The Characteristics of Retinal Emboli and its Association With Vascular Reperfusion in Retinal Artery Occlusion

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Purpose. To analyze the characteristics of retinal emboli and their association with vascular reperfusion in retinal artery occlusion (RAO).

Methods. In this retrospective comparative case series, we analyzed emboli in patients with acute central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) and visible emboli, and analyzed vascular reperfusion in patients with visible emboli causing blockage of perfusion. The patients were divided into emboli "movement" and "no movement" groups and their vascular reperfusion states were compared.

Results. There were 52/248 (21%) eyes with RAO and visible retinal emboli (31/187 [17%] eyes with CRAO and 21/61 [34%] eyes with BRAO) showing various embolic features. Platelet-fibrin emboli were observed most commonly, and showed the earliest and highest rate of movement. In the movement group, which comprised platelet-fibrin (60%) and cholesterol (40%) emboli, early complete reperfusion was observed in 80% of eyes; however, 67% of eyes in the no movement group, comprising cholesterol (67%) and calcific (33%) emboli, showed late incomplete reperfusion. There were no cases of permanent vascular blockage. The mechanisms of vascular reperfusion could be summarized as complete degradation, peripheral migration, partial dislodgement, angiophagy, and collateral circulation.

Conclusions. Retinal emboli in RAO patients have various characteristics that affect their movement. Movement of emboli may affect vascular reperfusion. Various mechanisms are associated with vascular reperfusion, including in cases without movement of emboli. These mechanisms may apply to cerebrovascular occlusion and stroke in general.

Keywords: retinal emboli, vascular reperfusion, retinal artery occlusion

Retinal artery occlusion (RAO) is a visually disabling ocular vascular occlusive disorder. It is usually divided into central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), and cilioretinal artery occlusion based on the site of occlusion.[1] Numerous studies of the visual prognosis of RAO have been published, and our group has also published articles recently on the incidence and visual prognosis of RAO, a study of optical coherence tomography in CRAO and BRAO, and cosmetic facial filler–related RAO.[2–9] However, while a few studies suggest that movable retinal emboli are responsible for most cases of RAO, there is still limited information about the natural course of retinal emboli and their association with vascular reperfusion, particularly in Asian people.[10,11]

The causes of vascular occlusion are thought to include emboli, blood clots, and lipid plaques, and similar mechanisms apply in RAO. A vascular etiology with stroke and embolism derived from carotid artery plaques is the most common pathogenetic mechanism.[12,13] In previous studies, emboli were detected in 60% to 70% of patients with RAO and comprised cholesterol, calcification, and platelet-fibrin.[1,11,13–16] The detection rate varies according to the constituents of retinal emboli, and these constituents in turn vary depending on the underlying disease. Therefore, the characteristics of emboli and their detection rates may differ according to race. However, only a few studies of retinal emboli in RAO have been reported thus far, so it is difficult to glean substantial information on this area of research in the general population, including for different races.

Various features of emboli are observed in RAO patients clinically, as are different forms of vascular perfusion, which can be assessed by fluorescein angiography (FA).[11] However, there is limited information available on the natural course of movement of emboli and their association with vascular reperfusion, much less the rate, timing, and mechanisms of vascular reperfusion in RAO.[10,11]

This study aimed to analyze the various characteristics of retinal emboli and to examine the associations between movement of emboli and vascular reperfusion in patients with RAO.

