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MINIREVIEWS

Retinal emboli

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Abstract

Retinal emboli are opacities identified in retinal arterioles and are often incidental findings on ophthalmic examination. They are generally composed of cholesterol, platelet-fibrin, or calcium and are thought to arise from carotid arteries, coronary arteries, or cardiac valves. In the general population, the estimated prevalence is 0.2% to 1.3%, and the estimated incidence is 0.9% to 2.9%. The transient nature of retinal emboli likely explains the variations between and within these reported figures. The strongest risk factor for retinal emboli is smoking, which has been reported consistently across many studies. Other likely risk factors include older age, hypertension, male sex, total cholesterol, coronary artery disease, and history of coronary artery bypass grafting. The presence of multiple risk factors, as is common in many patients, confers a higher risk for retinal emboli. Several studies suggest that retinal emboli predict an increase in stroke-related, all-cause, and possibly cardiovascular mortality. Due to these sequelae, patients often undergo further workup, most commonly carotid ultrasonography. However, given the low prevalence of significant carotid disease in patients with retinal emboli, further workup, such as carotid ultrasound, should be reserved for those with risk factors for carotid disease. All patients would benefit from medical optimization and coordinated care with the primary care physician.

Key words: Retinal emboli; Hollenhorst plaque; Stroke; Carotid disease; Cardiovascular disease

Core tip: Retinal emboli occur in up to 3% of the population and predict an increase in stroke-related, all-cause, and possibly cardiovascular mortality. The strongest risk factor for retinal emboli is smoking, which has been reported consistently across many studies. Other likely risk factors include older age, hypertension, male sex, total cholesterol, coronary artery disease, and history of coronary artery bypass grafting. Because many patients with retinal emboli have multiple co-morbidities, they would benefit from medical optimization and coordinated care with the primary care physician. Further workup, such as carotid ultrasound, should be reserved for those with risk factors for carotid disease.

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INTRODUCTION

As early as 1862, retinal emboli were identified as discrete opacities in retinal arterioles. Many more accounts of these emboli have since surfaced, including a large case series by Hollenhorst that identified an association with carotid disease[1]. He described 3 main constituents of retinal emboli - cholesterol, platelet-fibrin, and calcium – which have been confirmed in histopathology reports[2-5]. Cholesterol emboli are the most common and are characteristically bright orange-yellow, highly reflective, migrate frequently, and are thought to originate from ulcerated atherosclerotic lesions on cardiac valves or from aortic and carotid endothelium[1,6,7]. Coronary arteries may also

Table 1 Prevalence and basic demographic features of patients found to have retinal emboli in large population-based studies

Ref.	Prevalence	No of participants	% male	Average age	Ethnicity
Wong *et al*[18]	0.2%	15466	44%	63	Mixed (21% black, 79% white)
Hoki *et al*[15]	0.4%	5959	42%	55	Latino
Cheung *et al*[14]	0.6%	3265	52%	59	Asian Malays
Klein *et al*[16]	1.3%	4926	44%	62	White
Mitchell *et al*[17]	1.4%	3654	43%	66	White

be a source, supported by the observation that coronary angiography can liberate cholesterol emboli into retinal arterioles[8-10]. Another less common source is an atherosclerotic lesion in renal arteries[11]. Cholesterol emboli are generally asymptomatic because their thin, flat shape usually does not result in an occlusion[7,12]. Platelet-fibrin emboli are creamy-white, irregularly shaped, immobile, and are postulated to arise from mural thrombus formation in carotid or coronary arteries[1,4,6]. Lastly, an "extremely white," irregular embolus represents calcium likely originating from calcified cardiac valves[1,13]. Given these likely sources, retinal emboli are thought to be indicators of cerebrovascular and cardiovascular disease. The remainder of this review will thus focus on the incidence, risk factors, outcomes, and management of retinal emboli.

