Comprehensive assessment of systemic arteriosclerosis in relation to the ocular resistive index in acute coronary syndrome patients

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Comprehensive assessment of systemic arteriosclerosis in relation to the ocular resistive index in acute coronary syndrome patients

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This study aimed to investigate the relationship between ocular vascular resistance parameters, evaluated by laser speckle flowgraphy (LSFG), and systemic atherosclerosis, renal parameters and cardiac function in acute coronary syndrome (ACS) patients. We evaluated 53 ACS patients between April 2019 and September 2020. LSFG measured the mean blur rate (MBR) and ocular blowout time (BOT) and resistivity index (RI). 110 consequent patients without a history of coronary artery disease who visited ophthalmology as a control group. Significant positive correlations were observed between ocular RI and systemic parameters in ACS patients, including intima-media thickness (r = 0.34, P = 0.015), brachial-ankle pulse-wave velocity (r = 0.41, P = 0.002), cystatin C (r = 0.32, P = 0.020), and E/e' (r = 0.34, P = 0.013). Ocular RI was significantly higher in the ACS group than in the control group in male in their 40 s (0.37 ± 0.02 vs. 0.29 ± 0.01, P < 0.001) and 50 s (0.36 ± 0.02 vs. 0.30 ± 0.01, P = 0.01). We found that the ocular RI was associated with systemic atherosclerosis, early renal dysfunction, and diastolic cardiac dysfunction in ACS patients, suggesting that it could be a useful non-invasive comprehensive arteriosclerotic marker.

Abbreviations

A	Peak mitral A wave velocity
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
baPWV	Brachial-ankle pulse-wave velocity
BOT	Blowout time
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
E	Peak mitral E wave velocity
e'	Peak early diastolic myocardial velocity at septal position recorded by tissue Doppler imaging
E/e', ratio	Ratio of peak mitral E wave velocity to peak early diastolic myocardial velocity at the septal position by tissue Doppler imaging
eGFR	Estimated glomerular filtration rate
HbA1c	Hemoglobin A1c
HDL-Cho	High-density lipoprotein cholesterol
HFpEF	Heart failure with preserved ejection fraction
IMT	Intima-media thickness
IOP	Intraocular pressure
L-FABP	Liver-type fatty acid-binding protein
LDL-Cho	Low-density lipoprotein cholesterol

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LSFG	Laser speckle flowgraphy
LV	Left ventricular
MBR	Mean blur rate
ONH	Optic nerve head
PCI	Percutaneous coronary intervention
RI	Resistivity index
U-Alb	Urinary albumin excretion
U-β2MG	Urinary β2 microgloblin
U-Creatinine	Urinary creatinine
U-NAG	Urinary N-acetyl-β-D-glucosidase

Atherosclerotic diseases have dramatically increased in Japan with the westernization of diet and rapid aging of the population. The risk factors for atherosclerotic disease systemically affect all vasculature regions, as evidenced by coronary artery disease, cerebrovascular disease, and peripheral artery disease, all linked to one another[1]. Atherosclerosis is generally found in large blood vessels, such as the carotid and lower limb arteries, arteriosclerosis is known to occur in small vessels of the kidneys and retina[2,3] (so called "arteriolosclerosis"). Nonetheless, the possible association between atherosclerosis and other-region arteriosclerosis and retinal microvessels remains unclear. The laser speckle flowgraphy (LSFG) technique has made it possible to non-invasively detect impairment of the ocular microcirculation by measuring blood flow velocity[4]. Among various parameters measured by LSFG, ocular blowout time (BOT) and resistivity index (RI) were used as indicators of vascular resistance or arteriosclerosis of microvessels[5,6].

Acute coronary syndrome (ACS) or heart failure with preserved ejection fraction (HFpEF) are associated with old age, hypertension, and type II diabetes mellitus, all strongly related to systemic arteriosclerosis[7]. HFpEF increases the left ventricular and systemic arterial stiffness, and promotes diastolic dysfunction[8]. Diastolic dysfunction was associated with coronary artery calcium score, indicating an association with atherosclerosis[9]. Moreover, it has been reported that transient retinopathy (soft exudate) occurred in patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI), suggesting that ACS might be involved in ocular circulation impairment[10,11]. Despite a high systemic atherosclerotic burden in ACS patients, there are few data that investigate whether systemic arteriosclerosis and diastolic function are linked to the ocular RI and BOT values. This study aimed to investigate the association between systemic atherosclerotic parameters (carotid intima-media thickness [IMT] and brachial-ankle pulse-wave velocity [baPWV]), renal biomarkers, and cardiac function assessed by transthoracic echocardiography, and ocular RI and BOT evaluated by LSFG in ACS patients.

Results

Patient characteristics. Table 1 summarizes the patient characteristics and the results of optic nerve head (ONH) pulse waveform and transthoracic echocardiographic parameters. A typical fundus image with soft exudate, taken 13 days after AMI, is shown in Fig. 1.

Relationship between systemic atherosclerosis and mean ocular RI and BOT. Table 2 shows the relationship between systemic atherosclerosis and mean ocular RI and BOT. The mean RI was positively correlated with the mean IMT (r = 0.34, P = 0.015; Fig. 3A) and baPWV (r = 0.41, P = 0.002; Fig. 3B), but not with laboratory parameters such as low-density lipoprotein cholesterol (LDL-C), triglycerides, and glycosylated hemoglobin (HbA1c) (Table 2). The mean BOT was negatively correlated with the mean baPWV (r = −0.44, P = 0.001; Fig. 3C). BOT was also not correlated to the laboratory parameters (Table 2).

Relationship between renal parameters and mean ocular RI and BOT. Table 2 shows the relationship between the renal parameters and mean ocular RI and BOT. The mean RI was positively correlated with blood urea nitrogen (BUN; r = 0.27, P = 0.047; Fig. 4A), cystatin C (r = 0.32, P = 0.020; Fig. 4B), urinary β2 microglobulin (U-β2MG, r = 0.30, P = 0.029; Fig. 4C), and liver-type fatty acid-binding protein (L-FABP; r = 0.28, P = 0.046; Fig. 4D). No correlation was found with other parameters, including creatine, estimated glomerular filtration rate (eGFR), urinary N-acetyl-β-D-glucosidase (U-NAG), U-creatine, and urinary albumin excretion (U-Alb) (Table 2). The mean BOT was not correlated with any of the renal parameters (Table 2).

Relationship between cardiac parameters and mean ocular RI and BOT. Table 2 shows the relationship between the mean ocular RI and BOT and cardiac parameters assessed by transthoracic echocardiography. The E/e' ratio positively correlated with the mean RI (r = 0.34, P = 0.013; Fig. 3D) and marginally and negatively with BOT (r = −0.27, P = 0.051; Table 2).

Differences in systemic atherosclerotic, renal and cardiac parameters, and ocular parameters between ACS patients with and without retinopathy. ACS patients with (n = 32) and without (n = 21) retinopathy, diagnosed by the existence of soft exudate in the retina, were similar in systemic atherosclerosis, renal, and cardiac parameters. They were also similar in the ocular parameters (RI, 0.40 ± 0.10 vs. 0.41 ± 0.08, P = 0.71; BOT, 48.7 ± 5.7 vs. 49.2 ± 4.0, P = 0.77).

Ocular RI and BOT values in ACS patients and controls. Table 3 shows the characteristics of the control group subjects (n = 110). We compared the RI and BOT values between the ACS and control groups in each

Baseline clinical data	*N* = 53
Age, years	66 ± 13
Male, *n*(%)	47 (89)
Systolic blood pressure, mmHg	114 ± 14
Diastolic blood pressure, mmHg	66 ± 10
Heart rate, beat per minutes	70 ± 8
HTN, *n*(%)	37 (70)
DM, *n*(%)	14 (26)
DLP, *n*(%)	33 (62)
CKD, *n*(%)	8 (15)
Smoking, *n*(%)	38 (72)
STEMI, *n*(%)	39 (74)
SYNTAX score	15 ± 8
Atrial fibrillation, *n*(%)	4 (8)
Laboratory data	
BUN, mg/dL	15 (12–20)
Creatinine, mg/dL	0.83 (0.71–1.0)
eGFR, ml/min/1.73 m^2	72.0 ± 22
LDL-Cho, mg/dL	121 ± 35
HDL-Cho, mg/dL	44 (38–50)
TG, mg/dL	113 (68–168)
HbA1c, %	6.0 (5.6–6.7)
NT-ProBNP, pg/mL	285 (64–2518)
Cystatin C, mg/L	0.88 (0.79–1.06)
U-NAG, U/L	7.4 (4.7–15.6)
U-β2MG, μg/L	257 (125–714)
L-FABP, ng/mL	4.7 (1.0–9.8)
U-Creatinine, mg/dL	75 (36–144)
U-Alb, mg/L	40 (23–151)
Medications	
ACEI or ARB, *n*(%)	18 (34)
β-blocker, *n*(%)	6 (11)
Statin, *n*(%)	10 (19)
Systemic atherosclerosis parameter	
IMT, mm	0.9 (0.75–1.2)
ba-PWV, cm/s	1468 (1232–1881)
Echocardiographic data	
LVDd, mm	48 ± 6
LVDs, mm	33 ± 7
LVEF, %	58 ± 10
E, cm/sec	69 (54–87)
A, cm/sec	73 (62–87)
e', cm/sec	6 ± 2
E/e' ratio	11 (9–16)
Ophthalmic parameters	
Soft exudate, *n*(%)	21 (40)
Continued	

