Dynamic Contour Tonometry와 안혈류분석계로 측정된 안구박동크기 관련 인자 분석

Evaluation of Ocular Pulse Amplitude-related Parameters Measured by Dynamic Contour Tonometry and Ocular Blood Flow Analyzer

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Purpose: To evaluate ocular rigidity-related factor (ORF) derived from ocular pulse amplitude (OPA) measurements with regard to the severity of glaucoma.

Methods: This study was conducted in 31 eyes of 31 normal and 38 eyes of 38 normal tension glaucoma (NTG) patients with cross-sectional and retrospective design. OPA was measured using dynamic contour tonometry (DCT). Pulse amplitude (PA), pulse volume (PV), and pulsatile ocular blood flow (POBF) were measured using ocular blood flow analyzer (OBFA). Intraocular pressure (IOP) was measured by Goldmann applanation tonometry (GAT), DCT and OBFA. ORF was calculated from OPA and PV, measured with both devices, based on the Friedenwald equation. $ORF = [\log(DCT\ IOP + OPA) - \log DCT\ IOP]/PV$. The severity of glaucoma was estimated by both mean deviation (MD) of visual field (VF) tests and retinal nerve fiber layer (RNFL) thickness of Stratus optical coherence tomography (OCT) in medically treated NTG patients.

Results: Both IOP and OPA of NTG patients were lower than those of normal subjects whereas PA, PV and POBF was not significantly different between groups. The calculated ORF of NTG patients did not differ from that of normal subjects. OPA showed significant correlation with IOP measured by both GAT and DCT but PA did not. OPA and POBF correlated significantly with the spherical equivalent of refractive error but not with central corneal thickness and blood pressure. Both POBF and ORF were significantly correlated with IOP measured by all the three devices. Although OPA and POBF did not correlate with glaucoma severity, ORF showed significant correlation with MD of VF and RNFL thickness measured by OCT in NTG patients.

Conclusions: Although both OPA and POBF significantly correlated with IOP level, they did not correlate with the severity of glaucoma. ORF, derived from measurements of ocular pulse amplitude, could be related to the severity of glaucoma in treated NTG patients.

Key words: Dynamic contour tonometry, Ocular blood flow analyzer, Ocular pulse amplitude, Ocular rigidity

Introduction

In addition to intraocular pressure (IOP), hemodynamic

disturbances are thought to be related to the pathogenesis of glaucomatous optic neuropathy in NTG patients.¹⁻⁴ Pulsatile ocular blood flow (POBF), measured using a pneumatic applanation tonometer, has been reported to be related to the pathogenesis of glaucoma.^{2,5,6} and is derived from measurements of cyclic changes of IOP, called ocular pulse amplitude (OPA). OPA is thought to be generated by systemic blood pressure differences during the cardiac cycle, but its correlation with systemic hemodynamic parameters has been reported to be negligible^{7,8} because it can be affected by many other factors, including IOP, vascular resistance,

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choroidal thickness, autoregulation, and ocular rigidity.⁹⁻¹³ These confounding factors generating OPA have been suggested to be related to the pathogenesis of glaucoma. Additionally, ocular rigidity has been considered to be one of the important factors related to the individual susceptibility of the optic nerve head to glaucomatous damage and is determined by the pressure/volume relationship within the eyeball.¹⁴⁻¹⁶ Non-invasive methods for ocular rigidity measurements have been reported using devices that can measure ocular pulsatile components.^{17,18} However, ocular rigidity measured by these methods has shown contradictory results in relation to glaucoma, and estimated rigidity coefficients differed from those measured by invasive methods during cataract surgery.¹⁹

In this study, we compared ocular pulse amplitude measured by both DCT and ocular blood flow analyzer (OBFA) in terms of their relationship with other ocular and systemic parameters. Additionally, the ocular rigidity-related factor (ORF) was calculated from both DCT and OBFA measurements, based on previous studies that adopted non-invasive methods.^{17,18} Then, we evaluated ocular pulsatile components and ORF in relation to glaucoma severity in normal tension glaucoma (NTG) patients.

