CARDIOVASCULAR MEDICINE

Calcific retinal embolism as an indicator of severe unrecognised cardiovascular disease

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Objective: To describe the association between calcific retinal embolism (CRE) and cardiac valve stenosis.
Design and setting: Retrospective chart review of patients with clinical criteria for CRE.
Patients: 24 patients with CRE who underwent two dimensional echocardiography between 1976 and 1998.
Results: Nine patients (38%) had calcific valve stenosis, which was haemodynamically severe in five patients (four aortic and one mitral), four of whom had no cardiac symptoms. Six patients underwent surgical intervention (aortic valve replacement in three patients, mitral and aortic valve replacement in one patient, removal of calcific cardiac pseudotumour in one patient, and carotid endarterectomy in one patient).
Conclusions: CRE may be the presenting feature of otherwise asymptomatic, clinically important underlying cardiovascular disease and, in particular, haemodynamically severe calcific valve stenosis.

Calcific retinal embolism (CRE) is a rare cause of visual loss that is predominantly caused by embolism from calcified cardiac valves, particularly calcific aortic valve stenosis. The collective experience with CRE is limited to small series and isolated case reports.[1–8] Only a few of the reported patients had asymptomatic severe valvar stenosis, and the association between the site of calcification, severity of valve stenosis, and CRE remains unclear. Herein, we review our experience with 24 patients with documented CRE over a span of 22 years.

METHODS

We retrospectively identified all patients evaluated at Mayo Clinic, Rochester, Minnesota, USA, from 1976 through 1998 with the coded diagnosis ''embolism of eye''. CRE diagnosis was based on characteristic ophthalmological findings (that is, ovoid shape of embolus, size slightly larger than the lumen of the arteriole, primarily proximal branch arteriole location, yellowish white (fig 1), non-refractile nature, lack of mobility with globe massage, and persistence of embolus).

Baseline and follow up clinical variables were obtained from review of the medical records (table 1). Follow up information included patient management, recurrence of CRE, and all cause mortality. Patients who did not undergo two dimensional echocardiography or in whom CRE was the result of antecedent valve surgery were excluded. The study protocol was approved by the Mayo Foundation institutional review board.

At the time of initial patient evaluation, the severity of visual field defects and the location (superior or inferior, and temporal, nasal, or disk) of the retinal embolism was assessed by dilated retinal examination. Patients were considered to have symptomatic CRE if visual complaints, particularly visual loss, prompted the funduscopic examination. When they were measured, aortic valve area and mitral valve area were determined by the continuity equation and pressure half time measurement, respectively. Severe valve stenosis was confirmed by quantitative techniques (two dimensional echocardiography or cardiac catheterisation). Valve calcification and regurgitation were visually graded with two dimensional echocardiography as mild, moderate, or severe. The diagnosis of mild aortic valve stenosis was based on visual assessment or two dimensional Doppler echocardiography after it became available.

Descriptive analyses were summarised as mean (SD). If SD exceeded 50% of the mean, the results were reported as median and range.

RESULTS

During the study period, 344 patients had a coded diagnosis of retinal embolism, of whom 32 patients (9.3%) met the funduscopic criteria for CRE. Eight patients were excluded because two dimensional echocardiography was not performed. The remaining 24 patients formed the final study population. Twenty three patients (96%) were followed up for 1–238 months (median 43 months) after the diagnostic funduscopic examination.

Clinical characteristics

The mean (SD) age of patients was 65 (11) years (range 30–78 years). Eight patients (33%) were 70 years or older. There were slightly more women (n = 13). The median time interval from funduscopic examination to two dimensional

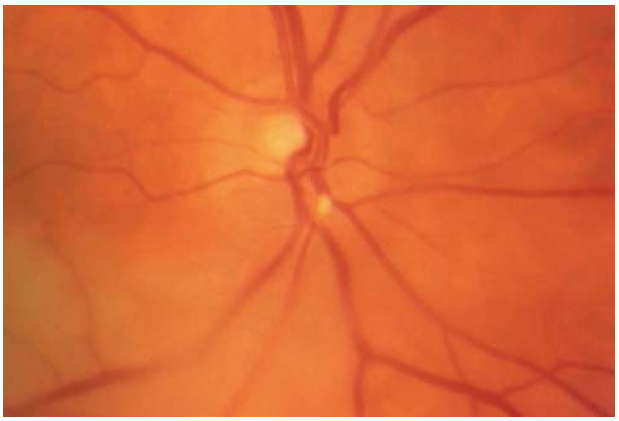

Figure 1 Calcific embolus below the right disk occluding the inferotemporal arteriole.