Intraocular pressure, mmHg	13 ± 3
Mean MBR	20.0 ± 5.5
Mean BOT	48.9 ± 5.3
Mean RI	0.40 ± 0.10

Table 1. Characteristic of the patients. Values are the mean ± 2SD, median and interquartile range, or *n*(%) of patients. A, peak mitral A wave velocity; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; baPWV, brachial-ankle pulse-wave velocity; BOT, Blowout time; BUN, blood urea nitrogen; CKD, chronic kidney disease; DM, diabetes mellitus; DLP, dyslipidemia; E peak mitral E wave velocity; e' peak early diastolic myocardial velocity at septal position recorded by tissue Doppler imaging; E/e' ratio, ratio of peak mitral E wave velocity to peak early diastolic myocardial velocity at the septal position by tissue Doppler imaging; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-Cho, high-density lipoprotein cholesterol; HTN, hypertension; IMT, intima media thickness; L-FABP, Liver-type Fatty Acid Binding Protein; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LDL-Cho, low-density lipoprotein cholesterol; MBR, mean blur rate; NSTEMI, non ST elevated myocardial infarction; NT-ProBNP, N-terminal pro-brain natriuretic peptide; RI, resistivity index; STEMI, ST elevated myocardial infarction; TG, triglyceride; U-Alb, Urinary albumin excretion; U-β2MG, urinary β2 microgloblin; U-Creatinine, urinary creatinine; U-NAG, urinary N-acetyl-β-D-glucosidase. *Obtained by Student *t* test, Mann–Whitney *U* test, Chi square test, or Fisher's exact test, as appropriate.

Figure 1. Ophthalmological manifestations 13 days after acute myocardial infarction (AMI). A 77-year-old male was diagnosed with AMI and underwent direct angioplasty 3.5 h after the first episode of severe chest pain. A cotton wool spot (arrow) appeared adjacent to the right optic disc 13 days after AMI. The patient visual acuity was 20/20, and there were no ocular symptoms. The mean ocular blur rate, resistivity index, and blowout time, parameters assessed by laser speckle flowgraphy, were 13.7, 0.58, and 44.1, respectively.

age category of 40–49 years, 50–59 years, 60–69 years, and ≥ 70 years, respectively, divided by sex (Fig. 5). Significant differences were found only among males, in the RI values in the 40–49 years and 50–59 years categories.

Discussion

This study had two main findings. First, the ocular RI obtained by LSFG in ACS patients was significantly associated with atherosclerosis and systemic arteriosclerosis. These trends were similar but weaker for ocular BOT. Second, the RI value in the ACS group was significantly higher in the male aged 40 s to 50 s group than in the same age male control group.

Clinical value of ocular RI and BOT measured by LSFG. Retinal blood flow is adequately regulated by ocular perfusion pressure and vascular resistance in response to various physiological stimuli[12]. Variations in vascular resistance are generally influenced by vascular endothelial function and smooth muscle elasticity. LSFG allows for quantitative estimation of blood flow in the ONH[13]. The speckle pattern change rates on LSFG are expressed numerically, the flow rate is assessed as MBR, and the RI and BOT are the indexes calculated by MBR waveform analysis[4]. Although these LSFG indexes are the only method that can directly and non-invasively evaluate arteriosclerosis of the microvessels, whether changes in these LSFG indexes are attributable to ocular or systemic (cardiovascular) vascular changes or both remains to be elucidated[3]. This study sheds some light on this

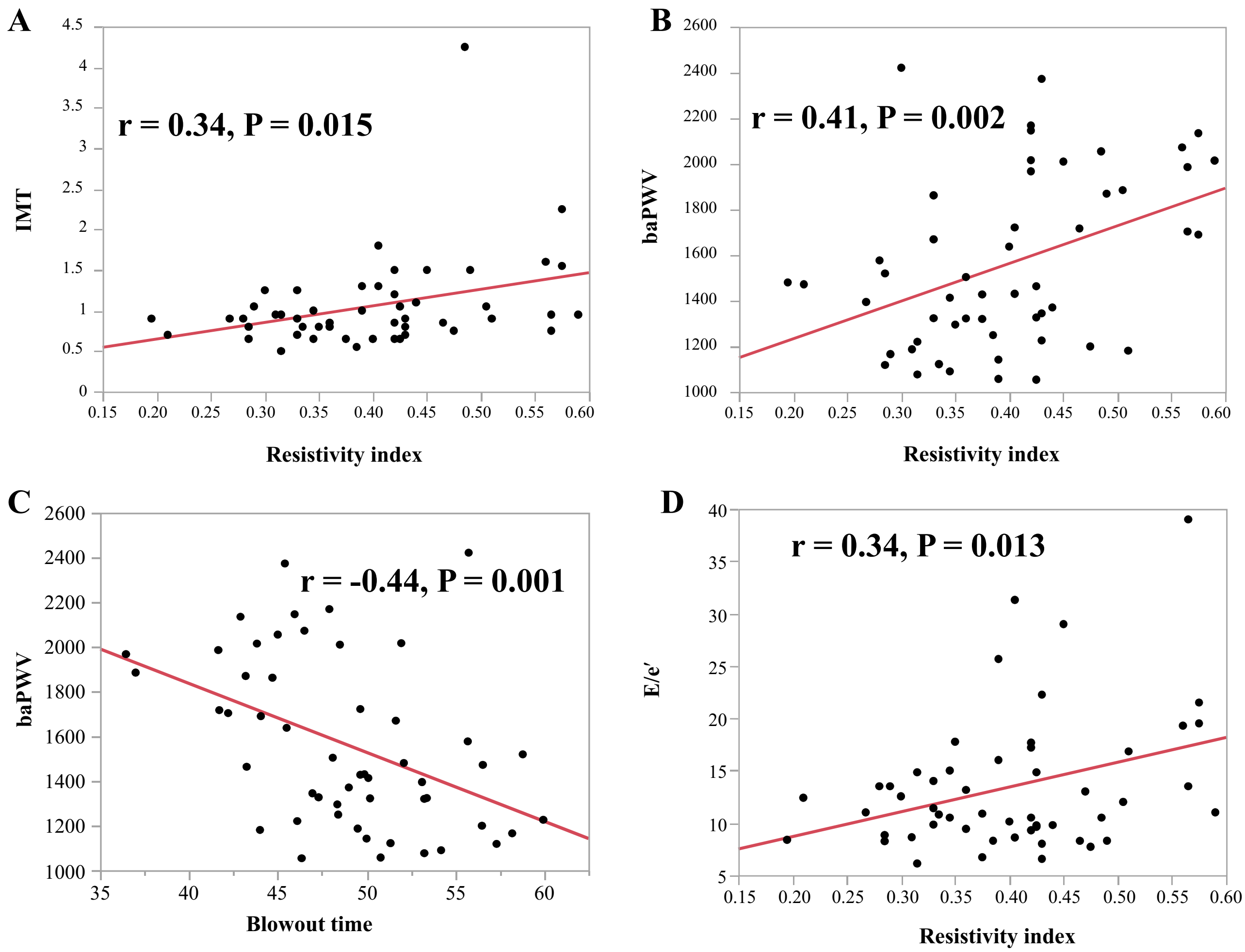

Figure 2. Correlations between resistivity index and intima-media thickness (IMT) (**A**), Brachia-ankle pulse-wave velocity (baPWV) (**B**), and early diastolic velocity to early diastolic myocardial velocity (E/e') ratio (**D**). Also shown are the correlations between blowout time and baPWV (**C**). The mean RI was positively correlated with the mean IMT (r = 0.34, *P* = 0.015; **A**), baPWV (r = 0.41, *P* = 0.002; **B**) and the E/e' ratio (r = 0.34, *P* = 0.013; **D**). The mean BOT was negatively correlated with the mean baPWV (r = −0.44, *P* = 0.001; **C**).

question and presents several important findings. The ocular RI correlated positively with systemic (IMT and baPWV), renal (BUN, cystatin C, U-β2MG, and L-FABP), and cardiac (E/e') parameters, with BOT showing a much weaker association, suggesting that ocular RI may be more appropriate index to systemic parameters than BOT, at least in ACS patients.

