some victims were associated with obesity and metabolic syndrome[62]. It is interesting that long-term effects of weight-reducing drugs in

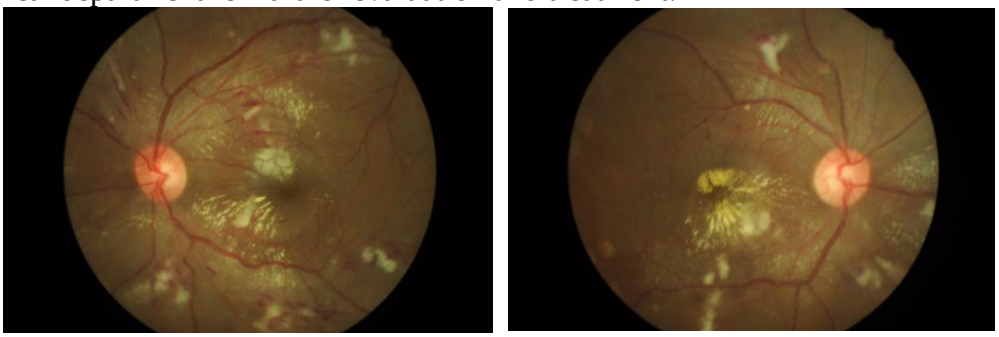
people with hypertension[63]. However, the etiologies of 90-95% of the hypertension are unknown. In the ophthalmic field, we could find that the morphology of hypertensive retinopathy, for example, retinal arterioles attenuation (copper wiring of the retinal arterioles caused by sclerosis and hyalinization of the vascular walls), arteriovenous crossing changes (nicking; AV crossing), cotton wool spots, and the advanced cases, retinal arteriolar exudation leading to macular edema and even scar formation which is one reason of blindness. Now Keith's classification is very popular and characterized by flame-shapes hemorrhages (grade III) and optic nerve edema (papilledema) (grade IV). Because of the critical stages, we can use the non-mydriatic ocular fundus photography to capture advanced malignant retinopathy as real time when patients complained about headache and the diagnosis of brain lesion was highly suspected to find papilledema or retinal disorders.[22,38]. Why did we must have make the decision in staging of the hypertensive retinopathy? The answer is that the stages of hypertensive retinopathy give us the correct guild-line and medical decision for diagnosis and treatment [64]. For example, the occurrence of grade III and grade IV hypertensive retinopathy may result in end-organ damage and even mortality and healthcare utilization. The advanced hypertensive retinopathy may bring about decreased vision and even blindness. Therefore, how to control the elevated BP becomes very important. For example, Cao and his workers demonstrated that any prescription for preventing and treating from stroke is essential. Besides, to give up the smoking habit may benefit hypertension and its associated complication[65]. Januszewicz et al. also reported that the role of the activation of the renin-angiotensin-aldosterone system and endothelial dysfunction in the pathogenesis of malignant hypertension has been well described. Besides, prognosis and survival rates in these patients have improved significantly owing to earlier detection, stricter BP control, lower BP targets, better choice of antihypertensive drugs, and availability of hemodialysis and renal transplantation[66]. In clinic, most of patients of hypertensive retinopathy is higher than 40 years and the victims may had hypertriglyceride, hyperglycemia and hyperlipidemia which need more complicated medical care. In our report, the patient is younger girl without any systemic diseases before this first visiting (fresh case).

Bevacizumab (Avastin, Genentech) is the first Food and Drug Administration (FDA) approved therapy applied intravenously as an adjunct for the treatment of metastatic colorectal cancer. It also improves progression-free survival rates in patients with previously untreated metastatic breast cancer. Indeed, bevacizumab is a monoclonal antibody that binds all isoforms of vascular endothelial growth factor A (VEGF-A). It is a potent inhibitor of angiogenesis, and has also been used effectively in the treatment of neo-vascular ARMD (age-related macular degeneration). Intravitreal injection of anti-VEGF agents has been reported effective in inducing the regression of new vessels in proliferative diabetic retinopathy (PDR), and neovascular glaucoma[14,15,16]. However, the benefit for controlling hypertensive retinopathy was rarely discussed. In our report, we will demonstrate that we successfully and safely treated a 22 female lady with malignant hypertension and grade III hypertensive retinopathy any residual l complications for 6 months.