Table 1 Cardiovascular findings and outcomes in 24 patients with calcific retinal embolism*

Patient (diagnosis year)/age (years)/sex	Predominant cardiac pathology at initial two dimensional echocardiography	Management	Cardiac symptom	Follow up	
				Status	Time (months)
1 (1979)/68/F	Mild AS†, severe MAC, moderate MR	Aspirin	Dyspnoea	Alive	43
2 (1980)/79/F	Moderate MAC, moderate MR	Warfarin	None	Died, MI	13
3 (1980)/63/M‡	Severe AS§ (peak gradient 108 mm Hg)	AVR	Syncope	Alive	238
4 (1981)/69/M	None	Not known	None	No follow up	0
5 (1981)/47/M	None	Warfarin	None	Alive	210
6 (1982)/64/M	Severe MS§ (MVA 0.9 cm^2), moderate AS§ (AVA 1.0 cm^2, mean gradient 34 mm Hg)	AVR and MVR recommended	None	Alive	29
7 (1982)/72/F	Severe MAC, moderate MR	Warfarin	Dyspnoea	Died, cause not known	150
8 (1982)/62/F	Mild AS†	Aspirin and dipyridamole	None	Died, MI	24
9 (1983)/67/M	Mild calcific aortic valve leaflets	Aspirin	None	Alive	179
10 (1983)/76/F	Mild calcific aortic valve leaflets	Aspirin and dipyridamole	None	Died, ischaemic bowel	21
11 (1984)/67/F	Moderate MAC	Aspirin	None	Alive	10
12 (1984)/30/M‡	Left ventricular calcified pseudotumour	Tumour resection	None	Alive	43
13 (1985)/75/M	Moderate MAC, mild MR	Aspirin	None	Died, pulmonary oedema (severe MR)	114
14 (1985)/73/F‡	Severe AS (AVA 0.68 cm^2, mean gradient 41 mm Hg)	AVR	None	Died, MI	41
15 (1988)/53/M	Mild MR	Aspirin	None	Alive	91
16 (1988)/75/M‡	Moderate MAC, mild MR	Carotid endarterectomy	None	Alive	1
17 (1988)/60/F	Mild AS (AVA 1.5 cm^2, mean gradient 12 mm Hg), severe MAC, indeterminate MR	Aspirin	None	Died, ischaemic bowel	33
18 (1988)/60/F	Mild calcific aortic valve leaflets	Aspirin	Dyspnoea	Alive	127
19 (1989)/59/M	Moderate MAC, mild MR	Not known	None	Died, stroke	63
20 (1991)/77/F‡	Severe AS (AVA 0.56 cm^2, mean gradient 36 mm Hg)	AVR	None	Alive	46
21 (1992)/67/F	Mild AS (AVA 1.2 cm^2, mean gradient 10 mm Hg), severe MAC, moderate MR	Aspirin	None	Alive	25
22 (1993)/78/M	Severe MAC, moderate MR	Aspirin	Dyspnoea	Alive	57
23 (1994)/53/F	Moderate MAC, mild MR	Not known	Dyspnoea	Alive	10
24 (1997)/68/F‡	Moderately severe AS (AVA 1.0 cm^2, mean gradient 46 mm Hg), moderate MS (MVA 1.7 cm^2), severe MAC, mild MR	AVR and MVR	None	Alive	64

*Symptomatic in all patients except 6, 21, and 23; †two dimensional echocardiographic visual assessment; ‡patient underwent surgery; §catheterisation derived. AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; F, female; M, male; MAC, mitral annular calcification; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve replacement.

echocardiography was three days (range 0–11 days). Two dimensional echocardiography was performed in 17 patients solely because of funduscopic evidence of CRE. In the remaining seven patients, the indications for two dimensional echocardiography were heart murmur (one patient), syncope (one patient), and dyspnoea (five patients).