Carotid artery assessment by ultrasonography effectively detected the presence of carotid and other atherosclerotic diseases[14]. Increased mean IMT is a major cardiovascular risk factor[15]. baPWV, the most widely used measure of arterial stiffness, was shown to be a strong predictor of future cardiovascular events such as ACS[16]. Previous studies showed that the BOT on LSFG was associated with baPWV and IMT thickening[17], but the relation between ocular RI and baPWV or IMT was not assessed before. Our results suggest that ocular RI, rather than BOT, could help identify the progression of systemic atherosclerosis in such high burden atherosclerotic patients as ACS patients.

Renal dysfunction is associated with an increased risk of cardiovascular morbidity and mortality. Renal diseases such as chronic kidney disease (CKD) reportedly progress with arteriosclerosis[18,19]. The cardiorenal syndrome is a disorder of the heart and kidney, in which one organ reportedly causes dysfunction of the other. The presence of renal disorder in ACS patients was reported to affect their prognosis[20]. Cystatin C, U-β2MG, and L-FABP are known to be better biomarkers for diagnosing acute kidney disease, which could transition to CKD, than creatinine and eGFR[21]. BOT obtained by LSFG in previous studies was correlated with renal function, and patients with CKD were found to experience an ocular circulatory disorder[22].

Evaluation of diastolic function after ACS is important because it correlates with infarct size. Diastolic dysfunction has a high risk of death and is associated with poor prognosis independently of left ventricular systolic function[23,24]. The E/e' ratio is an echocardiographic index used to assess left ventricular diastolic function. It was associated with left ventricular diastolic pressure (and mean pulmonary artery wedge pressure) earlier in the diastole[25]. Previous studies have stated that optic disc BOT obtained by LSFG is significantly correlated with left ventricular diastolic function (E/e' ratio) in healthy persons[26,27]. Our data showed a similar finding, but the

Variables	RI		BOT	
	r	*P* value	r	*P* value
A. Systemic parameters				
IMT	**0.34**	**0.015**	−0.25	0.08
baPWV	**0.41**	**0.002**	**−0.44**	**0.001**
LDL-Cho	−0.09	0.53	0.26	0.06
TG	−0.21	0.12	0.14	0.31
HbA1c	0.11	0.45	−0.06	0.69
B. Renal parameters				
BUN	**0.27**	**0.047**	−0.22	0.12
Creatinine	0.19	0.16	−0.13	0.36
eGFR	−0.11	0.42	0.18	0.19
Cystatin C	**0.32**	**0.020**	−0.23	0.10
U-NAG	0.03	0.85	0.10	0.49
U-β2MG	**0.30**	**0.029**	−0.21	0.13
U-Creatinine	−0.12	0.39	0.20	0.16
U-Alb	0.17	0.21	−0.25	0.07
L-FABP	**0.28**	**0.046**	−0.22	0.11
C. Cardiac parameters				
SYNTAX score	0.19	0.16	**−0.31**	**0.023**
LVDd	0.03	0.82	0.09	0.51
LVDs	−0.01	0.93	0.04	0.75
LVEF	0.17	0.24	−0.06	0.67
LVmass index	0.17	0.24	−0.16	0.25
E/e'	**0.34**	**0.013**	**−0.27**	**0.051**

Table 2. Relationship between the ocular RI and BOT and systemic atherosclerosis parameters. LVmass index, left ventricular mass index. Other abbreviations are shown in Table 1. Significant values are in [bold].

correlation coefficient was higher for RI than for BOT, suggesting that ocular RI assessment after ACS might be useful for determining the presence of diastolic dysfunction.

Role of transient retinopathy in the ACS patients. We found that 21 (40%) ACS patients had mild and transient retinopathy with soft exudate. Kinoshita et al.[28] reported that cotton wool spots developed within two months in more than half of the patients with AMI undergoing PCI and then tended to become quiescent without treatment. We found no difference in systemic atherosclerosis, renal, or cardiac parameters between patients with and without soft exudate in our study. Although the patient characteristics in the two studies were different, the results are comparable; the occurrence of soft exudate was unrelated to any ocular parameters measured by LSFG. The soft exudate is known as the representative of ischemic disorders in the local site of the ocular artery. Therefore, our findings and those of this previous study suggest that it may not always directly reflect systemic vascular resistance or atherosclerosis, especially for ACS patients in the subacute phase.

Clinical implications. Our results indicated a clinical importance that the non-invasive evaluation of ocular blood flow may be a robust marker for promoting the comprehensive evaluations for not only retinal but also systemic arteriosclerosis in ACS patients. Also, the high RI value in middle age patients of 40–60 years can be a potential to predict the vulnerability to cardiovascular disease.

Study limitations

This study has several limitations. First, this study was conducted in a single institution; the sample size was small because we focused on ACS patients without hemodialysis or assisted circulation apparatus. Particularly, for the comparison of RI and BOT values between the ACS and control groups, the number of subjects was small in each age category. The subject number who had a significant difference in the RI among of the age categories of 40–59 years (ACS $n = 17$ vs. control $n = 44$) might have been statistically acceptable. Second, because most of our ACS patients were male, sex differences could have had some influence on our results, as reported previously[29]. We at least indicated a descriptive result of comparing the male and female RI and BOT values between the ACS and control groups (Fig. 5) to show the sex difference. Third, control group data were collected from the subjects who had visited the Division of Ophthalmology in our hospital with no ocular disorders in the examined eye, so the absence of cardiovascular disease was assessed by the subject clinical record, but not by CAG or coronary CT image. Detailed coronary information was not obtained because control subjects did not have a history of episodes of ACS. Finally, the dates of a comprehensive assessment by ophthalmic examination and other modalities might have affected our results. We excluded ACS patients with severe systemic conditions such as hemodialysis or assisted circulation apparatus to minimize this effect. In addition, all assessments were

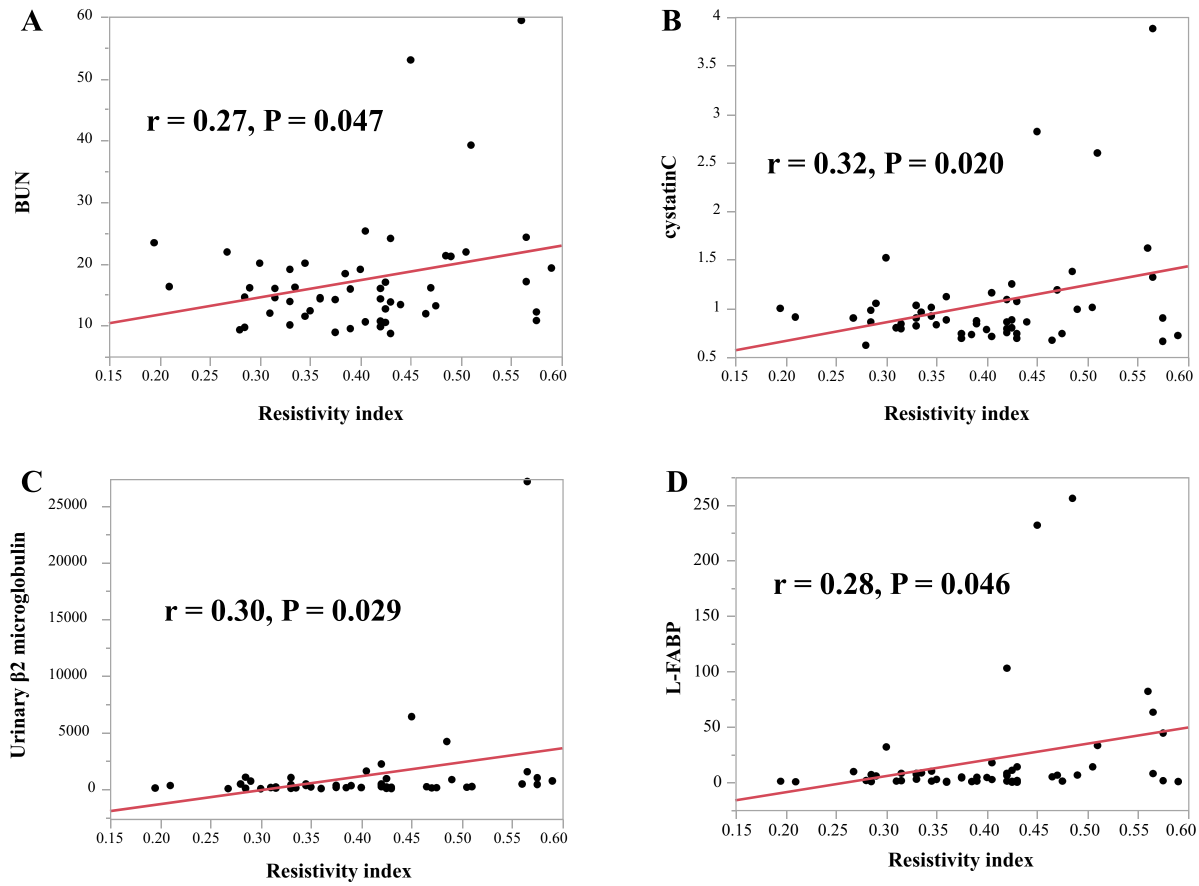

Figure 3. Correlation between the resistivity index and blood urea nitrogen (BUN) (**A**), cystatin C (**B**), Urinary β2 microglobulin (**C**), and liver-type fatty acid-binding protein (L-FABP) (**D**). The mean RI was positively correlated with blood urea nitrogen (BUN; r = 0.27, P = 0.047; **A**), cystatin C (r = 0.32, P = 0.020; **B**), urinary β2 microglobulin (U-β2MG, r = 0.30, P = 0.029; **C**), and liver-type fatty acid-binding protein (L-FABP; r = 0.28, P = 0.046; **D**).

performed in ACS patients who were considered to have good physical condition within 1 week after a blanking period following ACS onset.