Materials and Methods

This study was of a cross-sectional and retrospective design. The medical records of subjects who visited the glaucoma clinic at the Department of Ophthalmology of AJOU University Hospital from August 2012 to October 2012 were reviewed. Initially, there were 146 eyes of 79 patients who had Pascal Dynamic Contour Tonometry (DCT, Swiss Microtechnology AG, Switzerland) and ocular Blood-Flow Analyzer (Paradigm Medical, Salt Lake City, UT, USA) measurements and measurements of blood pressure within 30 min. The present study conformed to the Declaration of Helsinki and was approved by the Institutional Review Board of AJOU University Hospital. Comprehensive ophthalmic examinations including medical history, visual acuity, spherical equivalent (SE) of refractive error, slit lamp biomicroscopy, and fundus

examinations were performed. Central corneal thickness (CCT) was measured using ultrasonic pachymetry (DGH-500; DGH Technology, USA) and IOP was measured using Goldman applanation tonometry (GAT). IOP and OPA were measured using DCT. Average IOP, PA, PV, and POBF were measured using OBFA. VF tests (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA, USA), red-free RNFL photography (AFC-210; NIDEK, Gamagori, Japan), and optical coherence tomography (OCT; Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA) were carried out within 3 months before or after OPA and PA measurements in all subjects.

Patients were defined as normal when they had IOP less than 22 mmHg with GAT, normal VF test results, no sign of RNFL defect or optic disc findings corresponding to glaucoma on stereoscopic red-free RNFL photography. NTG patients who had a gonioscopically open angle, showed at least two reproducible VF test results compatible with glaucoma, based on the Anderson criteria, and RNFL defects corresponding to VF defects noted on OCT and/or red-free RNFL photography, were included. IOP measurements in all NTG patients were less than 22 mmHg at each visit before and after treatment.²⁰

Systolic BP (SBP) and diastolic BP (DBP) were measured using a brachial full-auto sphygmomanometer on the upper right arm after the subject had been seated for at least 3 min. Patients were asked to refrain from any physical activities that could affect BP. BP was taken twice and the lower value was used for the analysis. Mean arterial pressure (MAP) was estimated from the equation, $MAP = [2 \text{ DBP} + \text{SBP}] / 3$.²¹ Mean ocular perfusion pressure (MOPP) was calculated from the equation, $MOPP = 2/3 [\text{DBP} + 1/3 (\text{SBP} - \text{DBP})] - \text{GAT IOP}$.²² ORF was calculated based on the Friedenwald equation with modification:

$$\text{ORF} = (\log \text{IOP1} - \log \text{IOP2}) / (V1 - V2)$$

where IOP2 is DCT IOP, IOP1 is DCT IOP plus OPA measured by DCT, and $V1 - V2$ is PV measured by OBFA.¹⁶ OBFA estimates PV from pressure change in the eyeball assuming individual patients have a standard ocular rigidity coefficient, so the ocular rigidity estimated in our study

may not represent the actual value.²³ Thus, we called our estimated coefficient of ocular rigidity the “ocular rigidity-related factor.”

DCT and OBFA measurements followed the standard techniques provided by the manufacturers. DCT measurement was always followed by OBFA measurement and each measurement had at least 5 minute of time interval to minimize interference. DCT measurements for which the quality score (Q) was > 3 and OBFA measurements that were documented as incomplete or results in tests with high variance comments were excluded. Unreliable visual field (VF) tests (> 25% fixation loss, false negatives, and false positives) were excluded from our analysis. OCT images showing poor centration and signal strength < 7 were also excluded. Patients who had previous intraocular surgery,

refractive surgery, and laser surgery involving argon laser peripheral iridotomy were also excluded.

Statistical analyses for descriptive statistics, differences between the two devices, and correlations between parameters were conducted using the SPSS software ver. 20.0 (SPSS Inc., Chicago, IL, USA). One eye was selected at random using random number generators from a uniform distribution in SPSS software if both eyes of a patient met the inclusion criteria.