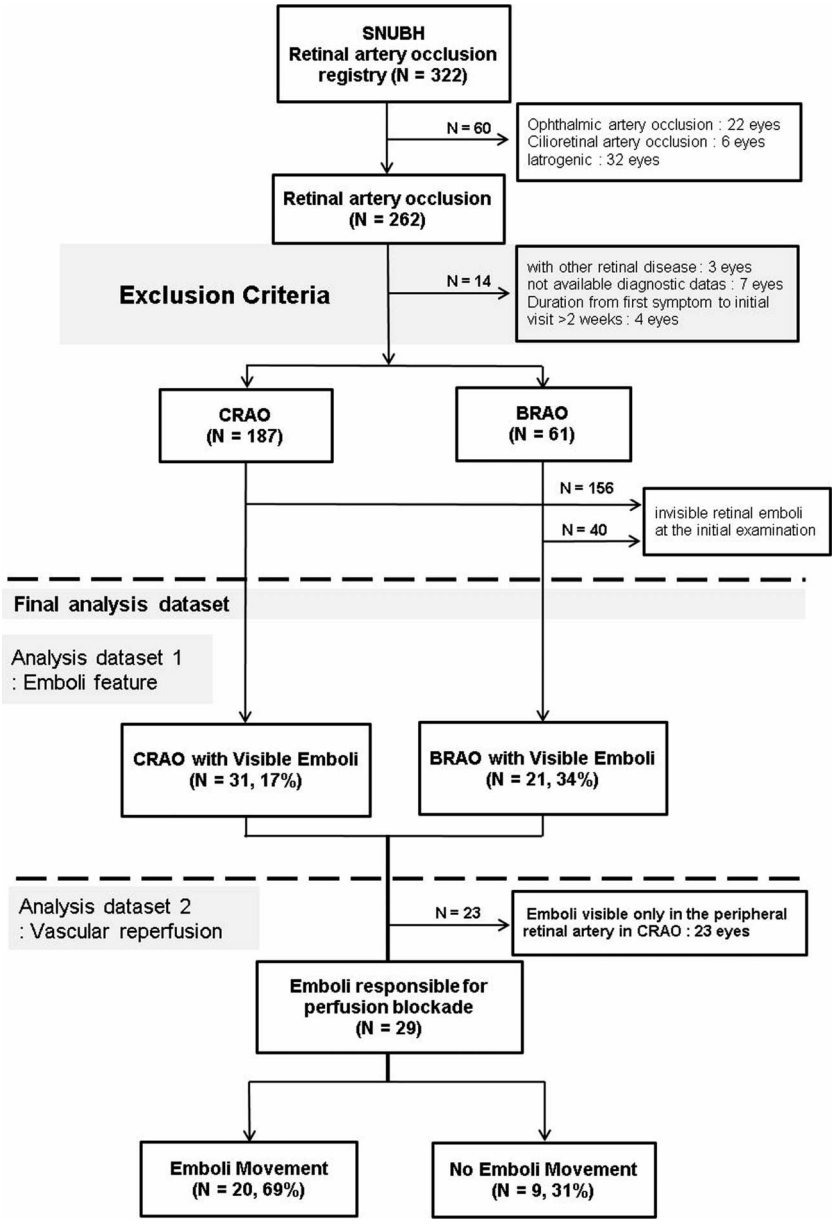

Figure 1. Flow diagram showing the selection and subgrouping process for the enrolled eyes with retinal artery occlusion. Emboli: emboli visible with fundus photography at the initial visit. Movement: peripheral migration or disappearance of emboli during the follow-up period. Iatrogenic indicates retinal artery occlusion with an iatrogenic cause (e.g., injection of facial filler).

Methods

This study took the form of a retrospective comparative case series. It was approved by the institutional review board of the Seoul National University Bundang Hospital (Seongnam, Korea), and was conducted in accordance with the Declaration of Helsinki.

Patient Selection

The RAO registry of the Seoul National University Bundang Hospital included records for 322 eyes of patients who had visited the hospital between January 2009 and October 2014 for loss of vision or a visual field defect occurring within 14 days of the initial visit. Cases of ophthalmic artery occlusion (n = 22), cilioretinal artery occlusion (n = 6; where there is usually associated central retinal vein occlusion or giant cell arteritis[17,18]), and iatrogenic cosmetic filler–induced RAO (n = 32) were excluded from analysis. In total, there were 262 eyes with spontaneous nonarteritic RAO.

All RAO patients had undergone fundus photography (FP) and FA evaluation at the initial visit, except for four patients in whom there was an interval of more than 2 weeks from symptom onset to the initial diagnostic test. Patients with a history of ocular trauma, ocular surgery other than cataract surgery, severe nonproliferative or proliferative diabetic retinopathy, retinal vascular disease other than RAO (n = 3; combined retinal vein occlusion), an interval of greater than 2 weeks between symptom onset and the initial visit (n = 4), or unavailable FP or FA data, and those who refused the FP or FA test (n = 7) were excluded. A total of 248 eyes from 248 patients with acute RAO (CRAO [n = 187] or BRAO [n = 61])

Table 1. Demographic Data and Overall Clinical Features of Retinal Artery Occlusion With Visible Emboli in Analysis Dataset

Characteristics	Mean or Number
Total patients (RAO with visible emboli/total RAO)	52/248 (21%)
CRAO (CRAO with visible emboli/total CRAO)	31/187 (17%)
BRAO (BRAO with visible emboli/total BRAO)	21/61 (34%)
Age, mean (y, range)	69.29 ± 8.99 (49–80)
Sex (male:female;%)	42 (81%):10 (19%)
Time from symptom onset to initial visit (d, range)	1.03 ± 3.88 (0–14)
Follow-up period (mo, range)	24.22 ± 23.65 (3–84)
Side of retinal artery occlusion (right:left;%)	28 (54%): 24 (46%)
Underlying disease/risk factor	
Diabetes mellitus (*n*, %)	11 (21%)
Hypertension (*n*, %)	31 (60%)
Hyperlipidemia (*n*, %)	12 (23%)
Current smoking (*n*, %)	7 (13%)
History of stroke (*n*, %)	6 (12%)
History of ischemic heart disease (*n*, %)	8 (15%)
Current use of antiplatelet agent (*n*, %)	10 (19%)

Continuous data are presented as mean ± SD.

were evaluated. Patients were included if they had emboli when the initial FP or FA was performed. Finally, 52 cases including 31 (17%) eyes of CRAO patients with emboli visible in the central retinal artery trunk or peripheral retinal artery and 21 (34%) eyes of BRAO patients with emboli visible in the branch retinal artery, based on the existence of emboli at the initial FP or FA, were included in this study.

Two groups comprising 52 patients (CRAO = 31, BRAO = 21) with emboli constituted analysis dataset 1. Additionally, 23 eyes of CRAO patients with emboli visible only in the peripheral retinal artery were excluded because such emboli are not directly related to the total vascular reperfusion state in CRAO; thus, 29 eyes with emboli causing blockage of perfusion were included in analysis dataset 2. Analysis dataset 2 was subdivided into emboli "movement" ($n = 20$, 69%) and "no movement" ($n = 9$, 31%) groups based on peripheral migration or disappearance of emboli during the follow-up period (Fig. 1).

Ophthalmic Examination

All patients were followed up for at least 6 months from the initial visit, and underwent slit-lamp biomicroscopy, indirect fundus examination, FP (standard FP or wide-angle FP; Vx-10, Kowa Optimed, Tokyo, Japan, or Optos PLC, Dunfermline, Scotland, UK), and FA (standard FA or wide-angle FA; Vx-10 or Optos PLC) at the initial visit, at 1, 3, and 6 months, and every year thereafter. Wide-angle FP and FA were available from 2011, which was the midpoint of this retrospective study, and 38/52 patients had these investigations performed at least once during the follow-up period. The findings of the initial FP and FA were compared with those obtained at the 1-month and final visits to assess changes in location of the emboli and the vascular reperfusion state.

Main Outcome Measurement

The primary outcome measures were the contents of the emboli and their movement. The secondary outcome measure was vascular reperfusion in patients with RAO according to movement of emboli.