Case Report

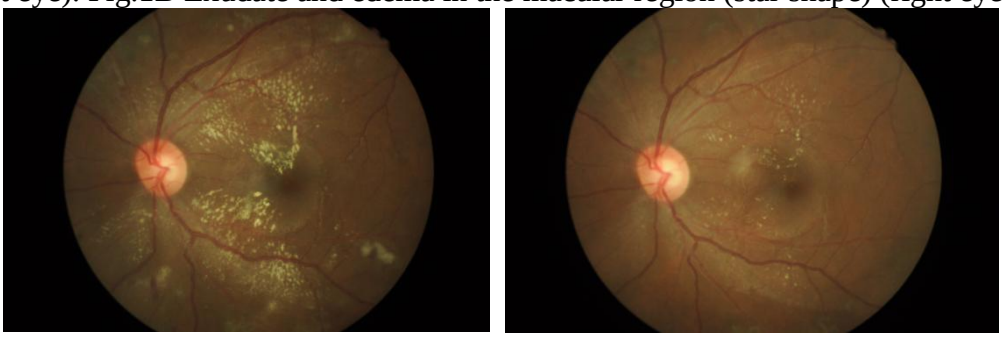
A 22-year-old female lady without past medical history presented with one

week of blurry vision in the both eyes on October 2015. She called at our out-patient department (Kaohsiung Armed Forced Hospital, Kaohsiung City, Taiwan, ROC). In ophthalmic department, we inquired her any history in detail and arranged the necessary physical examination. She told to us that there are no other special ocular, medical or surgical histories. Upon further history taking, she endorsed bi-temporal headache and peri-ocular strain over the past 2 weeks. Ophthalmic examination revealed Best corrected visual acuity (BCVA) of 6/30 in the both eyes by glasses. Her intraocular pressure (IOP) was approximate to 32 mmHg (both eyes) by air-puff tonometer (Kowa; Japan). Her pupils reacted normally without an affected pupillary defect. Furthermore, the extraocular motility, and ocular alignment in both eyes were normal. We also found that mild narrowing and sclerosis of arteries, dilated veins, cotton wool spots, yellow-exudates, flame-shape hemorrhage and mild macular edema (stare shape) in the both eyes which is defined as grade III hypertensive retinopathy (Figure 1A and 1B). At the same time, the optic coherence tomography (OCT; OPTOS; UK) revealed macular edema and neurosensory detachment in her bilateral eyes (Fig 4A). Therefore, the patient was treated with a deep periocular injection of avastin (0.3 CC) immediately in order to decrease the macular edema and retinal hemorrhage[16]. Besides, we used the anti-glaucoma agents(α-agonist) (Alphagan) to lower the IOP three times in one day. To our surprised, her BP shoed 200/160 mm Hg at sitting position repeatedly. Moreover, we also transferred to medical department for further evaluation and treatment.



(A) (B)

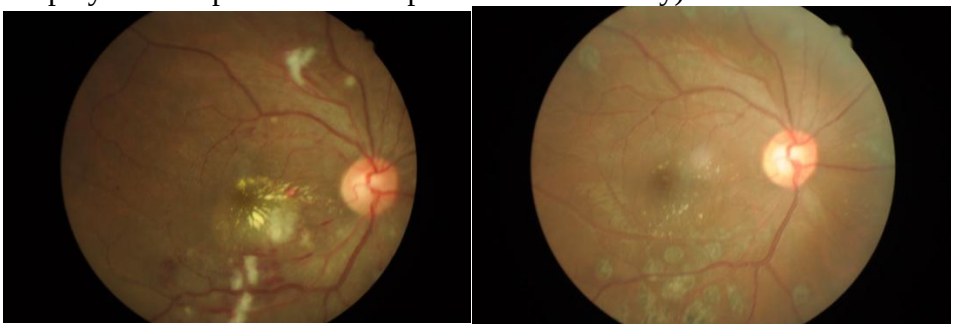
Fig.1A We could find that yellowish exudate, cotton wool spots and remarkable nerve fiber layer hemohages. Besides, macular edema and arterioles were also found (left eye). Fig.1B Exudate and edema in the macular region (star shape) (right eye).



(A) (B)

Fig.2A After 4 weeks, yellowish exudate, cotton wool spots and nerve fiber layer hemohages disappeared. (Two times of Avastin injection) (left eye). Fig.2B Exudate lesions and macular edema mild subsided; however the lower part flame-shape hemorrhage persisted (right eye) (Two times of Avastin injection).