Results

Among total 79 patients, 10 patients were excluded from final analysis. 8 patients excluded due to unreliable OBFA result and 2 patients showed unreliable DCT result. Ulti-

Table 1. Descriptive statistics of enrolled subjects

Parameter	Total (69 eyes)	Normal (31 eyes)	NTG (38 eyes)	<i>p</i> -value* Normal vs. NTG
Age (years)	50.0 ± 11.8	48.5 ± 9.21	51.2 ± 13.6	0.322
Male/female ratio	33:36	14:17	19:19	0.810 [†]
MAP (mmHg)	90.8 ± 11.6	93.8 ± 9.3	88.3 ± 12.9	0.050
PP (mmHg)	48.9 ± 9.0	49.9 ± 10.5	48.1 ± 7.8	0.392
MOPP (mmHg)	75.7 ± 11.0	77.7 ± 8.6	74.1 ± 12.5	0.177
PR	76.2 ± 12.7	77.6 ± 11.9	75.2 ± 13.3	0.435
CCT (μm)	542.3 ± 35.0	551.5 ± 35.2	534.9 ± 33.5	0.049
SE (diopter)	-2.114 ± 2.878	-1.713 ± 2.806	-2.441 ± 2.932	0.300
GAT IOP (mmHg)	15.1 ± 3.0	16.1 ± 3.2	14.2 ± 2.4	0.010
DCT IOP (mmHg)	19.02 ± 3.71	20.63 ± 3.96	17.70 ± 2.93	0.001
OPA (mmHg)	2.66 ± 0.94	2.92 ± 0.87	2.45 ± 0.95	0.038
BFA IOP (mmHg)	21.71 ± 5.09	22.74 ± 5.43	20.88 ± 4.71	0.131
PA (mmHg)	2.95 ± 1.09	3.17 ± 0.98	2.76 ± 1.14	0.124
PV (μL)	4.92 ± 2.02	5.17 ± 2.03	4.72 ± 2.02	0.369
POBF(μL/sec)	11.85 ± 3.92	12.40 ± 4.01	11.40 ± 3.83	0.295
ORF(mmHg/μL)	0.0122 ± 0.0032	0.0121 ± 0.0035	0.0124 ± 0.0031	0.713
MD (dB)	-2.756 ± 5.875	0.353 ± 1.215	-5.292 ± 6.894	<0.001
PSD (dB)	4.494 ± 4.195	1.713 ± 0.622	6.763 ± 4.502	<0.001
Average RNFL thickness (μm)	88.07 ± 18.44	100.43 ± 11.93	77.99 ± 16.64	<0.001

Values are presented as mean ± standard deviation unless otherwise indicated.

NTG = normal tension glaucoma; MAP = mean arterial pressure; PP = pulse pressure; MOPP = mean ocular perfusion pressure; PR = pulse rate; CCT = central corneal thickness; SE = spherical equivalent; GAT = Goldmann applanation tonometry; IOP = intra ocular pressure; DCT = dynamic contour tonometry; OPA = ocular pulse amplitude; BFA = blood flow analyzer; PA = pulse amplitude measured by BFA; PV = pulse volume measured by BFA; POBF = pulsatile ocular blood flow measured by BFA; ORF = ocular rigidity related factor; MD = mean deviation; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer.

*T-test; [†]Fisher's exact test.

Table 2. Correlations between IOP or OPA-derived parameters and systemic or other ocular parameters in total patients

	Age	MAP	PP	MOPP	CCT	SE
GAT IOP	-0.194 (0.110)	0.334 (0.005)	0.097 (0.428)	0.082 (0.501)	0.247 (0.041)	-0.267 (0.027)
DCT IOP	-0.091 (0.455)	0.382 (0.001)	0.147 (0.227)	0.194 (0.110)	0.156 (0.199)	-0.212 (0.080)
BFA IOP	-0.102 (0.402)	0.340 (0.004)	0.126 (0.302)	0.159 (0.193)	0.060 (0.623)	-0.131 (0.283)
OPA	0.064 (0.601)	0.000 (1.000)	0.179 (0.140)	-0.067 (0.583)	0.031 (0.798)	0.239 (0.048)
PA	-0.013 (0.915)	-0.025 (0.840)	0.039 (0.748)	-0.023 (0.851)	-0.081 (0.506)	0.368 (0.002)
POBF	-0.004 (0.977)	-0.219 (0.071)	-0.059 (0.629)	-0.168 (0.168)	-0.166 (0.174)	0.379 (0.001)
ORF	0.130 (0.286)	-0.008 (0.947)	0.253 (0.036)	-0.110 (0.366)	0.077 (0.532)	-0.134 (0.271)

