# Low Endogenous Recanalization in Embolic Central Retinal Artery Occlusion—The Retrobulbar "Spot Sign"

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## ABSTRACT

### BACKGROUND AND PURPOSE

**Central retinal artery occlusion (CRAO) is most often indirectly diagnosed by lack of retinal perfusion. Direct embolus characterization may help to understand the natural course and low response to treatment. In a previous study we identified a hyperechoic signal within the optic nerve and in the central retinal artery ("spot sign").**

### METHODS

**In this study we performed a follow-up investigation in 7 patients with CRAO and positive spot sign indicating the embolic cause of the occlusion after a median interval of 17 months (range 11-38 months) using a battery of tests (ocular color-coded sonography, optic coherence tomography [OCT], fundoscopy, amongst others).**

### RESULTS

**The spot sign persisted in all patients, none had high-grade internal carotid artery stenosis, stroke or transient ischemic attacks. Four patients were completely blind, 3 patients were able to recognize hand movements. OCT demonstrated retinal atrophy, and fundoscopy revealed only minimal arterial perfusion.**

### CONCLUSIONS

**The hyperechoic spot sign may be an important predictive prognostic marker for persistent loss of vision. Its persistence may indicate calcified or cholesterol emboli and may explain the low therapeutic success rate to thrombolysis. Further studies on their origin and significance in atherosclerotic disease are warranted.**

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MA and ME contributed equally to this paper.

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## Background and Purpose

Central retinal artery occlusion (CRAO), which occurs mainly in the elderly population, leads to severe retinal ischemia and is a common cause of sudden blindness.[1–3] Fundoscopic examination reveals a lack of perfusion of the retinal arteries, but direct evidence of the retrobulbar occlusion of the central retinal artery is scarce. Prognosis of CRAO is poor, regardless of natural course, conservative treatment or invasive strategies such as rapid superselective intraarterial thrombolysis and intravenous administration of recombinant tissue plasminogen activator (tPA), although with the latter outcomes are not consistent.[1,4–10] Recently, Schumacher et al published results of a multicenter trial comparing local intraarterial thrombolysis using rtPA versus best medical treatment and found a significantly higher rate of adverse events in the intraarterial thrombolysis group without difference in clinically significant visual improvement.[11] Because of poor outcomes and these severe complications, such as stroke, intracerebral haemorrhage or vascular injury (for example, internal carotid artery [ICA] dissection), most centers have abandoned those therapies.[4,12]

Although eye and brain share the same arterial supply, patients with ocular manifestation attributed to high-grade ICA stenosis have a significantly lower stroke risk than patients with stroke or TIA and ICA stenosis.[13] However, most studies are driven by a high number of amaurosis fugax and high-grade ICA stenosis, suggesting differences in plaque morphology and stability, and ultimately embolus composition amendable for spontaneous endogenous thrombolysis.[13–15] With regard to the general cardiovascular risk, patients who present with retinal infarction due to presumed atherothromboembolism or cardiogenic embolism are at increased risk of a coronary event and, to a lesser but still significant degree, of experiencing stroke.[16,17] In patients with known atrial fibrillation, prior retinal ischemia seems to increase the overall cerebrovascular risk.[18]

In a previous prospective study, in which our goal was to differentiate vasculitic from embolic CRAO leading to persistent loss of vision, we observed an echogenic structure

with absent flow in the central retinal artery–termed "spot sign"–on orbital color-coded sonography (OCCS) images in 10 (83%) of 12 patients, and we determined that the spot sign was highly predictive of embolic occlusion.[19] Authors of another noncomparative, retrospective observational study reported a lower frequency of the spot sign (31%, 9 of 29 patients) in cases of sudden ocular blindness of an embolic nature.[20] The histopathological nature of this spot sign has so far not been investigated. However, in an experimental study at canine and monkey objects, Hollenhorst et al fundoscopically found the typical retinal vessel status of CRAO with embolic occlusion, after they had intraarterially injected cholesterol crystals in the carotid.[2] A fibrin-platelet thrombus may be distinguished from cholesterol emboli by fundoscopy, which typically appears as a more yellowish, refractile plaque and those Hollenhorst plaques are thought to be a sign of severe atherosclerosis.[21]

In this study, we performed follow-up examinations in patients from our previous study that had presented with CRAO and the sonographic spot sign.[19] Persistence of the spot sign may be indicative of calcified emboli or even a cholesterol nature of the embolus (originating from so called "Hollenhorst plaques") as fibrin containing emboli have a higher rate of spontaneous resolvement. Characterization of CRAO by ultrasound echogenicity may provide further insight into why thrombolytic strategies often fail to reestablish sufficient blood flow to the retina.[4,5] In addition, further studies should evaluate the presence or absence of complex aortic plaques as a possible embolic source.