Conclusion

Ocular vascular assessment by LSFG in ACS patients revealed that ocular RI was strongly associated with systemic parameters, i.e., atherosclerosis and early renal and cardiac diastolic dysfunction whereas these associations were weak for BOT. Therefore, ocular RI might be a useful non-invasive and comprehensive arteriosclerotic marker in ACS patients.

Methods

We studied 58 patients admitted to the coronary care unit of Nihon University Itabashi Hospital for ACS between April 1 2019, and September 30 2020. All patients underwent PCI on admission day, followed by a visit to the Department of Ophthalmology (mean, 11 ± 5 days after ACS) once their general conditions were stable. The dates for comprehensive assessment by LSFG, ultrasonographic imaging of the carotid artery, brachial-ankle pulse-wave velocity, and transthoracic echocardiography were set within 1 week between the 4 modalities. Patients were excluded from this study if they had glaucoma, uveitis, optic neuropathy, or retinal or choroidal vascular disease, left ventricular (LV) ejection fraction < 30%, or underwent hemodialysis, assisted circulation apparatus or previous intraocular surgery or if they were unable to visit the Department of Ophthalmology on foot. After filtering, 53 patients met the study criteria. LSFG control data were collected from 110 consecutive healthy subjects without any ocular diseases in the examined eye and no history of cardiovascular disease, from whom informed consent was obtained for the evaluation of LSFG. Control subjects were chosen among normal subjects aged 40 years or older who visited the Division of Ophthalmology in our hospital. The institutional review board of Nihon University Itabashi Hospital approved this cross-sectional study, and all participants provided their informed consent for participating in the study. The study was conducted following the tenets of the Declaration of Helsinki.

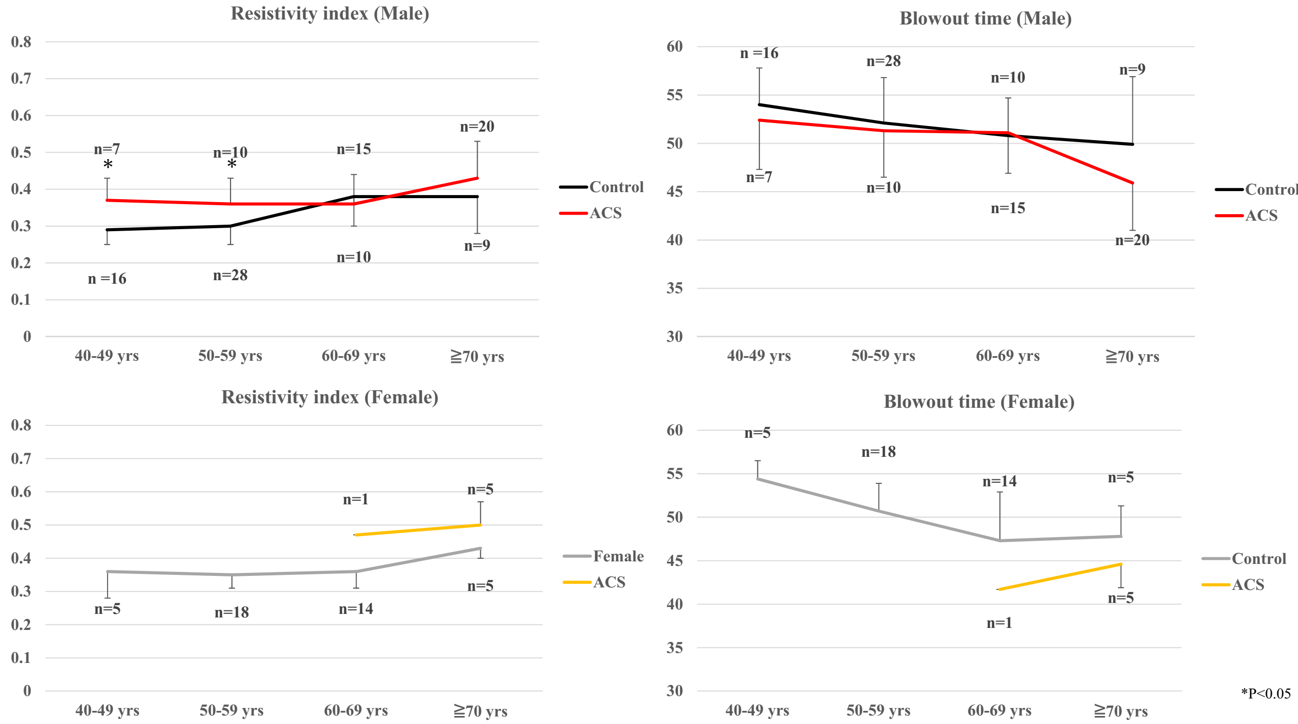

Figure 4. A comparison of the resistivity index (left panels) and blowout time (right panels) between patients with acute coronary syndrome (ACS) and controls in each age category divided by male and female sex. The mean ocular RI was higher in the male ACS patients than in the control male subjects in the 40 to 49 years (0.37 ± 0.02 vs. 0.29 ± 0.01, $P < 0.001$) and 50 to 59 years (0.36 ± 0.02 vs. 0.30 ± 0.01, $P = 0.01$) , while BOT was not different among age categories regardless of sex.

Baseline clinical data	$N = 110$
Age, years	58 ± 9
Male, *n*(%)	68 (62)
HTN, *n*(%)	30 (27)
DM, *n*(%)	5 (5)
DLP, *n*(%)	26 (24)
CKD, *n*(%)	13 (12)
Smoking, *n*(%)	43 (39)

Table 3. Patient characteristics of Control group. The abbreviations are shown in Table 1.

Measurement of the carotid intima-media thickness. One to two weeks after admission for ACS, we performed high-resolution ultrasonographic imaging of the carotid artery with an EUB-8500 device (Hitachi, Co. Ltd., Tokyo, Japan), using B-scan mode and a probe frequency of 7.5 MHz. Measurements were performed with the participants in the supine position, and their head slightly turned away from the sonographer. The procedures involved scanning the near and far walls of the carotid artery 1 cm proximally and distally to the carotid bulb in the longitudinal view, and the average of the maximum values on both sides[30] was used as the mean IMT for data analysis.

Measurements of brachial-ankle pulse-wave velocity. The baPWV was measured 1–2 weeks after admission for ACS, using a volume-plethysmographic device (baPWV/ABI; Nihon Colin Co., Tokyo, Japan) that simultaneously recorded heart sounds, electrocardiograms, and blood pressure at the left and right brachia and ankles. After the patients rested for a minimum of 5 min and while lying supine, pulse volume waveforms were recorded non-invasively from over the brachial and tibial arteries, and the two waveforms time delay (T) between the feet was measured. The distance (D) covered by the waves was estimated as the distance measured between the two recording sites. baPWV was calculated as follows: baPWV = D (cm)/T(s).

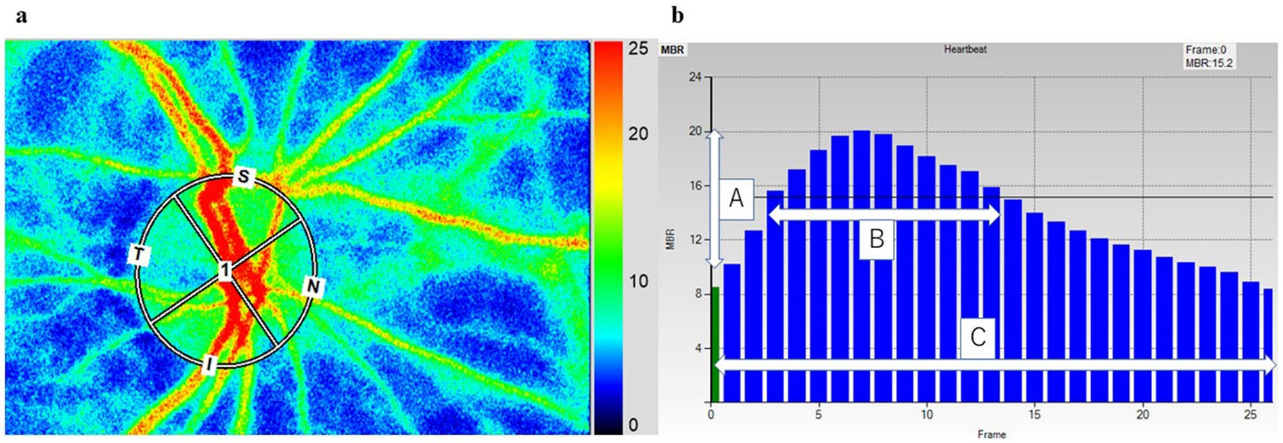

Figure 5. Methods of determining the pulse-wave velocity in the optic nerve head circulation by laser speckle flowgraphy (LSFG). The left panel shows a circle defining the area for measurements in the optic disc area. The right panel shows the normalization of one pulse. A = maximum mean blur rate (MBR)—minimum MBR. B = number of frames spent at one-half the value of A. C = number of frames spent at normalized one pulse.