Two weeks later, she came back and the BCVA return to 6/15. After pupil dilation, the cotton wool spots, yellowish exudate and hemorrhage had mild disappeared in the posterior segment. Because the symptoms and signs improved after injection, the secondary dose of avastin (0.3CC) was given again. Then, she was requested to visit our division after 14 days. After 2 weeks, her BP at peace time demonstrated 130/80 mmHg after the aggressive care from the physicians by taking oral medications for decreasing the systolic and diastolic BP. Furthermore, the symptoms and signs all improved (Fig 2A and 2B). Her BCVA had improved to 6/8.6 one month later; however, only mild floater persisted from patient's complaint. We found a little pre-retinal hemorrhage in both eyes and arranged focal retinal coagulation for diminishing the bleeding by Argon green laser (Meridian merilas 532nm; Swiss) at once. After two weeks, we found that the patient's BCVA returned to 6/6 and the retinal morphology resolved to near-normal view (Fig 3 A and 3 B). and the IOP remained within normal range (<20 mmHg). The nerve fiber layer hemorrhage and yellow exudates nearly disappeared and the OCT revealed normal macular shape (Fig 4B). The star-shape of hard exudates also showed resolution in maculae region within 6 weeks. After 6-month follow-up, all the ocular condition and BP of the patient maintained stably and no special complications were found. In our option, the reason of hypertension and ocular hypertension was due to too much near-distance reading. Therefore, she received our suggestion and gave up the habit of playing computerand smartphone for long time without enough relaxation (in the past, she played smartphone and computer 78-8 hours/day).



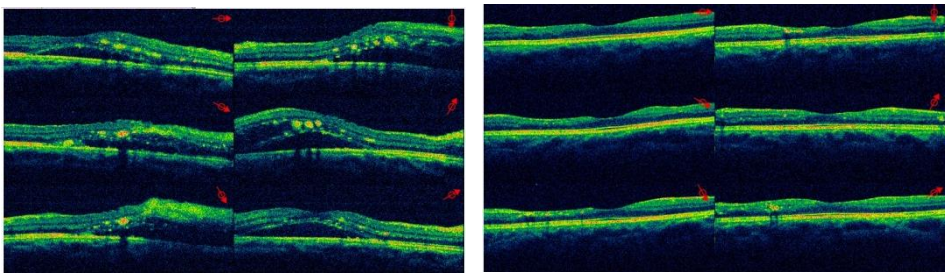
(A) (B)

Fig.3A Only little exudate and cotton wool spots were found. Furthermore, the retinal hemorrhage disappeared (After focal retinal laser) (left eye). Fig.3B Exudates and the flame-shape hemorrhage over the lower temporal region had absorbed (right eye) (After focal retinal photocoagulation)

Discussion

In 2005, 56 million people died, 5.6 million of them from a stroke. By 2015, this figure will rise 6.4 million stroke deaths a year, largely because of the worldwide aging populations. In many countries, such as China, Philippian, and Taiwan (Republic of China), stroke is the third cause of death only preceded by heart disease and total cancer. A systolic BP > 115 mmHg explains 60 % of the population-attributable risk of stroke[17]. In the Framingham cohort, the life time risk of stroke at age 55, 56, and 57 years was similar approximately 1 in 5 for women and 1 in 6 for men[18]. In many research, modifiable risk factors including smoking, excessive alcohol intake (> 60 g per day), obesity, dyslipidemia, DM, carotid artery diseases, atrial fibrillation, heart failure, and other forms of heart disease were

enrolled [19,20]. Among the risk indications, high BP has by the largest impact. In a quantitative overview of 61 cohort studies, the prospective studies collaboration demonstrated a strong long log-linear relation without threshold between stroke mortality and BP, starting at levels of 115 mm Hg systolic BP, 75 mmHg diastolic BP and consistent across the age range (50 to 89 years)[21] . More recently, the Asian Pacific Cohort Studies Collaboration reported that in both sexes systolic BP tended to be more predictive than diastolic BP in all age groups with exception of men < 50 years[22,23].



(A) (B)

Fig 4A Intinal retinal cross sections with optical coherence tomography (OCT). At first, it demonstrated diffuse intraretinal exduates and hemorrhage as well as a large serous retinal detachment at the level of the fovea and the macula (Right eye).
Fig. 4B After our various treatment (6 weeks later), the exudates, mild hemorrhage and retinal detachment disappeared from the view of OCT (Right eye).