## Methods

From the 10 patients identified as having CRAO and a positive spot sign in our previous study,[19] 7 patients agreed to a follow-up examination. One of the original patients had died, and 2 other patients declined to participate. The study protocol was approved by the local ethics committee at the University of Regensburg in accordance with guidelines of the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/); all 7 patients provided written consent.

We repeated the OCCS examinations that we had performed in the first study by using the same ultrasound machines and settings. The patients also underwent routine ophthalmological diagnostic tests, including assessment of best-corrected visual acuity (BCVA), measurement of intraocular pressure, slit lamp examination, fundoscopy, and optic coherence tomography (OCT).

### *Ultrasound Equipment and Data Acquisition*

The OCCS examinations were performed using two high-end color-duplex machines equipped with high-frequency linear array transducers (Siemens Acuson equipped with a 15L8 transducer, Siemens AG, Erlangen, Germany; and Toshiba Xario XG equipped with a PLT-1204BT transducer, Tokyo, Japan). We paid special attention to minimizing the acoustic output of the mechanical index to <.23 according to the ALARA principle ("as low as reasonably achievable") to avoid damaging the lens and retina, as previously described.[19,22,23] In this study, each patient was again examined by using the same equipment and settings (bandwidth, B-mode/color-mode gain, and spectral Doppler setting for low velocities). Images were stored in a separate archive system and transformed from DICOM II format to bitmaps. In the original study, OCCS had been performed by two experienced sonographers (ME, who holds a first-level DEGUM certificate, and FS, who has a third-level DEGUM certificate); in this study, all follow-up examinations were performed by a single examiner (FS), who reviewed printouts from the original investigation (including depth gain, focal zone, and overall gain) to obtain similar settings and angulations. All follow-up OCCS investigations were performed prior to ophthalmologic examination.

### *Optic Coherence Tomography (OCT)*

OCT was performed using the Heidelberg HRA+OCT Spectralis® OCT (Heidelberg Engineering Germany), which created six radial scans centered on the fovea centralis, in the same array as performed in the original investigation.[19] These exact conditions for follow-up were ensured by the eye-tracker feature.

### *Clinical Patient Characterization*

The following patient data were acquired before the clinical examinations, OCT and OCCS investigations: age and sex, cardiovascular risk profile, platelet inhibition prior to CRAO, results of the sonographic examination of cerebral arteries, exclusion of vasculitis in the original investigation (especially erythrocyte sedimentation rates, American College of Rheumatology criteria and, if performed, biopsy of the superficial temporal artery), and the time interval between acute onset of CRAO and the follow-up investigation.

## Results

Seven of 10 patients from our previous study,[19] who had initially presented with a positive sonographic spot sign due to acute onset of CRAO, were included and reexamined in this series. None of the patients had received any interventional treatment, especially no thrombolytic therapy. The patient population was composed of 6 men and 1 woman, ranging in age from 68 to 83 years (median age 77 years). The time interval between the onset of CRAO and the follow-up examination ranged from 11 to 38 months (median 17 months).

With respect to the patient's cardiovascular risk factors, 6 patients presented with hypercholesterolemia and 6 patients with arterial hypertension; 5 patients had a history of smoking; and 1 patient a history of migraine. Two patients reported recurrent tachyarrhythmia and received permanent warfarin medication. All other patients were treated with standard platelet inhibition (acetylsalicylic acid 100 mg daily). None had a history of stroke or TIA.

The BCVA assessment of the CRAO-affected eye showed perception of hand movement at 30 cm in 4 patients and total loss of vision with no light perception in 3 patients. Fundoscopic examination of the primarily unaffected eye did not show any new retinal vascular occlusions in any of the patients, visual acuity ranging from .2 to −.1 logMAR. One of these patients had developed a persistent vitreous hemorrhage in the non-CRAO

eye requiring surgery due to a retinal macroaneurysm. Development of retinal macroaneurysms is known to be strongly associated with hypertension and arteriosclerotic vascular changes.[24]

OCT of the macula revealed distinctive thinning of the inner retinal layers in all patients, indicative of persistent retinal atrophy. In the acute situation of CRAO, retinal edema with increased retinal thickness and hyperreflective inner retinal layers had indicated acute retinal ischemia (Figs 1G and H). Using Heidelberg HRA+OCT Spectralis® software in the follow-up examinations to measure the thickness of the retina 1,000 $\mu$m nasal to the foveal pit, we found that the retinal thickness ranged from 195 to 248 $\mu$m (median 212 $\mu$m), whereas in the same region of the contralateral eye the median retinal thickness was 348 $\mu$m, demonstrating a median difference of 136 $\mu$m between the affected and nonaffected eye.