Laboratory measurements. The following values were measured during the transport to our emergency department: BUN (mg/dL), creatinine (mg/dL), eGFR (mL/min/1.73 m^2), LDL-C (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), HbA1c (%), N-terminal pro-brain natriuretic peptide (pg/mL), cystatin C (mg/L), U-NAG (U/L), U-β2MG (μg/L), urinary creatinine (U-creatinine, mg/dL), U-Alb (mg/L), and L-FABP (ng/mL).

Echocardiographic parameters. Echocardiographic parameters were obtained during the stable phase (mean, 6 ± 4 days after admission for ACS). Echocardiography was performed with the patient in the supine position, using Vivid 7 or Vivid E9 cardiovascular ultrasonographic systems (GE Healthcare, Milwaukee, WI, USA), operated by experienced sonographers who were blinded to patient data. Echocardiographic measurements were performed following the American Society of Echocardiography guideline[31]. Briefly, LV diastolic diameter (LVDd), LV systolic diameter (LVDs), and left atrial diameter were measured on the parasternal long-axis view. LV ejection fraction was measured using the modified Simpson's method in apical 4- and 2-chamber views. The LV mass was calculated with the formula derived from the data of the American Society of Echocardiography[32]. The LV mass index was calculated as the ratio of the LV mass-to-body surface area. Transmitral flow velocity curves were recorded to measure the peak early (E) and late (A) diastolic velocities. Tissue Doppler imaging at the mitral annulus level was obtained in the septal position to measure the early (e') and late (A') diastolic myocardial velocities, as previously described[28].

Ocular fundus examinations. All patients underwent a baseline ophthalmic evaluation by a well-trained ophthalmologist (HY) before the ocular blood flow measurement. All patients had good visual acuity (VA > 20/20) and normal intraocular pressure (IOP < 20 mmHg). IOP was monitored by applanation tonometry (Haag Streit, Bern, Switzerland).

Laser speckle flowgraphy measurements. After the pupils were dilated with a 0.5% tropicamide eye drop, a commercially available LSFG-NAVI system (Softcare Co., Ltd., Fukutsu, Japan) was used to measure ocular circulation at the ONH. The principles of LSFG were previously described in detail[12]. Briefly, the LSFG images were obtained from a 21° section centered on the optic disc. This observation field comprised 750 pixels (width) × 360 pixels (height). The mean blur rate (MBR) was calculated from the moving erythrocytes illuminated by an 830-nm wavelength diode laser beam. The MBRs were expressed in arbitrary units and were considered an indicator of the relative erythrocyte velocity. A total of 118 MBR images were recorded from the ONH area over 4 s. Using accompanying analysis software (LSFG Analyzer, Version 3.3.0; Softcare Co., Ltd., Fukutsu, Japan)[22], a grayscale map of the still images was automatically created by averaging the MBR images (Fig. 2a). MBR can be determined for the entire ONH area (referred to as MA, "mean MBR of the entire area") or, separately, for vessels (MV, "mean MBR of vascular area") and tissue (MT, "mean MBR of tissue area").

The changing MBR pulse wave corresponding to each cardiac cycle was obtained on the analysis screen and displayed after being normalized to one pulse (Fig. 2b). The pulse wave analysis in the ONH circulation was performed on this screen, as was previously described[13]. Briefly, the RI was calculated as the ratio of the difference between the maximum and minimum MBR (labeled A) to the maximum MBR. The number of frames showing one-half the value of A was designated B, and the number of frames showing one cardiac cycle was labeled C. The following formula: BOT = 100 × (B)/(C) was used to analyze the pulse wave in the optic nerve head circulation[33]. We measured MBR, RI, and BOT of the ONH area twice in each eye, and the average values calculated by the LSFG software were used for statistical analysis. All pulse wave analyses in this study were based on the pulse waveform obtained from the MV (corresponding to the large retinal vessels within the ONH area).

Statistical analyses. Continuous data are expressed as mean ± standard deviation if normally distributed or as median (interquartile range) if otherwise. Comparisons were performed using Student's *t*-test or Mann–Whitney *U* test. Categorical data are expressed as numbers and percentages and were compared using the chi-squared test or Fisher's exact test. Linear regression analysis with Spearman rank-order correlation coefficients was used to assess the correlations between the variable, including systemic atherosclerosis, renal, and transthoracic echocardiography cardiac parameters with the LSFG parameters. Statistical significance was defined as a 2-tailed P-value < 0.05. Statistical analyses were performed using JMP Version 14.0 (SAS Institute, Cary, NC, USA).

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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Author contributions

Y.E., T.N., D.F., and Y.O. designed and conducted the study. All authors were involved in the collection of data. Y.E., T.N., D.F., and Y.O. managed, analyzed, and interpreted the data. Y.E., T.N., D.F., and Y.O. prepared, reviewed, and approved the manuscript.

Competing interests

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・タイトル
急性冠症候群患者における全身性動脈硬化症と眼血管抵抗との関連性の包括的評価

・申請者氏名
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・本文
背景
動脈硬化性疾患は食生活の欧米化や急速な高齢化に伴い劇的に増加している。動脈硬化性疾患の危険因子は冠動脈疾患、脳血管疾患、末梢動脈疾患などが互いに関連し、全身血管に影響を及ぼしている。動脈硬化は一般的に頸動脈や下肢動脈などの大血管にみられるが、腎臓や網膜の小血管にも動脈硬化が起こることが知られている。しかし、他領域間における動脈硬化特に網膜微小血管との関連性は未だ不明である。レーザースペックルフローグラフィー(LSFG)により眼動脈の血流速度を測定することにより眼微小循環障害を非侵襲的に検出することが可能となっている。LSFG で測定される様々なパラメーターのうち blowout time(BOT)と resistivity index(RI)が微小血管の動脈硬化や血管抵抗の指標として注目されている。
急性冠症候群(ACS)や左室駆出率の保たれた心不全(HFpEF)は高齢、高血圧、2 型糖尿病と関連があり、いずれも全身性動脈硬化と強く関連している。HFpEF は左心室及び全身血管の硬さが悪化することで拡張不全を起こし発症するとされている。また、拡張不全は冠動脈カルシウムスコアと関連し動脈硬化との関連が示唆されている。
急性心筋梗塞患者において、経皮的冠動脈形成術(PCI)後に一過性の網膜症(軟性白斑)が発生することが報告されており、ACS が眼循環障害に関連する可能性が指摘されている。しかし、ACS 患者では全身の動脈硬化所見が強いにも関わらず、全身性動脈硬化所見と拡張機能が眼循環障害と関連しているかどうかを調査したデータはほとんどない。
本研究では ACS 患者において全身性動脈硬化パラメーター(頸動脈内膜中膜厚[IMT]や上腕足首脈波伝播速度[baPWV])、腎臓尿細管バイオマーカー、経胸壁心臓超音波検査で評価した心機能と、LSFG で評価した眼 BOT 値および眼 RI 値との関連性を検討することを目的とした。

方法
2019 年 4 月 1 日から 2020 年 9 月 30 日までに日本大学医学部附属板橋病院 Coronary Care Unit(CCU)に入院した ACS 患者 58 例について検討した。全例が入院同日に PCI を受け、その後全身状態が安定した安定期(ACS 発症後平均 11±5 日)に眼科受診をした。LSFG による眼血流評価、頸動脈超音波検査、baPWV 測定、経胸壁心臓超音波検査の 4 検査間の実施期間は 1 週間以内である。緑内障、ぶどう膜炎、視神経症、網膜脈絡膜血管疾患や眼内

手術既往のある患者、左室駆出率 30%未満、補助循環装置使用、徒歩で眼科受診ができない患者は除外した 53 例が研究基準を満たした。LSFG の対照群のデータは心血管疾患の既往や被検眼に眼疾患がない LSFG での評価についてインフォームドコンセントを得られた 40 歳以上の連続 110 名から収集した。