PREVALENCE AND INCIDENCE

Several studies in asymptomatic subjects in the general population have identified the prevalence and incidence of retinal emboli. Among 5 modern population-based studies (The Beaver Dam Eye Study, The Blue Mountains Eye Study, The Los Angeles Latino Eye Study, The Singapore Malay Eye Study, and The Atherosclerosis Risk in Communities and Cardiovascular Health Studies), the prevalence of retinal emboli has been reported to range from 0.2% to 1.3%[14-18]. The difference in the reported prevalence among these studies could possibly be explained by the variations in basic demographic characteristics between the study populations (Table 1).

Only 2 studies have reported the incidence of retinal emboli. The Blue Mountains Eye Study identified the 10-year incidence to be 2.9%[19], which is higher than the 1.4% prevalence reported in the same study group in their earlier study[17]. In the Beaver Dam Eye Study, the 5-year incidence was reported as 0.9%[16] and the 10-year incidence was calculated to be 1.5%[20], as compared to the 1.3% prevalence reported in the initial report[16].

Of the 3 different types of retinal emboli - cholesterol, platelet-fibrin, and calcium - the most common is cholesterol. An estimated 46%-80% of all retinal emboli are composed of cholesterol, followed by 6%-32% platelet-fibrin and 6%-16% calcific[14,17,19,21,22]. Since the majority of retinal emboli are of the mobile cholesterol type, it is not surprising then, that many studies report dynamic changes in the presence of retinal emboli on subsequent exams. Hollenhorst[1] reported such changes in 39% of his cases at a subsequent visit, Schwarcz *et al*[23] in 84% of cases, and The Blue Mountains Eye Study and The Beaver Dam Eye Study in 87%-90% of cases[16,19,20]. While the distal migration of emboli is the most commonly accepted theory, another proposed mechanism for the disappearance of these retinal emboli is through autophagy, in which the endothelium engulf the embolus and lead to its extravasation into perivascular spaces[24]. Whatever the mechanism, the transient nature of retinal emboli thus makes it difficult to identify their true prevalence and likely contributes to the variations between different studies and the apparent discrepancies between the incidence and prevalence even within the same study group.

RISK FACTORS

Given the likely sources of retinal emboli, it has been postulated that the risk factors for retinal emboli are similar to the risk factors for vascular disease. However, the definite risk factors for retinal emboli are difficult to assess due to the transient nature of retinal emboli, the presence of multiple co-morbidities, differing demographics across reported studies, and a survivor effect wherein subjects who may be at highest risk are not included in the cohort. Although there are some inconsistent results across the different studies (Table 2)[14-20,25], some generalizations can still be made. Smoking appears to be the strongest risk factor and has been consistently associated with the presence of retinal emboli in all studies reviewed here. Most of the traditional vascular risk factors appear to be significantly associated with retinal emboli with the exception of diabetes, which has fairly consistently been shown not to confer increased risk. Indeed, the incidental finding of retinal emboli has been reported in 0.9%-1.9% of patients who undergo screening for diabetic retinopathy[21,26], which is within the range of the prevalence and incidence of retinal emboli reported in the general population.

As is the case with patients afflicted by other vascular diseases, patients with retinal emboli often have multiple risk factors. The additive effect of multiple co-morbidities was demonstrated in The Blue Mountains Eye Study, which found that the presence of 2 or more risk factors conferred a greater risk of having retinal emboli as compared to none or 1 factor[27]. The combination of hypertension and current smoking conferred the highest risk of retinal emboli with an odds ratio of 6.0 in subjects under age 70[27]. Any 2 or more of hypertension, current smoking, history of vascular event, and history of vascular surgery also led to an increased risk with an odds ratio of 4.6[27].