Similar to the original findings of acute onset of CRAO, no visible intraarterial embolus could be detected fundoscopically in any of the patients (Figs 1E and F). No relevant increase in intraocular pressure was found in any patient: range 13-18 mm Hg (median 14 mm Hg).

A persistence of the retrobulbar spot sign was detected on OCCS images in all 7 patients (100%) (Figs 1A and B). Five patients were shown to have persistent and complete extinction of arterial retrobulbar blood flow in both color-coded duplex and spectral Doppler modes, as shown previously in the original examination (Figs 1C and D). Some arterial reperfusion of the retina at low flow levels was detected in the other 2 patients in spectral Doppler measurements but not in color-coded duplex mode of OCCS. This arterial reperfusion in those two patients however did not result in any functional, fundoscopic or OCT improvements compared with the other patients.

In summary, persistence of the retrobulbar spot sign and an absent or highly reduced arterial flow on OCCS images were identified in all 7 patients, and these findings matched the patients' persistent retinal atrophy and loss of visual acuity. The clinical characteristics and outcomes of these 7 patients are summarized in Table 1.

## Discussion

In this prospective series we demonstrate, for the first time, the persistence of the retrobulbar spot sign as a possible sonographic correlate to calcified or cholesterol containing emboli in CRAO. All patients who were examined suffered from persistent visual impairment. In all of them, a positive spot sign was evident on OCCS images during acute onset of CRAO and still remained at the time of the follow-up examination a median of 17 months later. Further studies on central retinal artery occlusions, retinal branch occlusions and nonarteritic anterior/posterior ischemic neuropathy in correlation to atherosclerotic carotid disease should identify the embolic source and its relevance with respect to cardiovascular risk. Furthermore, characterization the composition of retinal emboli and also plaque morphology may further help to identify new therapeutic strategies in this devastating disease.

Neurovascular investigations in sudden ocular blindness including amaurosis fugax due to CRAO includes screening for high-grade ICA stenosis as a possible embolic source.[25] The clinical picture of amaurosis fugax suggests rapid lysis of the occluded ocular artery without permanent residue. However, transient or permanent ocular ischemia in patients with high-grade ICA stenosis follow a more benign course than in patients with cerebral events in terms of stroke risk–a finding that is ill explained. In the study by Howard et al, 261 of 323 patients (80.8%) with high-grade ICA stenosis presented with amaurosis fugax, yet a subgroup analysis did not reveal any differences in carotid plaque composition for single amaurosis fugax, multiple ocular symptoms and retinal artery occlusion.[15] None of our 7 patients had a ICA stenosis greater than 50% according NASCET criteria.[23] In addition, we survey 9 additional patients with CRAO and spot sign on OCCS including 3 patients from the original study[19] not available for follow-up. All were with significant atherosclerosis but without >50% ICA stenosis (according NASCET [23]) stenosis (average age 75 years) and only a single patients suffered from simultaneous cerebral stroke. The latter was attributed to severe aortic arch plaque embolism. Another explanation for the diverse finding in patients with high-grade ICA stenosis and ocular symptoms might be the tendency to attribute ocular findings only to this ICA, yet, a large variety of other vascular factors might lead to permanent or transient loss of vision.[26] The overall incidence of the "spot sign" in CRAO ranges between 31%[20] and 81% in our previous study,[19] suggesting a different emboli composition or study population with ICA stenosis than in our study. A possible embolic source, that is often underestimated, is the aortic arch with complex atheroma[27] and carotid artery atherosclerosis is a strong predictor for proximal aorta atherosclerosis.[28] Future studies will need to investigate this possible relation and may further help to identify secondary preventive therapies,[29] but not consistently investigated in our study population.