頸動脈超音波検査は ACS 入院から 1〜2 週間後に施行した。測定手順は頸動脈の近位壁と遠位壁を頸動脈球の 1cm 近位と 1cm 遠位で縦断的に走査し、両側頸動脈で得られた平均値を平均 IMT として用いた。

baPWV は ACS 入院から 1〜2 週間後に施行した。5 分以上安静にした後に仰臥位で上腕動脈と脛骨動脈上から非侵襲的に脈波形を記録し、両足間の 2 波形の時間の遅れ(T)を測定した。脈波の距離(D)は 2 か所の記録部位間の測定距離で推定し、baPWV=D(cm)/T(s)の式で計算した。

心臓超音波検査は ACS 入院から平均 6±4 日目に施行した。米国心エコー図学会のガイドラインに従って測定した。

全患者は眼底血流測定前に十分な訓練を受けた眼科医による基本的な眼科診察を行った。尚、すべての患者は良好な視力と正常眼圧であった。LSFG は 0.5%トロピカミド点眼薬で散瞳させた後に LSFG-NAVI システムを用いて視神経乳頭の眼循環を測定した。LSFG の測定方法であるが、波長 830nm のダイオードレーザー光を赤血球に照射し平均のブレ率(MBR)を算出し、相対的な赤血球の速度の指標として用いた。視神経乳頭領域から 4 秒間で合計 118 枚の MBR 画像を記録し解析ソフトを用いて MBR を平均化したグレースケールマップを作成し、各心周期に対応する MBR を 1 心拍に適正化したもの(図 1)を解析した。最大 MBR と最小 MBR の差を最大 MBR で除した値を RI とし、最大 MBR と最小 MBR の差の半分の値を維持できる時間を 1 心周期の時間で除した値を BOT として算出した。MBR、RI、BOT を片眼ずつそれぞれ 2 回測定し平均したものを解析に用いた。LSFG に精通した熟練眼科専門医 2 名によって計測を行うことで再現性を担保した。

結果

表 1 は ACS 群の患者背景であり、平均年齢は 66 歳で男性が 89%、既往は高血圧が 70%、脂質異常 62%、糖尿病が 26%、慢性腎臓病 15%であった。脂質パラメーターや腎機能で目立った所見はなく、心機能も保たれ E/e’の中央値は 11 と拡張障害は強くなかった。IMT は平均 1.0mm 未満だが、PWV は基準値の 1400 を超えており全体として動脈硬化所見を認めている群であった。急性心筋梗塞から 13 日経過した軟性白斑を認めた典型的な眼底所見を図 2 に示す。

表 2 は各種パラメーターと RI や BOT との関連について示したものである。

全身性動脈硬化所見と RI、BOT の関連については、RI と IMT(r=0.34, p=0.015, 図 3A)、baPWV(r=0.41, p=0.002, 図 3B)で有意に正の相関関係にあり、BOT と baPWV(r=0.41, p=0.002, 図 3C)では有意に負の相関を認めた。腎臓パラメーターと RI との関連について

は、BUN(r=0.27, p=0.047, 図 4A)、シスタチン C(r=0.32, p=0.020, 図 4B)、尿中β2 ミクログロブリン(r=0.30, p=0.029, 図 4C)、尿中 L-FABP(r=0.28, p=0.046, 図 4D)と有意に正の相関を認めた。心臓超音波パラメーターと RI との関連については、E/e'(r=0.32, p=0.020, 図 5)と正の相関関係にあったが、その他の心臓超音波パラメーターとの関連は認めなかった。

対照群の患者背景を表 3 に示すが、平均年齢は 58 歳で 68%が男性、既往は高血圧 30%、脂質異常が 26%で糖尿病 5%、慢性腎臓病 13%であった。RI と BOT を ACS 群と対照群で 40-49 歳、50-59 歳、60-69 歳、70 歳以上のそれぞれ男女別で比較したところ(図 6)、40 歳代男性(0.37±0.02 vs. 0.29±0.01, p＜0.001)と 50 歳代男性(0.36±0.02 vs. 0.30±0.01, p=0.01)では ACS 群が対照群より有意に高い眼 RI 値を示していた。

考察

本研究では主に 2 つの知見を得ることができた。

まず ACS 患者における LSFG で得られた眼 RI、眼 BOT ともに全身性動脈硬化と関連していたが、眼 RI の方が強い関連性を認めた。第 2 に ACS 患者における眼 RI 値は 40 歳代から 50 歳代の男性で同年代の男性対照群に比べ有意に高い値を示していた。

網膜血流は眼球灌流圧と血管抵抗により様々な生理的刺激に対応して適切に調節されている。血管抵抗の変動は、一般に血管内皮機能及び平滑筋の弾性に影響される。LSFG はスペックルパターンの変化率を MBR として表すことで血流量を数値化し、MBR 波形をさらに解析することで RI や BOT として算出するものである。これらの LSFG 指標は微小血管の動脈硬化を直接かつ非侵襲的に評価できる唯一の方法であるが、これらの LSFG 指標の変化が眼血管や全身血管の変化をどのように反映しているかは未だ不明である。

眼 RI は全身性動脈硬化所見(IMT, baPWV)や腎臓尿細管マーカー(シスタチン C, 尿中β2 ミクログロブリン, L-FABP)及び心臓拡張機能(E/e')と正の相関を示していた。眼 BOT も相関関係にあったが眼 RI に比べその相関性は低いことから、少なくとも ACS 患者では眼 BOT よりも眼 RI の方が動脈硬化パラメーターに適した指標である可能性が示唆された。

頸動脈超音波検査による頸動脈評価は、頸動脈疾患及びその他の動脈硬化性疾患の存在を効果的に検出することが可能である。頸動脈超音波検査で計測される平均 IMT の増加は主要な心血管因子であると報告されている。また、全身性動脈硬化指標として広く使用されている baPWV の上昇も ACS のような心血管イベント発症の強い予測因子として知られている。以前の報告では LSFG で算出される眼 BOT は IMT 肥厚と baPWV と関連することが示されているが、眼 RI と IMT 肥厚や baPWV との関連は不明であった。今回の結果は ACS 患者のような高度動脈硬化患者においては眼 BOT ではなく眼 RI が全身性動脈硬化進行の判断に役立つ可能性を示唆している。

慢性腎臓病などの腎疾患は動脈硬化の進行とともに増悪することが知られている。腎機能障害は心血管疾患の罹患率及び死亡率のリスク上昇と関連し、ACS 患者においても同様

に腎機能障害の有無は予後に影響することも報告されている。このように、心臓と腎臓機能障害は強い関連性があることから、心腎症候群といった概念も提唱されている。先行研究ではLSFGで得られた眼BOTは腎機能と相関があり、慢性腎臓病患者の多くに眼循環障害を有することが報告されている。今回の結果は、ACS 患者において尿細管障害を早期に診断し得る非侵襲的検査として、LSFGでの眼RI測定が有用である可能性を示唆している。一方、本研究において眼RIがBUNと関連していたが、腎機能障害マーカーであるクレアチニンやクレアチニンから算出されたeGFRが関連を認めていなかった。これは、BUNが体蛋白異化・同化、蛋白質摂取量、脱水、利尿剤使用など腎機能以外の他の影響を受けるパラメーターであることや、ACS 群に腎機能低下例が少なかったためであると考える。さらに尿細管障害マーカーである尿中β-2 ミクログロブリンや L-FABP が眼 RI と関連していたにも関わらず、同じ尿細管障害マーカーである尿中NAGが関連していなかった。これについても腎機能正常例が多かったことが影響していると考える。

ACS 後の拡張機能の評価は梗塞サイズと関連があるため重要である。拡張機能障害は死亡リスクが高く、左心室収縮機能とは無関係に予後不良となる。E/e'比は左心室拡張機能を評価するために使用される心臓超音波検査指標であり、拡張期の早い段階での左心室拡張期圧(及び平均肺動脈楔入圧)と関連している。先行研究では LSFG によって得られた眼BOT は健常者の左心室拡張機能(E/e'比)と有意な相関があると報告されている。今回の研究でも同様の結果が得られたが、相関係数は眼BOTよりも眼RIで高く、ACS後の眼RI評価は拡張機能障害の有無を判断するのに有用である可能性が示唆された。

本研究はACS患者の全身性動脈硬化所見を総合的に評価する上で、非侵襲的な眼血流の評価が有用であるという臨床的重要性を示している。また、40歳から60歳代の中年男性において眼 RI 値が高いことは心血管疾患への脆弱性を予測する可能性があると考えられた。これらのことは、今後の臨床において、LSFG測定は動脈硬化指標や冠動脈疾患発症高リスク群を推定するスクリーニングで使用可能であることを示唆している。また、全身動脈硬化測定が困難な施設、精通していない医師でも、眼科医による全身動脈硬化のスクリーニング手法として展開できる可能性もある。さらには、症例毎での動脈硬化の経時的変化を把握することで、動脈硬化評価の 1 つのモダリティとして早期診断・早期精査治療介入が可能となる点も有益な点であると考える。