OUTCOMES

The presence of retinal emboli may be a harbinger of future vascular events and has been associated with increased mortality. In a 7-year follow-up study of 208 patients by Hollenhorst[28] and Pfaffenbach *et al*[29], the

Table 2 Risk factors for retinal emboli

Probable risk factors	Unlikely risk factors	Insufficient data
Smoking (8/8)	History of angina (2/5)	Elevated pulse pressure (2/2)
History of coronary artery bypass graft (3/3)	History of myocardial infarction (2/5)	Known carotid artery plaque (2/2)
Hypertension (5/7)	Body mass index/obesity (1/7)	LDL cholesterol (1/1)
Older age (4/6)	Diabetes (1/7)	Mean arterial blood pressure (1/1)
Coronary artery disease (2/3)	Aspirin use (1/3)	Previous vascular surgery (1/1)
Serum fibrinogen (2/3)	History of stroke (0/6)	Serum lipoprotein (1/1)
Systolic blood pressure (3/5)	Diastolic blood pressure (0/4)	Congestive heart failure (0/1)
Male sex (3/6)	Alcohol use (0/3)	Hemoglobin A1C (0/1)
Total cholesterol (3/6)	Hematocrit (0/3)	Hormone replacement therapy (0/1)
	Platelet count (0/3)	Serum triglycerides (0/1)
		Carotid artery bypass surgery (0/2)
		Serum glucose (0/2)

The numbers in parentheses indicate the fraction of studies reviewed in this article that report a statistically significant association with retinal emboli. A potential risk factor was considered to have insufficient data if there were fewer than 3 studies investigating its relationship to retinal emboli.

all-cause mortality rates were 8% at 3 mo, 15% at 1 year, 29% at 3 years, and 54% at 7 years in patients with a median age of 64 years at initial embolus detection. The most common cause of death was coronary artery disease (42% of deaths), followed by stroke (10% of deaths), other atherosclerotic vascular disease (10% of deaths), and ruptured aortic aneurysm (8% of deaths). Savino *et al*[30] reported the overall mortality as 28% during a 9-year follow-up period, with the largest proportion of deaths similarly attributable to cardiovascular disease (46% of deaths). The next largest cause of death was stroke (29% of deaths), which corresponded to a 4 to 5-fold annual increased stroke-related mortality compared to an age and sex-matched population. Howard *et al*[31] reported a 2.3-fold increased risk of death and 12-fold risk of fatal stroke as compared to age and sex-matched controls during a 6-year follow-up period. The Beaver Dam Eye Study[20] similarly reported a 2.4-fold increased stroke-related mortality and no statistically significant association with ischemic heart disease.

To achieve greater statistical power, a study was performed pooling mortality data from The Blue Mountains Eye Study and The Beaver Dam Eye Study. When adjusted for age and sex, there was a mild increase in cardiovascular mortality (HR = 1.46, 95%CI: 1.03-2.06), a moderate increase in stroke-related mortality (HR = 2.33, 95%CI: 1.34-4.07), and a mild increase in all-cause mortality (HR = 1.52, 95%CI: 1.18-1.96)[32]. After adjusting for multiple systemic factors, such as body mass index, hypertension, diabetes, current smoking, total cholesterol, high-density lipoprotein cholesterol, history of stroke, history of angina, history of acute myocardial infarction, retinal emboli were still significantly associated with increased stroke-related mortality (HR = 2.02, 95%CI: 1.07-3.81) and all-cause mortality (HR = 1.34, 95%CI: 1.02-1.76), although at a lesser magnitude. The risk of cardiovascular mortality became statistically insignificant (HR = 1.18, 95%CI: 0.80-1.73). These findings suggest that the presence of retinal emboli may be an independent risk factor for all-cause and stroke-related mortality. In reality, most patients do tend to have multiple systemic risk factors, which further increases mortality risk.