Characteristics of Emboli as Determined by Fundus Photography

Analysis of the characteristics of emboli, including movement, location, and multiplicity was performed following categorization of their contents. The emboli were compared for platelet-fibrin versus cholesterol, cholesterol versus calcification, and platelet-fibrin versus calcification (Fig. 1, analysis dataset 1). The contents were categorized as platelet-fibrin, cholesterol, or calcification. Platelet-fibrin emboli were identified based on an "appearance as dull, grey-white, mobile intravascular material, occupying a long arteriolar segment before breaking up." Cholesterol emboli were distinguished based on the following description: "small, bright yellow-white, reflective, and often multiple." Calcification was assigned based on the following description: "most often large, white and unique, and commonly impacted into the proximal retinal arterial branches."[19–21] The presence or absence of emboli movement was determined via serial FP during the follow-up period, where a change in emboli location when compared with the position measured on FP at the first visit was classified as "movement," for which there are two types (i.e., distal movement and complete disappearance).

Location was categorized into two groups as follows: (1) optic disc; central retinal artery trunk in CRAO and central retinal artery bifurcation on the optic disc in BRAO, indicating proximal branch occlusion, and (2) peripheral retinal artery; located in a peripheral retinal artery branch as determined by

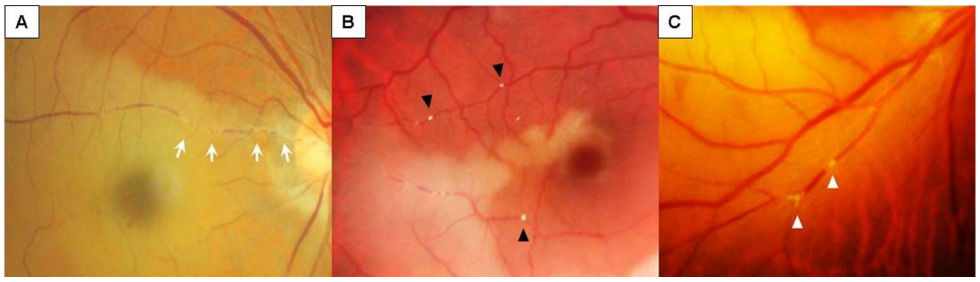

Figure 2. Representative FP images showing the nature of retinal arterial emboli. (**A**) Platelet-fibrin emboli, (**B**) cholesterol emboli, and (**C**) calcific emboli at the initial visit. (**A**) Platelet-fibrin emboli (*white arrow*) appeared as whitish lesions within a section of the arteriole, (**B**) cholesterol emboli (*black arrowhead*) appeared as multiple bright yellow-white plaques on the vascular periphery, and (**C**) calcific emboli (*white arrowhead*) appeared as whitish plaques on the bifurcation of the arteriolar branch.

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Table 2. Various Features of Emboli in Patients With Retinal Artery Occlusion With Visible Emboli

Features	Platelet-Fibrin	Cholesterol	Calcific	*P* Value		
				Platelet-Fibrin vs. Cholesterol	Cholesterol vs. Calcific	Platelet-Fibrin vs. Calcific
Total *N*, %, (CRAO:BRAO)	27, 52% (20:7)	21, 40% (10:11)	4, 8% (1:3)	0.060*	0.328‡	0.732‡
Movement						
Movement (*n*, %)	27, 100%	12, 57%	0, 0%	**0.001***	0.125‡	**<0.001‡**
Movement time-point (mo)	1.18 ± 0.72	3.18 ± 1.97	0	**<0.001†**	–	–
Location				0.887*	0.276‡	0.242‡
Optic disc (*n*, %)	10, 37%	7, 33%	0			
Peripheral retinal artery (*n*, %)	21, 78%	16, 76%	4, 100%			
Multiplicity				**0.04***	0.618‡	0.149‡
Single (*n*, %)	9, 33%	14, 67%	3, 75%			
Multiple (*n*, %)	18, 67%	7, 33%	1, 25%			
Embolic source evaluation	21, 78%	15, 71%	2, 50%			
Carotid artery stenosis (*n*, %)	13, 62%	7, 47%	1, 50%	0.364*	0.735‡	0.640‡
Atrial fibrillation (*n*, %)	1, 5%	1, 7%	0, 0%	0.667‡	0.882‡	0.913‡
Valvular heart disease (*n*, %)	0, 0%	0, 0%	1, 50%	–	0.118‡	0.087‡
Underlying disease/risk factor						
Diabetes mellitus (*n*, %)	6, 22%	4, 19%	1, 25%	0.539‡	0.671‡	0.662‡
Hypertension (*n*, %)	18, 67%	11, 52%	2, 50%	0.315*	0.672‡	0.447‡
Hyperlipidemia (*n*, %)	4, 15%	7, 47%	0	0.174‡	0.294‡	0.601‡
Current smoking (*n*, %)	5, 19%	2, 10%	0	0.445‡	0.700‡	0.475‡
History of stroke (*n*, %)	3, 11%	3, 14%	0	0.537‡	0.578‡	0.651‡
History of ischemic heart disease (*n*, %)	4, 15%	3, 14%	1, 25%	0.644‡	0.527‡	0.525‡
Current use of antiplatelet agent (*n*, %)	6, 22%	3, 14%	1, 25%	0.377‡	0.527‡	0.662‡

$P < 0.05$ was deemed to indicate clinical significance, values in boldface are statistically significant. Continuous data are presented as mean ± SD. Location, location of emboli on initial fundus photography, counted overlap in cases of multiple emboli; Optic disc, central retinal artery trunk in CRAO and central retinal artery bifurcation on the optic disc in BRAO, meaning proximal branch occlusion; Embolic source evaluation, the number of patients who have diagnostic imaging data including carotid angiography, magnetic resonance angiography, electrocardiogram, or echocardiography; Carotid artery stenosis is classified by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria and moderate (50%–70%) to severe (>70%) stenosis were presented.

* Chi-square test.

† Independent *t*-test.