Retinopathy is the more manifestation of hypertension in the eyes. Moreover, hypertension retinopathy is often symmetrical between eyes. It is possible that some retinopathy was missed because of the too small and too peripheral lesion of the involved eyes not being photographed. In our study, the female young girl is only 22 years and did't have any systemic disease. We checked all the articles in the Medline and pubmed medical library, relatedly younger patient with grade III hypertensive retinopathy and malignant hypertension had never reported. Why this type is rare in clinics? Indeed, hypertensive choroidopathy is an uncommon manifestation of hypertension seen in young patients secondary to an increase in BP. Its predilection for young patients is not well understood but though to be related to elasticity and palpability of younger blood vessels[24]. The choroid is uniquely susceptible to acute rises in BP due to the structure of this vascular network. The vessels of the choriocapillaris branch at right angles, leaving them more susceptible to acute branching vessels of the retina[25]. However, some chorioretinopathy are associated with poor visual and systemic prognosis due to their association with systemic illness seen in young patients with acute rises in BP: toxemia of pregnancy, renal disease, phenochromcytoma, and hypertensive emergency. Furthermore, it is very important that retinopathy is associated with an increased risk of cerebrovascular disease. Therefore, any method including various antihypertensive agents, public health promotion and the cooperation between the associated departments for whole people care.

Malignant hypertension is a hypertensive emergency characterized by a severe elevation of blood pressure, and ischemic retinal lesions. The earliest findings are a general retinal-arteriolar narrowing due to vasospasm and increased vascular tone. As hypertension becomes more chronic, one observes diffuse and focal narrowing and pacification of the arteriolar wall, leading to the classically described

cooper-wire and silver appearances. It may induce the thickening of the arterioles which further compressed the venues at the common adventitial crossings (so called" arteriovenous nickink). Besides, it may include the bilateral presence of cotton-wool spots, flame-shape hemorrhages, and papilledema[26,27,28,29]. The possible pathophysiology mechanism for the development of malignant hypertension originates from the idea that microvascular damage and pressure natriuresis, included by a critical elevation of BP, results in ischemia of the vascular bed and paradoxical activation of the renin-angiotensin system which further result in damage or failure of several organs. Stimulation of the renin-angiotensin system, in turn, may further promote BP increase by high levels of circulating angiotensin II and lead to more vascular damage[30]. They develop severe elevation of BP and profound endothelial damage with evidence of a thrombotic micro-angiopathy early in life. Furthermore, the direct vasculotoxic effect and the decrease of platelet count result in the complications of ischemic effects[31]. Some research revealed that that ischemic retinal changes that corroborate malignant hypertension may be considered as a reliable indicator for ischemic vascular lesions elsewhere, particular. The paradoxical activation of renin-angiotensin in malignant hypertension may result in further vascular damage,[32,33,34]. It was lucky that this female patient called at and searched for urgent medical care at one and received the correct procedure right now. Indeed, patients with grade III hypertensive retinopathy and hypertensive crisis were very dangerous (blindness, stroke or death). It may suddenly cause microvascular damage in both the cerebral and retinal circulation [35,36]. The retinal hypertensive abnormality that have been corrected with a higher risk of cerebrovascular diseases, The principle "hypertensive - related eye abnormalities and the risk of stroke, must keep in our mind [37].

DellaCroce and his medical team had reported that systemic BP has been associated with microvasculature including various grades for retinopathy (ie, grade I to grade IV retinopathy), choriodiopathy, optic nerve neuropathy, as well we increased risk of ocular vascular abnormalities such as arterial and venous occlusion disease such as arterial and venous occlusive disease, retinal arteriolar macroaneurysm formation and embolic events[33]. Furthermore, hypertension may also confer increased risk for development and progression of diabetic retinopathy, glaucoma and ARMD. Now the stages of hypertension were first staged by Keith system in 1939 and a more recent 3- grade classification which is suggested by Wong and McInto. They paid much attention to divide the relatively severity of morphology by means of the symptoms and signs[38,39,40,41,42].

In 1953, Scheie proposed 50 stages classification system in which the changes of hypertension and arteriolosclerosis were graded separately and correlated with concomitant changes in the arteriolar light reflexes along with the color and the appearance of the retinal arterioles. A more recent grade III classification of hypertensive retinopathy has been suggested by Wong and McIntosh and is based on the relative severity of hypertensive retinopathy signs and their relation to systemic diseases and their prognosis significant. The relationship between the neuropathy from IIII/V hypertensive retinopathy, are less well characterized. Additionally, little is known regarding hypertensive retinopathy and the use of healthcare resources. Determining the risk factors for grade III and IV hypertensive retinopathy and the condition's effects healthcare utilization may guild examination and treatment

strategies in the emergency department. There are presenting symptoms and associated in patients with hypertensive crisis and advanced retinopathy. At first, we did not realize the symptoms of advanced III/V hypertensive retinopathy. We are glad to some research about it. For example, Van der Born and his workers had reported several problems in hypertensive problems in hypertensive problems in hypertensive crisis including headache(63%), visual disturbances (59%), gastrointestinal symptoms (i.g., nausea, vomiting, and body weight loss) (49%), heart failure (30%), neurological sequelae (i.e. leukoencephalopathy, myelopathy) (17%), left ventricular hypertrophy (86%), severe renal impairment (creatinine > 300 μmol/l) (33%), mild to moderate renal impairment (115-300 μmol/l) (46%) and even microangiopathic haemolytic anaemia (28%)[11]. Amnda et al. reported that the individuals with dialytic BP > 120 mmHg easily had the fundus picture of grade III/IV hypertensive retinopathy such as papilledema and greater A/V ratio (A: arteritis; V venues) [21]. Some research revealed that the BP of patients' greater than 180/120 mmHg needs urgent admission for the purpose of needing intensive care and avoiding the possible stork and mortality [8,43].