While associated mortality has been published in many studies, less commonly reported are morbidities linked to the presence of retinal emboli. Due to significant impact of disabilities on quality of life, these morbidities should not be ignored. The most common morbidity is non-fatal cerebrovascular infarction. In a study of 70 men with asymptomatic retinal emboli seen at the Albuquerque Veterans Affairs Medical Center, Bruno[12] reported an 8.5% annual rate of non-fatal stroke, which corresponds to a 10-fold increased risk of cerebral infarction as compared to controls matched for age and vascular risk factors. More specialized brain imaging techniques like diffusion weighted imaging has allowed the detection of subclinical strokes, with a study by Helenius *et al*[33] reporting that 20% of patients whose sole presenting complaint was acute monocular vision loss were found to have brain infarcts on the ipsilateral side. Other morbidities reported by Pfaffenbach *et al*[29] include claudication (9% of patients), angina or abnormal electrocardiogram (7% of patients), transient ischemic attack (3% of patients), and amaurosis fugax (1% of patients). However, the lack of statistical analyses provided for these sequelae make it difficult to ascertain whether the presence of retinal emboli confers an increased risk for these phenomena or whether these are related to the patients' other comorbidities and underlying vascular disease.

Because of the increased stroke mortality and morbidity in patients with retinal emboli, carotid ultrasonography and angiography are sometimes performed. However, data reported in the literature vary widely, not only with regards to the prevalence of carotid disease, but also in the way results are reported and how "significant" disease is defined. Among studies that do not specify the degree of carotid stenosis, as low as 23% and as high as 95% of patients with retinal emboli are estimated to have some carotid disease[18,25,31,34]. Significant carotid artery stenosis defined as at least greater than 50% was present in 17%-22% of patients with asymptomatic retinal emboli[25,34,35]. Other studies that defined significant carotid stenosis as greater than 70% reported a prevalence of

9%-22% in asymptomatic patients[21,26,36]. Lastly, when significant stenosis was defined as greater than 75%, a prevalence of 20% was reported[22]. Despite stroke-related mortality being most commonly reported sequela of retinal emboli, it should be noted that carotid disease, especially high grade stenosis, is still only found in a minority of these patients.

It has been postulated that the presence of visual symptoms could be an indicator of carotid disease. Bunt[37] reported that 17% of asymptomatic patients, 73% of patients with amaurosis fugax, and 100% of those with focal visual loss had significant stenosis. Bakri *et al*[36] found that there was a significant difference in the proportion of symptomatic and asymptomatic patients (25% *vs* 9%) when stenosis was defined as > 69% but not when defined as > 40%. This study also suggests that asymptomatic patients with a carotid bruit are more likely to have carotid stenosis. These findings may seem intuitive, but are not replicated in all studies. For example, O'Donnell *et al*[22] reported a similar proportion of carotid disease in symptomatic (21%) and asymptomatic patients (18%).

Since most patients with asymptomatic retinal emboli do not have significant carotid disease, only a small proportion undergoes carotid endarterectomy. Hadley *et al*[21] reported that 25 of 190 patients with retinal emboli (13%) had significant stenosis between 70%-99%, and only 10 of these patients underwent ipsilateral carotid endarterectomy. By the end of the study period (up to 7 years of follow-up), 4 of these 10 in the surgical group had died, but none from a stroke. Of the 15 who did not have surgery, 5 died during the follow-up period, none from a stroke although one patient did experience a non-fatal stroke. In Bunt's study[37], 28% of patients with asymptomatic retinal emboli underwent carotid endarterectomy, and no patients in either the non-surgical group or any of the surgical groups developed any subsequent symptoms of vision loss or cerebral ischemia during an 18-mo follow-up period. Schwarcz *et al*[23] reported that whether patients underwent carotid endarterectomy or not, both groups experienced recurrent retinal emboli and subsequent transient ischemic attacks. These reports seem to suggest that perhaps carotid endarterectomy for these patients does not affect mortality. However, the effect on long-term outcomes is limited in these studies due to short follow-up, small sample sizes, lack of data on medical interventions that were provided concurrently to the surgical group, and lack of data on medical interventions done to the non-surgical group.