‡ Fisher's exact test.

FP and FA. Where multiple emboli were present, the location of each embolus was recorded. Multiplicity was determined based on the initial FP and FA, resulting in a single embolus group and a multiple emboli group.

Evaluation of Retinal Embolic Source

Evaluation of carotid artery stenosis by transfemoral carotid angiography or magnetic resonance angiography, atrial fibrillation by electrocardiogram, and valvular heart disease by medical chart review or echocardiography were performed to search for the source of the retinal embolus. In our analysis dataset, only 38 patients (73%) underwent evaluation of their carotid arteries and cardiac status. We graded carotid artery stenosis based on the North American Symptomatic Carotid Endarterectomy Trial criteria as follows: absent, mild (<50%), moderate (50%–70%), or severe (≥70%),[22] and included only moderate and severe stenosis, given that it is only these degrees of stenosis that can cause emboli to form.

Evaluation of Vascular Reperfusion by Fluorescence Angiography

Fluorescein angiography was used to analyze vascular flow according to movement of emboli in the RAO patients with visible emboli (Fig. 1, analysis dataset 2). Vascular flow corresponding to the position of the embolus was assessed during FA in order to detect impaired vascular flow caused by an embolus, and the phase of vascular reperfusion accompanying movement of the embolus during the follow-up period. To compare changes in vascular reperfusion accurately, the same time frame used in the early phase, when vascular obstruction can be most easily distinguished during initial FA, was used to compare the follow-up FA. In CRAO, complete reperfusion was defined as shortening of the vascular filling time, rather than being based on evaluation of prior FA, and less than 20 seconds of arm to retina time on FA. In BRAO, complete reperfusion was defined as observation of the same fluorescence filling time as that for the flow in a neighboring normal retinal artery or the same retinal artery branch in the unaffected eye. Vascular reperfusion was classified into three groups according to reperfusion time determined by follow-up FA as follows: early complete reperfusion (complete perfusion in less than 1 month); late complete reperfusion (complete perfusion from 1–6 months); and late incomplete reperfusion (incomplete reperfusion at 6 months). Further, medical charts were reviewed until final follow-up for evidence of new vessel formation in the retina or neovascular glaucoma indicating development of neovascularization.

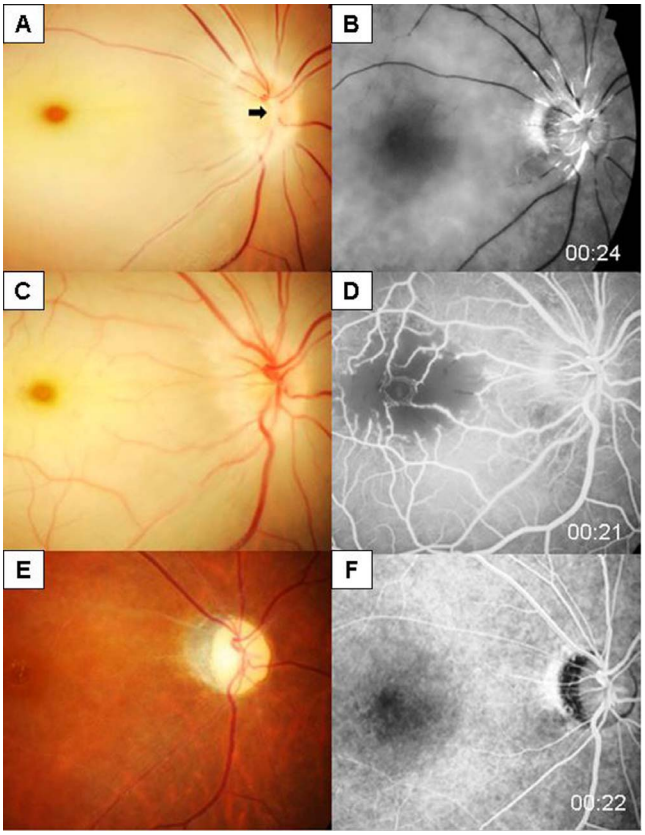

FIGURE 3. A case of CRAO with a visible embolus in the central retinal artery trunk, which disappeared with vascular reperfusion. Fundus photography (*left column*) and FA (*right column*) images following temporal change in movement group with central retinal artery occlusion. (**A**, **B**) Platelet-fibrin embolus (*black arrow*) and fluorescein filling delay were observed at the initial visit. (**C**, **D**) Disappearance of the embolus and recovery of perfusion was observed at 1 month, but no reflow phenomenon was observed. (**E**, **F**) Complete vascular reperfusion was observed at 6 months follow-up.

In order to ensure accurate judgment from subjective observations, FP and FA were measured separately and independently by two retina specialists (KHC, JHC) who were blinded to the patients' details. If there was disagreement between the two observers, a third retina specialist (SJW, a principal investigator) made the judgment.

Statistical Analysis

Data for continuous variables were expressed as the mean ± SD, and percent distributions were computed for the demographic variables in all patients. Continuous emboli data were compared using the Wilcoxon signed-rank test, and frequency emboli data and vascular reperfusion data were compared using Fisher's Exact test.

Cohen's kappa coefficient was computed to evaluate interobserver agreement with regard to determination of emboli classification characteristics and grading of vascular perfusion status.[23] In the qualitative analysis as determined by FP and FA, there was excellent interobserver agreement between the two investigators, with Cohen's kappa values of 0.801 and 0.845, respectively.

Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA). A P value of less than 0.05 was considered to indicate a statistically significant difference.