Pearson correlation coefficient R and *p*-value in parenthesis

IOP = intraocular pressure; OPA = ocular pulse amplitude measured by DCT; MAP = mean arterial pressure; PP = pulse pressure; MOPP = mean ocular perfusion pressure; CCT = central corneal thickness; SE, spherical equivalent; GAT = Goldmann applanation tonometry; DCT = dynamic contour tonometry; BFA = blood flow analyser; PA = pulse amplitude measured by BFA; POBF = pulsatile ocular blood flow measured by BFA; ORF = ocular rigidity related factor.

Table 3. Correlations between OPA-derived parameters and IOP measurements in total patients

	GAT IOP	DCT IOP	BFA IOP	OPA	PA	POBF
OPA	0.249 (0.039)	0.297 (0.013)	0.192 (0.113)		0.767 (<0.001)	0.562 (<0.001)
PA	-0.011 (0.926)	0.002 (0.987)	0.077 (0.531)	0.767 (<0.001)		0.750 (<0.001)
POBF	-0.236 (0.049)	-0.251 (0.038)	-0.356 (0.003)	0.562 (<0.001)	0.750 (<0.001)	
ORF	0.377 (0.001)	0.262 (0.029)	0.434 (<0.001)	0.224 (0.065)	-0.298 (0.013)	-0.394 (0.001)

Pearson correlation coefficient R and *p*-value in parenthesis

OPA = ocular pulse amplitude measured by DCT; IOP = intraocular pressure; GAT = Goldmann applanation tonometry; DCT = dynamic contour tonometry; BFA = blood flow analyzer; PA = pulse amplitude measured by BFA; POBF = pulsatile ocular blood flow measured by BFA; ORF = ocular rigidity related factor.

mately, 69 eyes in 69 patients were included in the analysis. Of them, 31 eyes of 31 patients and 38 eyes of 38 patients were divided into the normal and NTG groups, respectively. IOP measurements by the three devices were lower in the NTG group than in normal patients ($p < 0.05$), likely because all NTG patients were using topical IOP-lowering medications (average number of meds = 1.7 ± 1.1). OPA was also lower in the NTG group. There were no significant differences in the ocular pulsatile component measurements by OBFA (PA, PV, and POBF) or ORF between normal and NTG groups (Table 1).

As shown in Table 2, all IOPs measured by each device were positively correlated with MAP, but PP and MOPP were not correlated with IOPs measured by all devices. OPA, PA and POBF were not correlated with MAP, PP, and MOPP whereas ORF significantly correlated with PP. CCT correlated positively with GAT IOP ($r = 0.247$, $p = 0.041$) but not with DCT IOP ($r = 0.156$, $p = 0.199$) and with OBFA

IOP ($r = 0.060$, $p = 0.623$). CCT did not correlate significantly with OPA, PA, POBF, or ORF. SE of refractive error was significantly correlated with OPA, PA and POBF but not with ORF (Table 2).

As shown in Table 3, DCT OPA correlated positively with GAT and DCT IOPs, and showed a significant correlation with PA ($r = 0.753$, $p < 0.001$) and POBF ($r = 0.512$, $p < 0.001$) measured by OBFA. In contrast, OBFA PA was not significantly correlated with any IOP measurements by the three devices. POBF showed a negative correlation with IOPs ($r = -0.236$ to -0.356 , $p < 0.05$) but a positive correlation with OPA ($r = 0.562$, $p < 0.001$) and PA ($r = 0.750$, $p < 0.001$). ORF correlated positively with all IOPs ($r = 0.262$ to 0.434 , $p < 0.03$), but negatively with PA ($r = -0.298$, $p = 0.013$) and POBF ($r = -0.394$, $p = 0.001$).