Other less commonly used workup for retinal emboli include transcranial Doppler and echocardiogram. The incidence of cardiac pathology, such as valvular disease and wall motion abnormalities, was reported in 8%-43%[26,27,35]. It is unknown how many of these patients underwent cardiac surgery as a result. Ultimately, it is estimated that up to 45% of patients will have no identifiable cause despite extensive evaluation[35], suggesting that maximal extensive workup is neither cost-effective nor informative.

MANAGEMENT

The increased morbidity and mortality rates suggest a need for additional interventions in patients found to have retinal emboli. Given the coexistence of multiple medical problems, the presence of retinal emboli may simply be a marker of their underlying metabolic and vascular disease. Medical therapy should be the mainstay of management and should emphasize risk factor modification, such as stricter blood pressure control, the initiation of cholesterol-lowering medication, counseling for smoking cessation, encouragement of weight loss, diabetes management, the initiation of antiplatelet therapy, and monitoring through carotid auscultation[15,16,21,26,27,36,38].

The current guidelines[39] for the use of carotid ultrasonography in asymptomatic patients list the following indications: suspected of having carotid disease; have a carotid bruit; have symptomatic coronary artery disease, peripheral arterial disease, or atherosclerotic aortic aneurysm; or have at least 2 associated risk factors (hypertension, hyperlipidemia, tobacco smoking, a family history of a 1st degree relative with manifestations of atherosclerosis before age 60, or family history of stroke). The routine screening of the general population is not recommended. It has been suggested that carotid ultrasonography should be offered to all patients with retinal emboli[40], but given the low prevalence of significant carotid disease in these patients, it may be more reasonable to reserve carotid ultrasonography for patients who meet the aforementioned indications. Other imaging modalities like echocardiogram and transcranial Doppler are low yield and have not been recommended in the literature.

The currently established indications[39] provide strongest evidence for the use of carotid endarterectomy in symptomatic patients with at least 70% stenosis on carotid ultrasound (or at least 50% on catheter angiography) with low or average surgical risk and low anticipated perioperative mortality; and asymptomatic patients with greater than 70% stenosis and low perioperative risk of stroke, myocardial infarction, or death. Ideally, surgery should be performed within 2 wk of the index event. Surgery in asymptomatic patients with retinal emboli who are subsequently found to have significant carotid stenosis is more controversial[41], since carotid endarterectomy is an invasive procedure that itself carries a significant risk of perioperative mortality and postoperative stroke[39,42,43]. As previously discussed, small studies of the short-term outcomes of carotid endarterectomy are not suggestive of a mortality benefit of surgical management. Therefore, this subset of patients may benefit from referral to a vascular surgeon, during which it should be carefully considered whether the benefits of stroke prevention would outweigh the perioperative risks, taking into account the patient's comorbidities, individual risk factors, life expectancy, and complication rates of the surgical center. Large, prospective, randomized, controlled studies addressing the effects of carotid endarterectomy in this unique patient population will determine the out-

comes of this proposed algorithm.

CONCLUSION

Retinal emboli occur in up to 3% of the general population, particularly in those with risk factors similar to that of other vascular diseases. As such, there is significant overlap in patients with retinal emboli and other metabolic and vascular conditions. Therefore, management should involve working with the primary care physician to maximally control the underlying comorbidities and risk factors, such as smoking cessation, control of blood pressure, and lowering of serum cholesterol.

Carotid ultrasound has a low-yield for detecting significant carotid disease in patients with retinal emboli, suggesting that it should not be done routinely in this population but instead reserved for those who meet an established indication. Those who would benefit most from surgery are patients with significant stenosis > 70% and symptoms of an impending cerebrovascular event, such as unilateral weakness, unilateral sensory loss, aphasia, sudden monocular vision loss, or homonymous hemianopsia. The subset of asymptomatic patients with significant stenosis should be referred to a vascular surgeon for consideration of the risks and benefits of this invasive procedure.

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