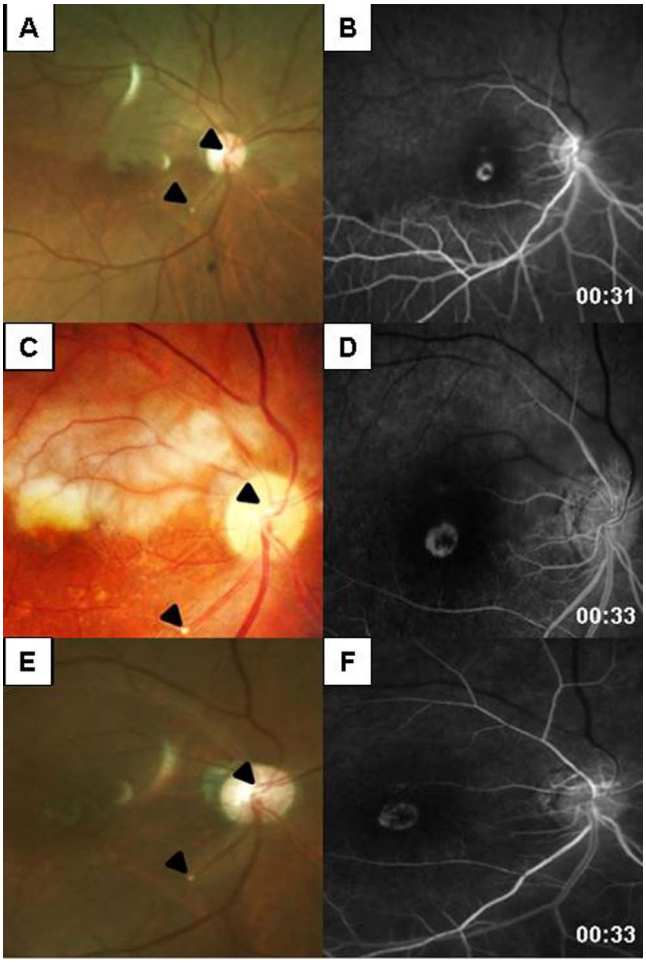

FIGURE 4. A case of BRAO with visible emboli without movement during the follow-up period. Representative wide-angle FP (*left column*) and FA (*right column*) images following temporal changes in the no movement group with BRAO. (**A**, **B**) Two cholesterol emboli (*white arrowhead*) and delayed fluorescein filling were observed at the initial visit. Cholesterol emboli remained at the same location and perfusion delay was observed at (**C**, **D**) 1 month and (**E**, **F**) 6 months.

RESULTS

Clinical Characteristics and Analysis of Various Emboli Features in Retinal Artery Occlusion

Table 1 shows the clinical characteristics of the study subjects. Representative FP images of platelet-fibrin, cholesterol, and calcific emboli are shown in Figure 2.

Emboli observed in patients with RAO were analyzed after subdividing them according to their contents. Platelet-fibrin emboli were observed in 27/52 (52%) eyes, with a CRAO:BRAO ratio of 20:7. Cholesterol emboli were observed in 21/52 (40%) eyes, with a CRAO:BRAO ratio of 10:11. Calcific emboli were observed in in 4/52 (8%) eyes, with a CRAO:BRAO ratio of 1:3.

Emboli movement, location, multiplicity, and source were compared according to content (platelet-fibrin versus cholesterol, cholesterol versus calcific, and platelet-fibrin versus calcific). Movement rates and movement time-points for each of the emboli are shown in Table 2. When compared according to content, platelet-fibrin emboli showed more rapid and higher rates of movement than cholesterol or calcific emboli. The location of emboli did not differ significantly according to content. The multiplicity of platelet-fibrin emboli differed

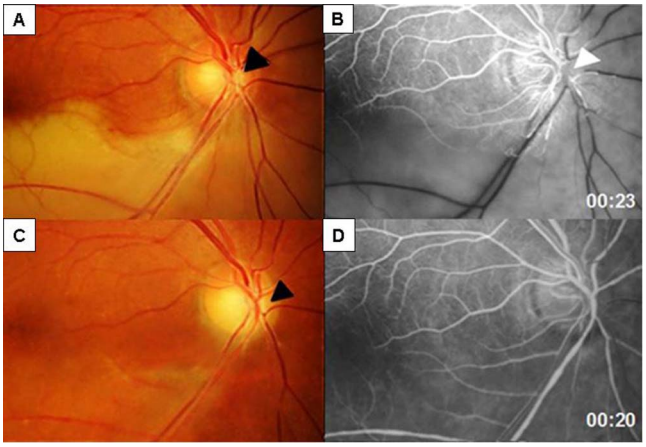

FIGURE 5. Fundus photography and FA images following temporal change in the no movement group with branch retinal artery occlusion. (**A**, **B**) Embolus in the retinal artery bifurcation in the optic disc (*black arrowhead*) and blocked retinal artery perfusion were observed at the initial visit. (**C**, **D**) After 1 month, the embolus appeared to be moving beside its location, and perfusion had recovered completely via the angiophagy mechanism.

significantly from that of cholesterol and calcific emboli; in contrast with cholesterol and calcific emboli, platelet-fibrin emboli were associated with significantly more instances of multiple dominant emboli. The carotid artery was the dominant source of platelet-fibrin and cholesterol emboli but a cardiac origin was not often found. There were no significant differences in embolic contents when the embolic source and underlying disease/risk factors were considered. All *P* values for each comparison are presented in Table 2.

Analysis of Vascular Reperfusion According to Retinal Emboli Movement

Twenty-nine eyes in RAO patients had visible emboli causing blockage of vascular perfusion. Of these eyes, 20 were in the movement group (7 eyes with CRAO and 13 eyes with BRAO) and 9 were in the no movement group (1 eye with CRAO and 8 eyes with BRAO). The emboli content also differed significantly between the movement and no movement groups ($P = 0.002$). The movement group included 12/20 (60%) eyes with platelet-fibrin emboli and 8/20 (40%) eyes with cholesterol emboli that showed complete degradation or peripheral movement. In the no movement group, there were 6/9 (67%) eyes with cholesterol emboli and 3/9 (33%) eyes with calcific emboli that showed partial dislodgement, angiophagy, and collateral circulation.