Why the patient's BP should reach 200/160 mmHg? Recently, the association between glaucoma and blood pressure was highly concerned and valued [30,37,39,41,44]. It is well-known that glaucoma is commonly defined as optic neuropathy characterized by progressive loss of retinal ganglion cells which is associated with characteristic structure damage to the optic nerve and visual field. Rick factors related to glaucoma include IOP, age, family history, clinical appearance of the optic nerve, race, and potential vascular disease'[45,46]. Among these risks, systemic hypertension may contribute to increase IOP via overproduction or impaired outflow of aqueous humor[47]. Furthermore, the relationship BP between IOP was closer[48]. For example, Foster and his co-workers found statistically significantly positive association between diastolic BP[40]. In other word, the higher BP is combined with higher IOP, controversially. The majority of population-based studies reported a positive association or correlation between systolic BP, diastolic BP and IOP[49]. A recent meta-analysis showed a pooled average IOP increase of 0.26 mmHg (95% CI, 0.23-0.28, I^2, 42.5%) and 17 mmHg (95% CI, 0.11-0.23, I^2, 91.2%) associated with a 10 mmHg and 5 mmHg increase in dialytic BP, respectively, with similar results in cross-sectional and longitudinal studies[46]. These trends may be because systemic hypertension increases IOP via overproduction or impaired out of aqueous humor [50]. Furthermore, we had ever found that when we read books or used smartphones (30 cm in distances) for one hour without relaxation, the swelling of lens may block the outflow of aqueous flow through the trabeculum and elevated IOP (3mm Hg/1 hour) (data not published yet). Moreover, the increased effects may sum totally. Hence, the female lady's IOP may add the 15mmHg (5 hours x 3) to the baseline IOP without taking a rest. In general, the IOP of the girl may reach 30-40 mmHg in the condition. She may suffer from headache and periocular strain. Furthermore, the elevated IOP accompanied at the same time for long-term near work. Unfortunately, we found that the mean BP of the patient showed 200/160 mmHg and the IOP was 32 mmHg average which may result in visual system disorders, neurological defects and even death. In clinic, her BCVA was only 6/20 at the beginning and the hypertensive retinopathy grade III combined with macular edema was noted. We arrange two dose of deeper periocular injection (one time in every 2 weeks) and focal argon laser

around the tortuosity of the vessels for improving absorption of mild vitreous hemorrhage and intra-retinal hemorrhage. Finally, the cotton wonton spots, exudation, and hemorrhages nearly disappeared. The key point is that the macular edema absorbed and the photoreceptors maintain their function primarily by the pharmacologic effects of advanced agents (Genetech; "Avastin"). It is essential to alarm the public about that retinopathy is associated with coronary heart disease; Furthermore, the importance of intraocular pressure and blood pressure is compatible. Besides, the retinopathy-stroke association may partly reflect microvascular, rather than purely macrovascular processes.

Recently, an important clinical marker of hypertensive end-organ damage is the presence of retinopathy [24,51], a spectrum of lesions seen in the retina resulting from hypertensive injury to the microvasculature (retinal hemorrhages, microaneurysms). Therefore, early detection of the hypertensive retinopathy becomes very important. The treatment of hypertensive retinopathy includes urgent antihypertensive management which may support the protective mechanisms against acute end-organ damage. Hypertensive retinopathy is considered as a condition of increasing amount of vascular endothelial growth A (VEGF-A) which may promote the proliferation of the new vessels with the peri-retinal and intra-retinal layers. If too much blood leaked from the fragile blood vessels into the vitreous cavity, vitreous hemorrhage would persist and blurry vision of the patient would develop. Now Bevacizumab (Avastin), an antibody that binds all isoform of VEGF-A, has been used effectively in treating neo-vascular age-related macular degeneration (ARMD), mild or severe PDR, neo-vascular glaucoma, and intra-ocular hemorrhage, any retinopathy with macular edema[52,53,54,55,56]. We could effectively use the principle of potent inhibiting and inducing the regression of the new vessels. In the previous article, only one document revealed the function of avastin in treating hypertension retinopathy. Kim et al. utilized the method of intravitreal bevacizumab in treating malignant hypertensive retinopathy (grade V). They suggested that it is a useful adjunctive therapy in decreasing the macular edema and optic disc head edema after 3 months (BCVA only reached 20/25). Besides, the hard exudates over the posterior segment and macula had absorbed [57]. Besides, the method of intravitreal injection is relative dangerous and the complication of endophthalmitis, cataract, glaucoma, vitriris and even eye rupture [67,68]. In our case, we developed a new safer method (deep periocular injection). During our experiences, the efficacy was good and no complication was found[16]. This procedure deserved promotion.