研究の限界

本研究における限界としては大きく4点ある。第1には単一施設での研究であり透析患者・補助循環を要したACS患者・眼底所見観察不能患者を対象外としたため症例数が少なかった。特にACS群と対照群の眼RI値・眼BOT値の比較では各年齢区分で対象者数が少なくなった。また、症例数の関係上、単回帰分析のみ行っているが、今後症例数を重ねて多重回帰分析を行い、LSFGパラメーターに最も寄与する因子の判定を同定する必要があると考えている。第2にACS患者のほとんどが男性であったため性差が結果に影響を及ぼした可能

性がある。しかし、そのような状況下で性差示すために ACS 群と対照群の眼 RI・眼 BOT 値を男女で比較して検討した。第 3 に、対照群データは被検眼に眼疾患がない当院眼科を受診した被験者から収集している。そのため心血管疾患の有無は臨床記録から評価しており、冠動脈造影検査含めた画像所見での評価は行えていない。第 4 に、眼科検査や他のモダリティによる評価までの期間が結果に影響を与えた可能性がある。この影響を最小限にするため血液透析や補助循環装置などの重症全身性疾患を有する ACS 患者を除外した。第 5 に、本研究において抗血栓薬内服が結果に影響を与えた可能性があるが、抗血栓薬は研究の性質上全例で内服しており除外は困難である。心房細動も影響を与えた可能性があるが、全体の 8%程度と割合は少なく与えられた影響も最小限であると考える。最後に腎機能障害マーカーとしてシスタチン C 値からの eGFR を用いずシスタチン C 値そのものを用いたこと、尿細管障害マーカーとして尿中 L-FABP/Cr 比を用いず L-FABP 値そのものを用いたことが今回の結果に影響を与えた可能性がある。

結語

本研究では ACS 患者において LSFG による眼循環評価指標である眼 RI が全身性動脈硬化パラメーター、腎尿細管マーカー、心臓拡張障害マーカーと関連していた。これらの関連は眼 BOT では弱く、今後 ACS 患者における非侵襲的で総合的な動脈硬化指標として眼 RI が有用である可能性がある。

表 1. 患者背景

患者背景	N=53
年齢, 歳	66 ± 13
男性, n(%)	47 (89)
収縮期血圧, mmHg	114 ± 14
拡張期血圧, mmHg	66 ± 10
心拍数, beat per minutes	70 ± 8
高血圧症, n(%)	37 (70)
糖尿病, n(%)	14 (26)
脂質異常症, n(%)	33 (62)
慢性腎臓病, n(%)	8 (15)
喫煙歴, n(%)	38 (72)
ST 上昇型急性心筋梗塞, n(%)	39 (74)
SYNTAX スコア	15 ± 8
心房細動, n(%)	4 (8)
血液検査データ	
尿素窒素, mg/dL	15 (12-20)
クレアチニン, mg/dL	0.83 (0.71-1.0)
eGFR, ml/min/1.73m^2	72.0 ± 22
LDL-Cho, mg/dL	121 ± 35
HDL-Cho, mg/dL	44 (38-50)
中性脂肪, mg/dL	113 (68-168)
HbA1c, %	6.0 (5.6-6.7)
NT-ProBNP, pg/mL	285 (64-2518)
シスタチン C, mg/L	0.88 (0.79-1.06)
U-NAG, U/L	7.4 (4.7-15.6)
U-β2MG, μg/L	257 (125-714)
L-FABP, ng/mL	4.7 (1.0-9.8)
尿中クレアチニン, mg/dL	75 (36-144)
尿中アルブミン, mg/L	40 (23-151)
内服歴	
ACEI or ARB, n(%)	18 (34)
β 遮断薬, n(%)	6 (11)
スタチン, n(%)	10 (19)

全身性動脈硬化パラメーター	
IMT, mm	0.9 (0.75-1.2)
ba-PWV, cm/s	1468 (1232-1881)
心臓超音波パラメーター	
LVDd, mm	48 ± 6
LVDs, mm	33 ± 7
LVEF, %	58 ± 10
E, cm/sec	69 (54-87)
A, cm/sec	73 (62-87)
e', cm/sec	6 ± 2
E/e' ratio	11 (9-16)
眼科パラメーター	
軟性白斑, n(%)	21 (40)
眼内圧, mmHg	13 ± 3
平均 mean blur rate	20.0 ± 5.5
平均 blowout time	48.9 ± 5.3
平均 resistity index	0.40 ± 0.10

数値は平均値±2SD、中央値と四分位範囲、または患者数(%)である。

A, 僧帽弁口血流速波形 A 波; ACEI, アンジオテンシン変換酵素阻害薬; ARB, アンジオテンシン受容体拮抗薬; baPWV, 上腕-足首脈波伝播速度; E, 僧帽弁口血流速波形 E 波; e', 中隔側僧帽弁輪運動速波形の拡張早期波高; E/e' ratio, 中隔側僧帽弁輪運動速波形の拡張早期波高と僧帽弁口血流速波形 E 波との比; eGFR, 推算糸球体濾過量; HbA1c, ヘモグロビン A1c; HDL-Cho, 高比重リポタンパク; IMT, 内膜中膜複合体肥厚度; L-FABP, 肝臓型脂肪酸結合蛋白; LVEF, 左室駆出率; LVDd, 左室拡張末期径; LVDs, 左室収縮末期径; LDL-Cho, 低比重リポタンパク; NT-ProBNP, ヒト脳性ナトリウム利尿ペプチド前駆体 N 末端フラグメント; U-β2MG, 尿中 β2 ミクログロブリン; U-NAG, 尿中 N アセチル-β-D-グルコサミニダーゼ.

*適宜スチューデントの *t* 検定, マン・ホイットニーの *U* 検定, カイ二乗検定, またはフィッシャーの正確確立検定を用いて算出した

表 2. resistivity index と blowout time と全身動脈硬化指標との関連

	RI		BOT	
	r	P 値	r	P 値
A. 全身パラメーター				
IMT	**0.34**	**0.015**	-0.25	0.08
baPWV	**0.41**	**0.002**	**-0.44**	**0.001**
LDL-Cho	-0.09	0.53	0.26	0.06
中性脂肪	-0.21	0.12	0.14	0.31
HbA1c	0.11	0.45	-0.06	0.69
B. 腎臓パラメーター				
尿素窒素	**0.27**	**0.047**	-0.22	0.12
クレアチニン	0.19	0.16	-0.13	0.36
eGFR	-0.11	0.42	0.18	0.19
シスタチン C	**0.32**	**0.020**	-0.23	0.10
U-NAG	0.03	0.85	0.10	0.49
U-β2MG	**0.30**	**0.029**	-0.21	0.13
尿中クレアチニン	-0.12	0.39	0.20	0.16
尿中アルブミン	0.17	0.21	-0.25	0.07
L-FABP	**0.28**	**0.046**	-0.22	0.11
C. 心臓パラメーター				
SYNTAX スコア	0.19	0.16	**-0.31**	**0.023**
LVDd	0.03	0.82	0.09	0.51
LVDs	-0.01	0.93	0.04	0.75
LVEF	0.17	0.24	-0.06	0.67
LVmass index	0.17	0.24	-0.16	0.25
E/e’	**0.34**	**0.013**	**-0.27**	**0.051**

LVmass index, 左室心筋重量係数. その他の略語は表 1 参照.

表 3. 対照群の患者背景

基礎臨床背景	N=110
年齢, 歳	58 ± 9
男性, n(%)	68 (62)
高血圧, n(%)	30 (27)
糖尿病, n(%)	5 (5)
脂質異常症, n(%)	26 (24)
慢性腎臓病, n(%)	13 (12)
喫煙歴, n(%)	43 (39)