In our study population, CRAO with spot sign persisted over a mean observational period of 17 months with only minor residual flow, if any, thus endogenous thrombolysis did not occur. One might speculate that this finding might also explain in the response to systemic or selective thrombolytic therapy for CRAO. Most centers have abandoned this invasive therapy because of poor outcomes–only a few successful cases have been reported–and because of the potential for severe complications as described earlier.[4–12] Low endogenous thrombolysis may indicate low content of fibrin bonds and our findings are in line with those from an experimental study in which persistent CRAO was found to be caused by cholesterol crystal emboli,[2] but may also be relevant to calcified emboli. Dunlap et al found Hollenhorst crystal plaques or central retinal artery occlusion to be associated with a low prevalence of extracranial cerebrovascular disease and a low risk for subsequent cerebral stroke.[30] However, the authors found no difference in CRAO or retinal Hollenhorst plaques and these ocular findings were not associated with a high risk for hemispheric neurological events. Findings of this study may provide a possible explanation as to why thrombolytic therapy is often ineffective and only works in rare cases. They also indicate how we might be able to differentiate patients more or less likely to benefit from thrombolytic therapy. Hollenhorst crystal plaques are thus far restricted to retinal branch occlusion as they are smaller than the central retinal artery.[2] Cholesterol crystal plaques are probably not as susceptible as fibrin-dominant clots to solvation by endogenous tPA from the endothelium or recombinant tPA thrombolysis, and thus the persistence of the sonographic spot