In the past, the grid photocoagulation was used to control the processes of diseases including hemorrhage and exudates deposition. Sometime the macular and other retinal edema should be solved by this method. However, retinal laser treatment own some disadvantage such as night blindness loss, decreased contrast sensitivity and even intragenic laser damage.

Conclusion

At now, the **h**ypertensive-related complications (i.e., left ventricular hypertrophy, hypertensive kidney disease and stroke) and even higher mortality should be highly respected. Furthermore, the higher prevalence of hypertensive retinopathy was associated with an increased risk of cerebrovascular diseases and mortality [58,59,60]. Now it becomes a public health issue and clinical implication. The

case about long-term and near-distance watching smartphones induced ocular hypertension and even hypertensive crisis (200/160 mmHg) was never reported in the world. From this experience, we learned more about the patho-physiology of human eye and the "micro-wave" effect from the smart phone for safe concern.

Reference

1. Bartges JW, Willis AM, Polzin DJ. Hypertension and renal disease. Vet Clin North Am Small Anim Pract 1996; 26: 1331-45.
2. .Wong TY, Klein R, Duncan B, et al. Racial differences in the prevalence of hypertension retinopathy. Hypertension 2003; 41 : 1086-91.
3. Scheie HG. Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. Arch Ophthalmol 1953; 49: 117.
4. Wong TY, Mclntosh R. Systemic associations of retinal microvascular signs : a review of recent population studies. Ophthal Physiol Opt 2005; 25: 195-204.
5. Niemuth JN, De Voe RS, Jennings SH, et al. Malignant hypertension in western lowland gorilla (Gorilla gorilla gorilla). J Med Primatol 2014; 43: 276-9.
6. Miller CL, Schwartz AM, Barnhart JS Jr, et al. Chronic hypertension with subsequent congestive heart failure in a Western Lowland Gorilla (Gorilla gorilla gorilla). J Zoo Wildl Med 1999; 30: 262-7.
7. Suzuki K, Masawa T, Takatama M. The pathogenesis of cerebrovascular lesions in hypertensive rats. Med Electron Microsc 2001; 34: 230-9.
8. Kapinos G, Sanelli PC. Hypertensive crisis. Neurology 2014; 83: 1996-7.
9. Ong YT, Wong TY, Klein R, et al. Hypertensive retinopathy and risk of stroke. Hypertension 2013; 678-9.
10. Zhang H, Thijs L, Stassen JA. Blood pressure lowering for primary and secondary prevention of stroke. Hypertension 2006; 48: 187-95.
11. GO AS, Morzaffarian D, Roder VL, et al. Heart disease and stroke statistics-2013 upstate: a report from the American Heart Association. Circulation 2013; 27(1): e6-245.
12. Lamy C, Oppenheim C, Mas JL. Posterior reversible encephalopathy
13. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2 controversies surrounding patho-physiology of vasogenic edema. ANJR Am J Neuroradiol 2008; 29: 1043-9.
14. Akal A, Adibelli MF, Karakas EY, et al. Papilledema in a hypertensive adult with grade 4 retinopathy. J Clin Hypertens (Greenwich) 2015; 17(9) 740.
15. de Havenon A, Joos Z, Longenecker L, et al. Posterior reversible of encephalopathy syndrome with spinal involvement. Neurology 2014; 83: 2002-6.
16. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevaciumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003 ; 349: 427-34.
17. Klein R, Klein BE, Moss SE, et al. The relation of systemic hypertension in the retina vasculature: the Beaver Dam Eye Study. Tran Am Ophthalmol Soc 1997; 95: 329-48.
18. Baliga BS, Weinberger J. Diabetes and stroke: part one- risk factors and pathophysiology. Curr Cardiol Rep 2006; 8: 23-8.
19. Chalmens J, Todd A, Chapman N, et al Internal Society of Hypertension (ISH):