In a subgroup analysis in the NTG group, OPA, PA and POBF did not show any significant correlation with MD, PSD, or RNFL thickness parameters. ORF was correlated

Table 4. Correlations between IOP or OPA-derived parameters and indices of glaucomatous damages in normal tension glaucoma patients

	MD	PSD	RNFL thickness				
			Temporal	Superior	Nasal	Inferior	Average
GAT IOP	-0.259 (0.116)	-0.003 (0.985)	-0.038 (0.819)	0.004 (0.981)	-0.182 (0.273)	-0.191 (0.252)	-0.117 (0.484)
DCT IOP	0.070 (0.674)	-0.226 (0.172)	0.035 (0.834)	0.091 (0.586)	-0.071 (0.674)	0.055 (0.742)	0.067 (0.688)
BFA IOP	-0.290 (0.077)	0.173 (0.298)	-0.037 (0.825)	0.086 (0.606)	-0.127 (0.449)	-0.269 (0.102)	-0.110 (0.509)
OPA	-0.033 (0.844)	0.013 (0.937)	0.046 (0.783)	0.013 (0.938)	0.003 (0.987)	0.032 (0.850)	0.041 (0.805)
PA	0.043 (0.796)	0.092 (0.582)	0.109 (0.515)	0.149 (0.373)	0.146 (0.383)	0.110 (0.511)	0.175 (0.293)
POBF	0.093 (0.580)	0.067 (0.687)	0.087 (0.604)	0.180 (0.281)	0.180 (0.280)	0.231 (0.164)	0.247 (0.135)
ORF	-0.389 (0.016)	0.088 (0.598)	-0.114 (0.495)	-0.191 (0.250)	-0.336 (0.039)	-0.439 (0.006)	-0.372 (0.022)

Pearson correlation coefficient R and *p*-value in parenthesis.

IOP = intraocular pressure; OPA = ocular pulse amplitude; MD = mean deviation; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer; GAT = Goldmann applanation tonometry; DCT = dynamic contour tonometry; BFA = blood flow analyzer; PA = pulse amplitude measured by BFA; POBF = pulsatile ocular blood flow measured by BFA; ORF = ocular rigidity related factor.

significantly with nasal ($r = -0.336$, $p = 0.039$), inferior ($r = -0.439$, $p = 0.006$), and average ($r = -0.372$, $p = 0.022$) RNFL thickness. ORF showed a significant correlation with the MD determined by VF tests ($r = -0.389$, $p = 0.016$), but POBF did not (Table 4). Although correlation between ORF and RNFL thickness could not be evaluated in total patients because most of normal subjects did not take OCT exam, ORF was significantly correlated with MD by VF tests ($r = -0.246$, $p = 0.042$) in total patients.

Discussion

Ocular rigidity was estimated by Jonas Friedenwald in enucleated human eyes using the Schiottz tonometer; the mean coefficient was $0.0215 \text{ mmHg}/\mu\text{L}$.¹⁸ In a study using the same Schiottz tonometry, glaucoma patients (0.0143) showed lower scleral rigidity than normal subjects (0.0217).¹⁴ In another report, axial length of the eye was measured by laser interferometry before and after acetazolamide intake in normal and glaucoma patients; the shortening of axial length was significantly smaller in the glaucoma group even though the IOP reduction was similar. This was interpreted as indirect evidence supporting increased ocular rigidity in glaucoma patients.¹⁵ Recently, two groups introduced non-invasive measurements of ocular rigidity using ocular pulsatile components based on Friedenwald's equation, but reported contradictory results.^{17,18} Hommer et al.¹⁷ measured

OPA using an OBF system and fundus pulse amplitude (FPA) by laser interferometry. In the equations, they substituted ΔV for FPA assuming that it was proportional to the change in ocular volume during the cardiac cycle. The calculated OR coefficient of the POAG group (0.0454) was significantly higher than that of normal subjects (0.0427). Wang et al.¹⁸ measured OPA by DCT and pulsatile choroidal blood flow (ChBFp) using laser Doppler flowmetry. They replaced ΔV with ChBFp assuming it represented the true change in choroidal volume in the subfoveal area. The equation was $\text{ChBFp} = (\text{systolic ChBF} - \text{diastolic ChBF}) / \text{systolic ChBF}$. The calculated ocular rigidity coefficient of the OAG group (0.188) was significantly lower than that of the OHT (0.235) and normal (0.230) groups. The calculated ocular rigidity coefficients in both studies had arbitrary units. A recent manometric measurement of ocular rigidity showed that the mean ocular rigidity coefficient of patients undergoing cataract surgery was $0.0126 \text{ mmHg}/\mu\text{L}$, which was similar to our results (Table 1).¹⁹ In our results, the ORF of treated NTG patients ($0.0124 \text{ mmHg}/\mu\text{L}$) was not significantly different from that of normal subjects ($0.0121 \text{ mmHg}/\mu\text{L}$; Table 1). The ORF of NTG patients would be expected to be higher than that of normal subjects because higher ORF correlated significantly with more glaucomatous damage, considering the RNFL thickness determined by OCT measurement and MD by VF test in our study (Table 4); however, it was not found to be so. It is possible