Vascular reperfusion rates differed depending on emboli movement ($P < 0.001$). In the movement group, 16/20 (80%) eyes showed early complete reperfusion with complete degradation of the emboli, and 4/20 (20%) eyes showed late complete reperfusion with complete degradation or peripheral migration of the emboli. Figure 3 depicts a case of CRAO with visible emboli in the central retinal artery trunk responsible for blockage of vascular perfusion that disappeared with vascular reperfusion. In the no movement group, there were 3/9 (33%) eyes with late complete reperfusion and 6/9 (67%) eyes with late incomplete reperfusion because of partial dislodgement, angiophagy, or a collateral circulation mechanism. Figure 4 shows a representative case of late incomplete reperfusion in a BRAO patient with visible emboli without movement that showed incomplete reperfusion at the 6-month follow-up time-point. Interestingly, in three eyes in the no movement group

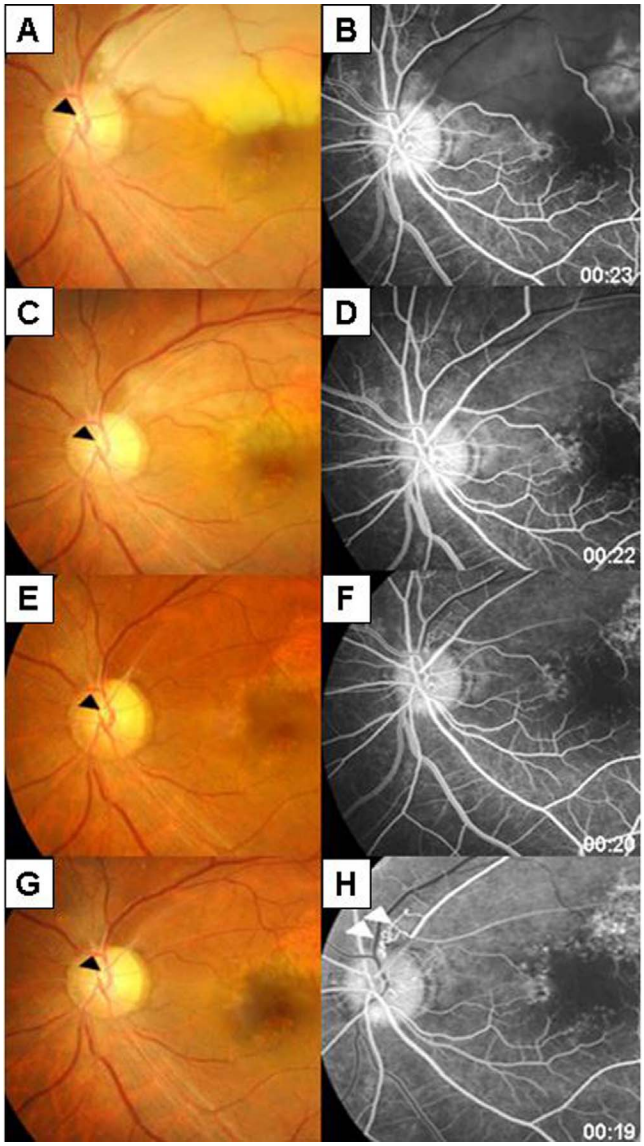

FIGURE 6. A case where reperfusion occurred through collateral vessels. (**A**, **B**) Cholesterol embolus (*black arrowhead*) and blocked perfusion were observed in superotemporal branch retinal artery occlusion. (**C**, **D**) Embolus had not moved and delayed perfusion was observed at 1 month. (**E**, **F**) At 6 months, follow-up images faintly revealed a collateral vessel around the blocked site. (**G**, **H**) This was more evident (*white arrowhead*) and perfusion had completely recovered at 1 year.

that exhibited late complete reperfusion, angiophagy and formation of a collateral circulation were deemed to be the operative mechanisms (Figs. 5, 6).

Development of ocular neovascularization presented as neovascularization in the iris and neovascular glaucoma was found only in patients with CRAO who had no movement of retinal emboli and with late incomplete reperfusion; this finding was of marginal significance ($P = 0.089$). The location of emboli did not differ significantly between the two groups ($P = 0.432$; Table 3).

DISCUSSION

This study investigated a number of features of retinal emboli in RAO. With regard to the content of the emboli, platelet-fibrin