statement on blood pressure lowering pressure and stroke prevention. J Hypertens 2003; 21: 651-63.
20. Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. JAMA 2002; 288: 1388-95. Van der Born B.J.H., Beutler JJ, Gaillard CAJM, et al. Dutch guideline for the management of hypertensive crisis. The Netherlands journal of Medicine. Neth J Med 2011' 69(5): 248-55.
21. Henderson AD, Biousse V, Newman NJ, et al. Grade III or grade IV hypertensive retinopathy with severely elevated blood pressure. West J Emerg Med 2012; 13(6): 529-34.
22. Breslin DJ, Gifford RW Jr, Fairbairn II, et al. Prognostic importance of ophthalmoscope findings in essential hypertension. JAMA. 1966; 195: 335-8.
23. Luo BP, Brown GC. Update on the ocular manifestations of systemic arterial hypertension. Curr Opin Ophthalmol 2004; 15(3): 203-10.
24. Tso MO, Jampol LM. Pathophysiology of hypertensive retinopathy. Ophthalmology 1982; 89(10): 1132-45.
25. Wong TY, Klein R, Duncan BB, et al. Racial differences in the prevalence of hypertensive retinopathy. 2003; 41: 1086-91.
26. Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities to atherosclerosis ? The Atherosclerosis Risk in Communities Study. Arterioscler Thromb Vas Biol 2000; 1644.
27. van den Born BH, Koopmans RP, van Montfrans GA. The renin-angiotensin system in malignant hypertension revisited: plasma renin activity, microangiopathic hemolysis, and renal failure in malignant hypertension. Am J Hypertens 2007; 20: 900-6.
28. Klien R. Retinopathy in a population-based study. Trans Am Ophthalmol Sox 1992; 90: 561-94.
29. Mitchell P, Wang JJ, Wong TY, et al. Retinal microvascular signs and risk of stroke and stroke mortality. Neurology 2005; 65: 1005-9.
30. McLeod SD, West SK, Quigley HA, et al. A longitundinal study of the relationship between intraocular and blood pressure. Invest Ophthalmol Vis Sci 1990 ; 31(11): 2361-6.
31. Mitchell P, Lee AJ, Rochtchina E, et al. Open-angle glaucoma and systemic hypertension: the Blue Mountain Eye Study. J Glaucoma 2004: 319-26.
32. Akai A, Adibelli MF, Karakas, et al. Papilledema in hypertensive adults with grade 4 retinopathy. J Clin Hypertens (Greenwich). 2015 Sep;17(9):740. doi: 10.1111/jch.12563. Epub 2015 Apr 17.
33. DellaCroce JT, Vitable AT. Hypertension and the eye. Curr Opin Ophthalmol 2008; 19: 493-8.
34. ChRocha,R, Rananudo S, et, al. Adoaterne play a pivotal in the pathogensis of thrombotic microangiothy in SHRSJ. 2003 ; nephrol: 14 : 1990-7.
36. van den Born BJ, Honnebier UP, Koopmans RP, et al. Microangiopathic hemolysis and renal failure in malignant hypertension. Hypertension 2005; 45: 246-51.
37. Mitchell P, Leung H, et al. Hypertensive retinal vessel wall signs in a general old population: the Blue Mountains Eye Study. Hypertension 2005;
38; 65: 1005-9.
37. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood

pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 2005; 46: 156-61.
38. Thulasi P, Fraser CL, Biousse V, et al. Nonmydriatic ocular fundus photography among headache patients in an emergency department. Neurology 2013; 80: 432-7.
39.Wang S, Xu L, Jones JB, et al. Major eye disease and risk factors associated with systemic hypertension in an adult Chinese population: the Bijiing Eye Study. Ophthalmology 2009; 116(12): 2373-80.
40.Chang YC, Lin JW, Wang LC, et al. Association of intraocular pressure with the metabolic syndrome and novel cardiometabolic risk factors. Eye 2010; 24(6): 1037-43.
41.Ideishi M, Kshikawa K, Kinoshita A, et al. High-renin malignant hypertension secondary to an aldosterone-producing adenoma. 1990; 54; 259-63.
42.Wong TY, Klein R, Sharrett AR, et al. Cerebral withe matter lesion, retinopathy and risk of clinical stroke : the Atherosclerosis Risk in the Communities Study. JAMA 2002; 288: 67-74.
43.Kapions G, Sanelli PC. Hypertensive crisis. Neuropathy 2014; 83: 1996-7.
44.Chen HY, Lai SW. Relation between intraocular pressure and systemic health parameters in Taiwan. South Med J 2005; 98(1): 28-32.
45. Dielemans I, Vingerling JR, Algra D, et al. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam Study. Ophthalmology 1995; 102(1): 54-60.
46.Zhao D, Cho J, Kim MH, et al. The association of blood pressure and primary open-angle glaucoma: a meta-analysis. Am J Ophthalmol 2014; 158(3): 615-27.
47.Hulsman CA, Vingerling JR, Hofman A, et al. Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study. Arch Ophthalmol 2007; 125(6):805-12.
48.Chung HJ, Hwang HB, Lee NY. The association between primary open-angle glaucoma and blood pressure: two aspects of hypertension and hypotension. Biomed Res Int 2015; 2015: 827516. doi: 10.1155/2015/827516. Epub 2015 Oct 18.
49.Yoshida M, Ishikawa M, Kokaze A, et al. Association of life-style with intraocular pressure in middle-aged pressure in middle-aged and older Japanese residents. Jpn J Ophthalmol 2003; 47(2): 191-8.
32. 50.Caprioli J, Coleman AL. Blood flow in glaucoma discussion. Blood pressure, and glaucoma. Am J. Ophthalmol 2010; 149(5): 704-12.
51. Wong TY, Klein R, Kielsch JM, et al. Retinal microvascular abnormalities with hypertension, cardiovascular and mortality. Surv Ophthalmol 2001: 46: 59-80.
52. Bashshur ZF, Bazabachi A, Schakal A et al. Intravitreal bevacizumab (avastin) for the management of choroidal neovascularization in age-related macular degeneration. Am J Ophthalmol 2006; 142: 1-9.
53. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage Retina ; 2006; 26: 275-278.
54. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for macular edema from

central retinal vein occlusion. Ophthalmic Surg Lasers Imaging 2005; 36: 336-9.
55. Tolentino PJ, Systemic and ocular safety of intravitreal anti-VEFG therapies for ocular neovascular diseases. Surv Ophthalmol 2011; 56: 95-113.
56. Yang CY, Chien KJ, Chang TH, et al. Treatment of the subretinal hemorrhage by the deep periocular injection of Bevacizumab --- A safer method. Life Sci J 2012; 9(4): 1237-41.
57. Kim,EY, Lew HM, Song JH. Effect of intravitreal Bevacizumab(Avastin). Therapy in malignant hypertensive retinopathy: a report of two cases. J Ocul Pharmacol Ther 2012; 28(3): 316-22.
58. Bourke K, Patel MR, Prisant LM, et al. Hypertensive choriodopathy. J Clin Hypertens Greenwick Conn 2004 6(8): 471-2.
59. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke. The Atherosclerosis Risk in the Communities Study. Lancet 2001; 358: 1134-40.
60. Chobanian AV, Blakris GL, Blackm HR, et al. The seventh report of the Joint National Commitee on prevention, detection, treatment. Detection, Evaluation, and Treatment of High Blood Pressure JMMA 2003 289: 2560-72.
61. Dikalov SI, Dikalova AE. Contribution of mitochondrial oxidative stress to hypertension. Curr Opin Nephrol HYpertens 2016; 25(2):73-80.
62. Seravalle G, Grassi G. Sympathetic Nervous System, Hypertension, Obesity and Metabolic Syndrome. High Blood Press Cardiovasc Prev. 2016 Mar 4. [Epub ahead of print].
63. Siebenhofer A, Jeitler K, Horvath K, et al. Long-term effects of weight-reducing drugs in people with hypertension. Cochrane Database Syst Rev. 2016 Mar 2;3:CD007654. [Epub ahead of print].
64. Saklayen MG, Deshpande NV. Timeline of History of Hypertension Treatment. Front Cardiovasc Med. 2016 Feb 23;3:3. doi: 10.3389/fcvm.2016.00003. eCollection 2016.
65. Cao Q, Pei P, Zhang J, et al. Hypertension unawareness among Chinese patients with first-ever stroke. BMC Public Health 2016 ;16(1):170.
66. Januszewicz A, Guzik T, Prejbisz A, et al. Malignant hypertension: new aspects of an old clinical entity. Pol Arch Med Wewn. 2016;126(1-2):86-93.
67. Kanchanaranya N, Rojdamrongratana D, Piyasoonthorn P**.** Incidence of post-intravitreal anti-VEGF endophthalmitis at Thammasat University Hospital. J Med Assoc Thai 2015 May;98(5):489-94.
68. Fasih U, Shaikh N, Rahman A,et al. A one-year follow-up study of ocular and systemic complications of intravitreal injection of bevacizumab (Avastin). J Pak Med Assoc. 2013 ;63(6):707-10.