that IOP-lowering therapy may have influenced the results because ORF correlated significantly with IOP level in our study (Table 3) and previous manometric studies also showed that ocular rigidity increased with increasing IOP.²⁴ Ocular rigidity-estimating methods using ocular pulsatile components may have an intrinsic limitation in that they cannot measure specific responses of important regions related to glaucoma pathogenesis: the lamina cribrosa or peripapillary sclera, for example. Recent research adopting a finite element model suggested regional differences in the response to mechanical stress related to glaucoma.^{24,25} Although the characteristics of ocular rigidity coefficients differed according to the estimating method used, they may represent different aspects of the same ocular property that connects the hemodynamic factors with biomechanical ones in the pathogenesis of glaucoma.²⁵ Glaucomatous damage may be associated with increased ocular rigidity, representing global stiffness of the eyeball, because a higher value indicates greater IOP elevation for a given change in ocular volume.^{15,17} In contrast, a lower rigidity of a specific region, such as the posterior sclera including the foveal area, may be interpreted as weaker scleral support for the optic nerve axons in the lamina cribrosa.¹⁸

Generally, lower OPA has been reported to be associated with more severe glaucomatous damage.^{3,26} However, neither DCT OPA nor OBFA PA showed any significant correlation with parameters representing glaucomatous damage in our study (Table 4). Although POBF in glaucoma patients is lower than in normal subjects, little information is available regarding a correlation between POBF and structural or functional changes in glaucoma.^{2,6} POBF in treated glaucoma patients was not correlated with VF or OCT parameters in one study.²⁷ In our study, although POBF did not show any significant correlation with parameters representing glaucomatous damage, ORF was correlated significantly with some OCT parameters and VF defect in NTG patients. This suggests that higher ocular rigidity may be associated with greater glaucomatous damage in NTG patients.

We derived ORF based on previous reports speculating that OPA and PV might represent change of IOP and ocular volume during measurement respectively. PV was calculated

from PA measured by OBF device and PA seemed not to be influenced by IOP in this study (Table 3), so we thought PV might represent ultrashort term change of ocular volume during measurement. This can be a major limitation of our study. We did not measure the axial length of the eyeball and included NTG patients treated with IOP-lowering topical medications because of the retrospective design of this study. This may be a limitation because OPA and POBF can be influenced by various factors, including axial length and IOP.^{5,9,13,28} IOP lowering medications could influence on the comparison of ORF between normal and glaucoma patients. However, a recent investigation of ocular rigidity using manometric method during cataract surgery showed that rigidity coefficient of treated glaucoma patients ($0.0220 \pm 0.0053 \mu\text{L}^{-1}$) was not significantly different from that of normal subjects ($0.0222 \pm 0.0039 \mu\text{L}^{-1}$).²⁹ In addition, decrement of ocular rigidity depending on decreasing IOP after medications might be minimal within narrow range of IOP between 10 to 21 mmHg in our study as shown in a study conducted by Dastiridou et al.¹³ We did not repeat measurements to determine diurnal variations in the parameters investigated. If these parameters had been measured at different times of the day and diurnal curves generated, our results would be more reliable. Finally, the small number of patients in our study may make it difficult to determine correlations between ocular pulsatile components and systemic or other ocular parameters due to the ranges of ocular and systemic variables being insufficient to be stratified for evaluation.

In conclusion, in treated NTG patients, it seems that increased ocular rigidity may be related to the severity of glaucoma. ORF, introduced in this study, should be further validated in other clinical settings. Moreover, the clinical implications of POBF and ORF in glaucoma pathogenesis should be investigated further in untreated NTG and glaucoma of various types.

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