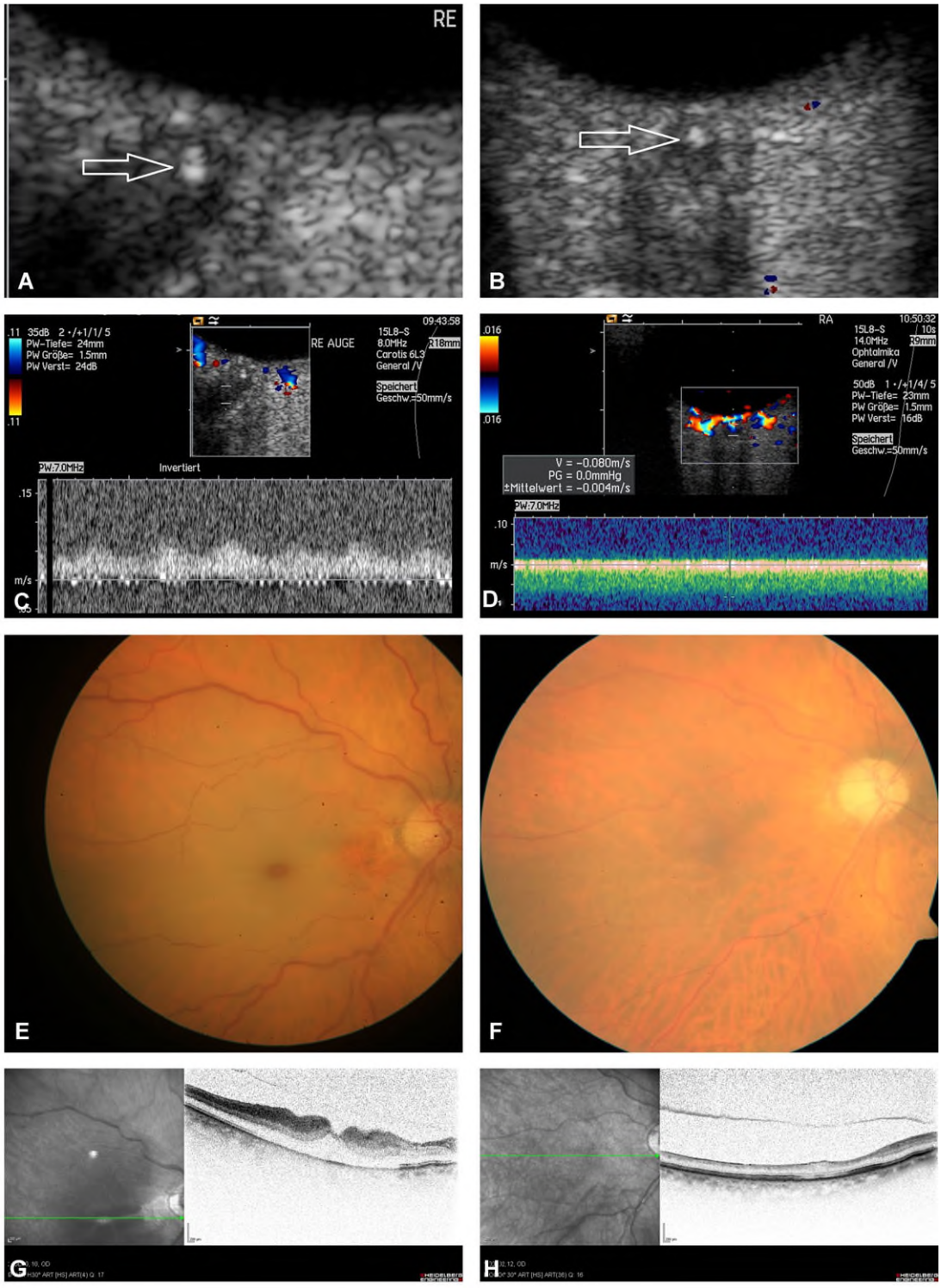


**Fig 1.** Clinical and imaging findings obtained in patient 6. Left panels (A, C, E, and G) were obtained at the time of acute onset of CRAO; right panels (B, D, F, and H) were obtained 17 months later at the follow-up examination. Acute (A) and persistent (B) appearance of a hyperechoic retrobulbar "spot sign" (arrows) on OCCS images. (C) and (D) Doppler sonography images demonstrating zero flow in the CRA. Fundoscopic images showing retinal edema, a cherry-red spot in the fovea centralis, and narrow arterial retinal vessels at CRAO onset (E), and a pale optic disc and narrow retinal vessels at follow-up (F). OCT images showing acute hyperreflective edema of the inner retinal layers at CRAO onset (G) and atrophic thinning of the retinal layers at follow-up (H).

Table 1. Clinical Characteristics and Findings in the 7 Patients in this Study

| Pat. Nr. | Follow-Up (Months) | Age (Years) | Best Corrected Visual Acuity | Cerebrovascular Risk Factors/ Diseases | Findings of Fundoscopy and Optic Coherence Tomography | Findings of Sonography of Cerebral Arteries | Orbital Sonography |
|---|---|---|---|---|---|---|---|
| 1 | 18 | 77 | Left eye: nulla lux | Hypercholesterolemia, former smoker | Pale optic disc, atrophic retinal layers | Plaques at level of bifurcation both sides | Persistent spot sign on left side, reduced reperfusion in central retinal artery (CRA) |
| 2 | 15 | 75 | Right eye: nulla lux | Hypercholesterolemia, hypertension | Pale optic disc, atrophic retinal layers | High grade atherosclerosis | Persistent spot sign on right side, zero flow in CRA |
| 3 | 38 | 83 | Right eye: Eccentric perception of hand movement | Hypercholesterolemia, hypertension, former smoker, history of recurrent tachyarrhythmia | Pale optic disc, atrophic retinal layers | Plaques at level of bifurcation both sides | Persistent spot sign on right side, reduced reperfusion in CRA |
| 4 | 17 | 77 | Left eye: Perception of hand movement | Hypertension | Pale optic disc, atrophic retinal layers | Plaques at level of bifurcation both sides | Persistent spot sign on left side, zero flow in CRA |
| 5 | 11 | 68 | Right eye: Perception of hand movement | Hypercholesterolemia, hypertension, former smoker | Pale optic disc, atrophic retinal layers | Left ICA stenosis (60% ECST criteria), high-grade atherosclerosis | Persistent spot sign on right side, zero flow in CRA |
| 6 | 17 | 80 | Right eye: Perception of hand movement | Hypercholesterolemia, hypertension, former smoker, history of recurrent tachyarrhythmia | Pale optic disc, atrophic retinal layers | Left ICA stenosis (50-60% ECST criteria), medium-grade ECA and subclavian artery stenosis on right side, high-grade atherosclerosis | Persistent spot sign on right side, zero flow in CRA |
| 7 | 32 | 78 | Left eye: nulla lux | Hypertension, hypercholesterolemia, former smoker, history of migraine | Pale optic disc, atrophic retinal layers | Plaques at level of bifurcation both sides | Persistent spot sign on left side, zero flow in CRA |

ECA = external carotid artery; ECST = European Carotid Surgery Trialists; ICA = internal carotid artery.

sign could support the assumption of a cholesterol nature of the embolic occlusion. Future studies may investigate not only the histopathology of emboli but also their echogenicity.[31] According to our theory the different composition of clots could explain the inconsistent outcomes of CRAO therapy documented in the literature and provide a fast, easy-to-use low-risk tool to identify patients with fibrin-dominant clots who could be candidates for thrombolytic therapy.

## Conclusions

In conclusion, the orbital ultrasound detection of a spot sign and persistence of that spot sign can be a useful, quick and safe diagnostic tool, and it may provide an explanation for the frequent ineffectiveness of thrombolysis in treating embolic occlusions of the central retinal artery. Additional research should focus on the origin of these echogenic emboli, try to differentiate calcified emboli, Hollenhorst crystal plaque, fibrin rich thrombi, amongst others with implied treatment options and investigate its relationship to overall cardiovascular disease risk including stroke. Finally, detection of a spot sign may also help to unravel the lower stroke risk in patients with ICA disease and ocular symptoms.


## Sources of Funding

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