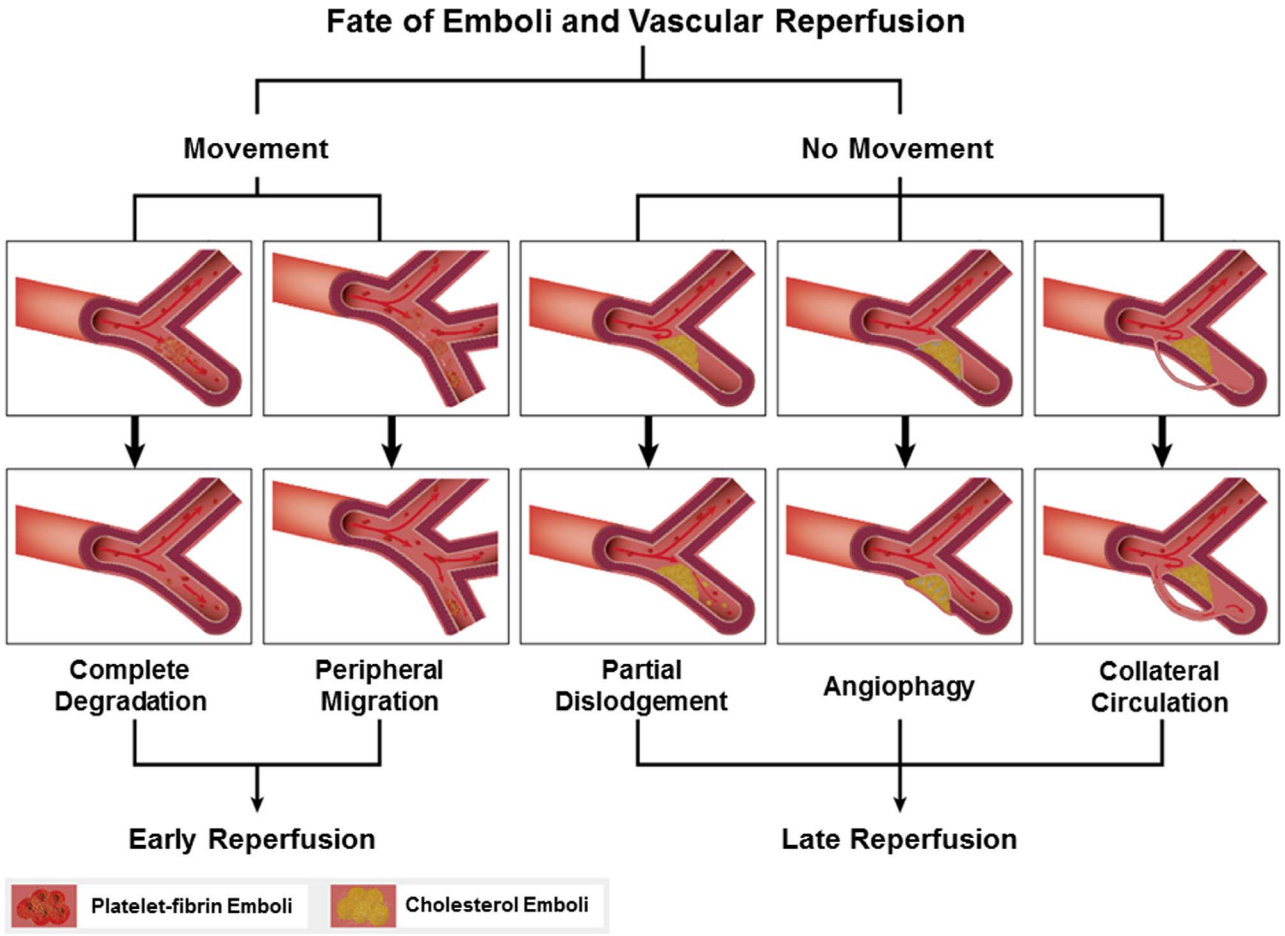

Figure 7. Schematic diagram of the fate of retinal emboli and the vascular reperfusion mechanism in patients with retinal artery occlusion.

and cholesterol were most frequently observed. In terms of location, emboli were most frequently observed in the optic disc or peripheral retinal artery in all groups. Differences in emboli content may arise from differences in the primary source of the emboli. In support of this idea, Hollenhorst[14] reported that cholesterol emboli are generated from ulcerated proximal atherosclerotic lesions, platelet-fibrin emboli originate from arterial atheromatous plaques in the absence of substantial luminal encroachment, and calcific emboli, which are comparatively rare, are generated by calcific aortic stenosis or calcific valvular heart disease.[24,25] In this study, both of the more common types of emboli were thought to originate from the carotid artery. This observation is consistent with previous reports, and it is widely known that the most common embolic source in RAO is the carotid artery.[1,26–29] However, the underlying diseases differ between races, and such differences may result in racial differences in the contents of retinal emboli, and may also have influenced the relatively low retinal emboli detection rates in this study of RAO patients.[1,3,30] As time from symptom onset to initial diagnosis is an important factor with regard to detection rates, the relatively low detection rate of 37.5% in the current study when compared with the detection rate of 71% in CRAO and 66% in BRAO reported by Hayreh et al.[1] can be explained on this basis. Additionally, the content of emboli may affect emboli movement, supporting the hypothesis that platelet-fibrin emboli, which show high movement rates, early movement times, and frequent spontaneous degradation, cause amaurosis fugax.[20]

The movement of emboli is less affected by location when compared with other factors. Movement rates are similar when emboli are located in the optic disc or peripheral retinal artery. Thus, the embolic content is a more important factor than location in determining emboli movement. Emboli movement is known to have a significant effect on vascular reperfusion.[11] In the current study, we observed that the vascular perfusion state returned to normal at an early stage in most cases with emboli movement. On the other hand, we observed vascular reperfusion, albeit in most cases delayed or limited, occurring over time when emboli maintained their position. Interestingly, there were no cases of no reperfusion in the no movement group.

Several hypotheses can be proposed for the mechanism of recovery of vascular flow on FA even in the presence of a blood vessel impacted by an embolus. We propose two mechanisms to explain vascular reperfusion in the emboli movement group (i.e., complete degradation and peripheral migration). There are also at least three possible mechanisms to explain vascular reperfusion in the no emboli movement group (i.e., partial dislodgement, angiophagy, and development of a collateral circulation). First, spontaneous partial dislodgement of emboli may occur via the hydrostatic pressure of a continuously applied blood flow or by the endogenous fibrinolytic system. This pattern of emboli is similar to that mentioned in a previous report on embolus characterization, which included fragments of cholesterol or thrombi origin partially filling the arterial lumen on optical coherence tomography.[31] Another possibility is that this is not true reperfusion, but filling by

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Table 3. Comparative Analysis of Retinal Emboli Features, Vascular Reperfusion, and Neovascularization Between the Movement Group and the No Movement Group in Patients With Retinal Artery Occlusion With Visible Emboli