図 1. レーザースペックルフローグラフィー(LSFG)の測定方法

1 心拍に正規化し A＝ 最大 mean blur rate(MBR)－最小 MBR、B＝A の値の 1/2 を維持できる時間、C＝1 心拍にかかる時間

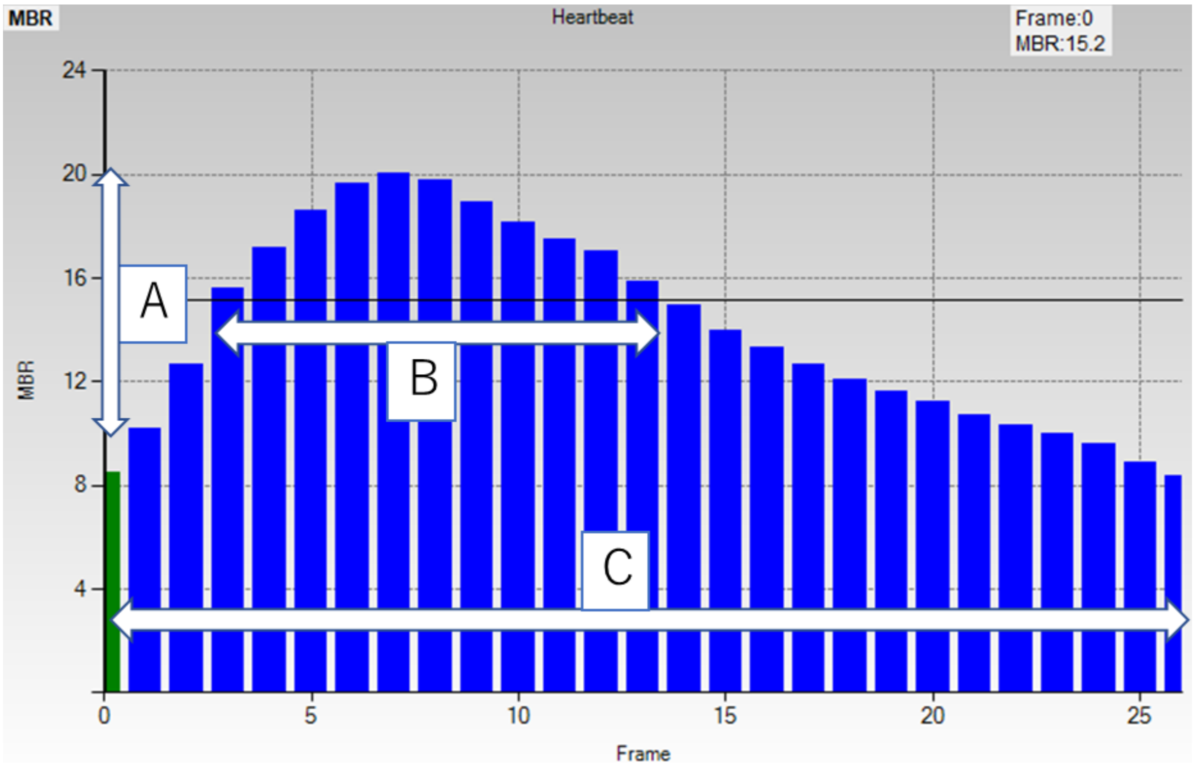

図 2. 急性心筋梗塞発症から 13 日経過した眼底所見。

77 歳男性で胸痛発症から 3.5 時間後に経皮的冠動脈形成術を行った。急性心筋梗塞発症から 13 日後に右視神経乳頭に綿花様白斑(黒矢印)を認めた。視力は 20/20 であり眼症状はなく、レーザースペックルフローグラフィーで測定した mean blur rate、resistivity index、blowout time はそれずれ 13.7、0.58、44.1 であった。

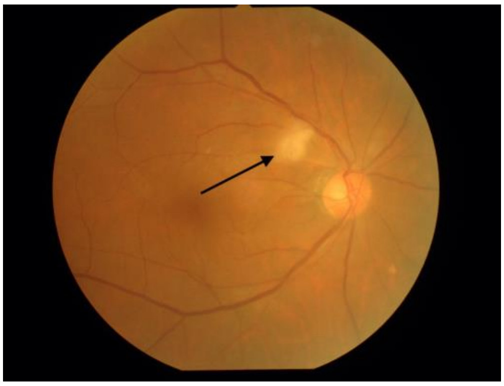

図 3. resistivity index(RI)と内膜中膜厚(IMT)(A)、上腕足首脈波伝播速度(baPWV)(B)との相関と blowout time(BOT)と baPWV(C)との相関。

平均 RI は平均 IMT(r=0.34, p=0.015, A)と baPWV(r=0.41, p=0.002, B)と正の相関を認め、平均 BOT は baPWV(r=0.41, p=0.002, C)と負の相関を認めた。

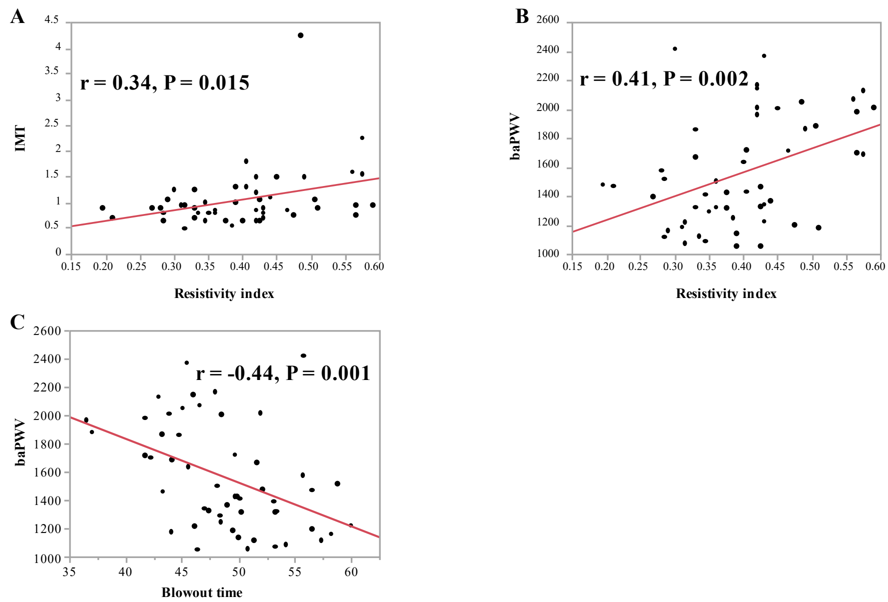

図 4. resistivity index(RI)と BUN(A)、シスタチン C(B)、尿中β2 ミクログロブリン(C)、L-FABP(D)との相関。

平均 RI は BUN(r=0.27, p=0.047, A)、シスタチン C(r=0.32, p=0.020, B)、尿中β2 ミクログロブリン(r=0.30, p=0.029, C)、L-FABP(r=0.28, p=0.046, D)と正の相関が認められた。

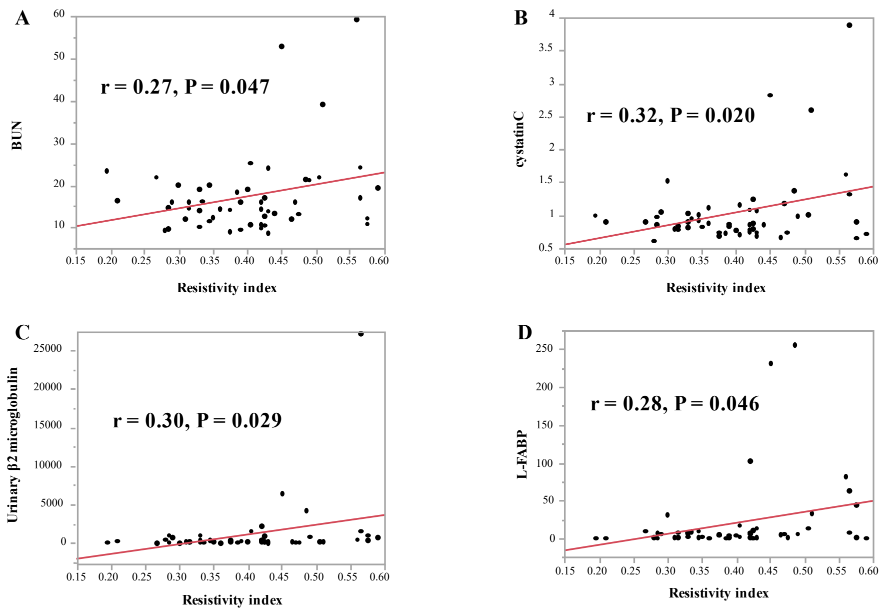

図 4. resistivity index(RI)と拡張早期左室流入血流速波形(E)/ 僧帽弁輪部運動拡張早期波形(e')比との相関。

平均 RI は E/e'(r=0.32, p=0.020)との正の相関を認めた。

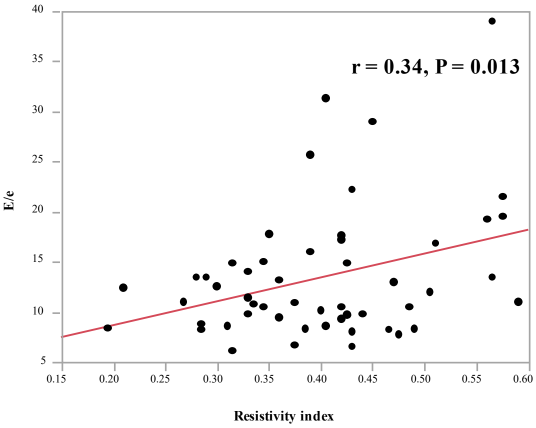

図 5. 急性冠症候群（ACS）患者群と対照群との resistivity index(RI)(左)と blowout time(BOT)(右)の男女年代別比較。

平均 RI 値は 40-49 歳(0.37±0.02 vs. 0.29±0.01, p＜0.001)と 50-59 歳(0.36±0.02 vs. 0.30±0.01, p=0.01)の男性 ACS 患者群で対照群より高かった。一方で平均 BOT は性別に関わらず年代別で差はなかった。