Features	Movement *n*, %	No Movement *n*, %	*P* Value
Total (CRAO:BRAO)	20 (7:13), 69%	9 (1:8), 31%	
Emboli contents			0.002
Platelet-fibrin	12, 60%	0	
Complete degradation	12	–	
Cholesterol	8, 40%	6, 67%	
Complete degradation	6	–	
Peripheral movement	2	–	
Partial dislodgement		4	
Angiophagy		1	
Collateral circulation		1	
Calcific	0	3, 33%	
Partial dislodgement		3	
Vascular reperfusion			<0.001
Early complete reperfusion	16, 80%	0	
Complete degradation	16	0	
Late complete reperfusion	4, 20%	3, 33%	
Complete degradation	2	0	
Peripheral migration	2	0	
Partial dislodgement	0	3	
Late incomplete reperfusion	0	6, 67%	
Partial dislodgement	0	4	
Angiophagy	0	1	
Collateral circulation	0	1	
Neovascularization* (CRAO:BRAO)	0	2, 22% (2:0)	0.089
Early complete reperfusion	0	0	
Late complete reperfusion	0	0	
Late incomplete reperfusion	0	2	
Location†			0.432
Optic disc‡	11, 55%	6, 67%	
Peripheral retinal artery	9, 45%	3, 33%	

$P < 0.05$ was deemed to indicate clinical significance (Fisher's Exact test). Early complete reperfusion, perfusion recovered within 1 month; Late complete reperfusion, perfusion recovered from 1 to 6 months; Late incomplete reperfusion: perfusion not recovered until 6 months.

* Neovascularization indicates neovascular iris or glaucoma.

† Location indicates location of the most proximal emboli in cases of multiple emboli.

‡ Optic disc indicates central retinal artery trunk in CRAO and central retinal artery bifurcation on the optic disc in BRAO.

retrograde flow from the adjacent normally filling retina in the late phase of FA, giving the appearance that reperfusion has occurred. This mechanism applies to platelet-fibrin emboli and cholesterol emboli.[11] However, calcific emboli are thought to have almost no effect on endogenous fibrinolysis. Lam et al.[32] have suggested the possibility of recovery of perfusion in vessels blocked by calcific emboli via the mechanism of extravasation of the embolus, or "angiophagy". This refers to engulfment by the endothelium and translocation through the microvascular walls of blood vessels from 2 to 7 days after occurrence of abnormal emboli. This has been suggested as an alternative mechanism for the clearance of emboli.[32–34] However, some view this as inhibiting early washout. The FA results from the no movement group in this study showed recovery of flow even in the presence of emboli at a position with an initial lack of flow (i.e., late incomplete perfusion, which may support the above hypothesis). However, FP is limited in that it is two-dimensional. More supporting data comparing temporal changes in ultra-thin sections of spectral domain optical coherence tomographic images around blood vessels where emboli are located is required to verify extravasation of retinal emboli. Lastly, although rarely the case, the development of a collateral circulation from the adjacent normally perfused retina may function as a possible mechanism of vascular reperfusion. As shown in Figure 6, when reperfusion fails, the development of a collateral circulation may promote retinal vascular flow as an alternative delayed mechanism. In cases with CRAO, we could not find a collateral circulation. It might be induced by relatively high complete reperfusion rates or racial differences in association with differences in the underlying disease or small case numbers.

In summary, there are three types of retinal emboli (i.e., platelet-fibrin, cholesterol, and calcific emboli). Platelet-fibrin emboli migrate frequently, as do cholesterol emboli but less often than platelet-fibrin emboli, while calcific emboli, which are rough in texture, become impacted, and usually do not migrate. Emboli movement is caused by complete degradation or peripheral migration, and may lead to early or late complete vascular reperfusion. On the other hand, in cases where emboli maintain their location, delayed complete or incomplete reperfusion may occur by partial dislodgement, angiophagy, or a collateral circulation mechanism (Fig. 7).

Our study had some limitations. First, the time from symptom onset to the first FP and FA examination varied from

1 hour to 14 days in the patients evaluated, which may have affected the FP and FA findings at baseline. Specifically, a longer duration between symptom onset and the initial visit may influence emboli movement and detection rate at the initial visit. Second, the use of wide-field FP and FA along with standard FP and FA in BRAO patients may have caused differences in the rates of detection of emboli in the periphery of the retina. Further, we included only a small number of CRAO patients, because detection of emboli in CRAO was limited and occlusion points in most cases are presumed to be invisible proximal to the lamina cribrosa. Lastly, intra-arterial thrombolysis was performed in 23 patients (23/54, 44%) after initial examination. Although the initial data are not related to intra-arterial thrombolysis, other follow-up data such as the fate of the emboli might have been affected by the procedure. However, despite its limitations, our study is significant in that it identified features of emboli together with vascular perfusion states in a relatively large number of RAO patients, and these parameters have rarely been investigated in previous studies. In this study, we observed that the pattern of movement of emboli differed according to the embolic contents, which might be contributed to underlying disease or risk factors and have an effect on vascular reperfusion. Clinically, this information might be helpful for predicting movement of emboli and vascular reperfusion at the initial diagnostic stage. Our study showed that no emboli movement is associated with late incomplete reperfusion and this could affect the chronic ischemia of the retina and eyeball. We believe that regular fundus FA and anterior segment inspection in eyes with incomplete reperfusion might be necessary to detect the complications related to chronic ischemia, although further research is needed in a larger cohort of patients before concluding a relationship between vascular reperfusion status and ocular complications. Furthermore, we need to evaluate cautiously the effects of emboli characteristics on the outcome of intra-arterial thrombolysis. A comparative analysis of several types of RAO, including idiopathic RAO without visible emboli and iatrogenic filler–induced RAO is needed in the future.

In addition, our findings can be applied to embolic infarction of the brain, where visualization of emboli is not possible. Thus, our study results might help to increase our understanding and elucidate the reperfusion mechanisms in cerebrovascular occlusion and stroke in general.[35–37]

In conclusion, this study has identified characteristics of emboli in RAO patients that affect their movement. Emboli movement may also affect vascular reperfusion. Further research in a larger cohort is needed before conclusions can be made with regard to ocular complications.

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