Twenty one patients presented with visual loss; onset was sudden in 14 patients (58%) and gradual in seven patients (29%). The median interval from onset of visual symptoms to two dimensional echocardiography was 10 days (range 1–46 days). CRE was an incidental finding during routine eye examination in the remaining three patients, who were otherwise asymptomatic. Six patients had a history of transient ischaemic attack or stroke.

Serum creatinine concentrations in the patients ranged from 53–221 µmol/l (mean (SD) 106 (44) µmol/l) at the time of CRE diagnosis, and six patients (25%) had a serum creatinine concentration higher than 115 µmol/l. Erythrocyte sedimentation rate, recorded in 14 patients, ranged from 1–53 mm in the first hour (median 14 mm in the first hour, reference range 0–29 mm in the first hour).

Visual findings

CRE was found in the right eye in 15 patients (63%); none of the patients had multiple or bilateral CRE. The retinal occlusion was superior in 11 patients (46%), inferior in nine patients (38%), and not documented in four patients (17%). CRE was localised to the temporal aspect in 11 patients (46%), the nasal aspect in three patients (13%), and the optic disk in 10 patients (42%).

Cardiovascular findings

Two dimensional echocardiography indicated calcific aortic disease, calcific mitral valvar disease, or both in 20 patients (83%) (table 1). Valve stenosis was severe in five patients: four aortic (patients 3, 14, 20, and 24) and one mitral (patient 6). Four of the patients with haemodynamically severe valve stenosis had symptomatic CRE but only one patient had cardiac symptoms at the time of diagnosis (patient 3). One patient with symptomatic CRE but without valvar disease or cardiac symptoms had a calcific pseudotumour adherent to the ventricular septum (patient 12) (fig 2). Seventeen patients (71%) had mitral annular calcification that was visually assessed to be severe in six patients, four of whom had concomitant moderate mitral valvar regurgitation.

Twenty one patients (88%) had an ejection fraction of 50% or greater (mean (SD) 63 (15)%) and four patients had evidence of regional wall motion abnormalities. Most patients presented before transoesophageal echocardiography (TOE) became a routine part of our clinical practice. TOE was performed in only two patients and showed mild fixed calcific atheromas in the ascending aorta and arch.

Carotid evaluation was pursued in 10 patients, four of whom had a documented history of stroke or transient ischaemic attack. Carotid ultrasonography showed minimal to no atherosclerotic plaque in six patients and moderate disease (50–79% stenosis) in two patients, one of whom underwent aortic valve replacement. Carotid angiography was performed in two patients, one of whom had haemodynamically severe stenosis in the right internal carotid artery but was asymptomatic.

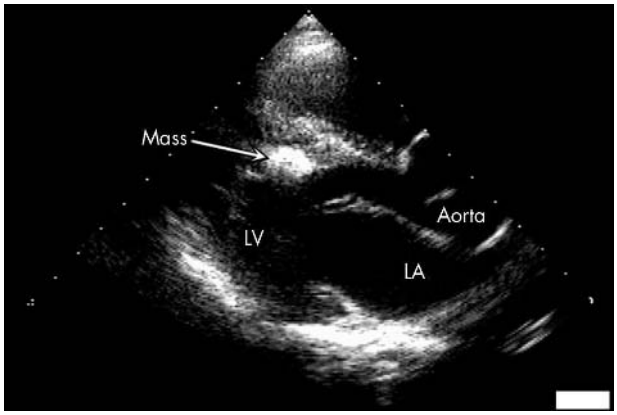

Figure 2 Two dimensional echocardiogram (parasternal long axis view) showing calcific pseudotumour (Mass) attached to interventricular septum. LA, left atrium; LV, left ventricle.

Surgery

Six patients (25%) had cardiovascular surgery (table 1): aortic valve replacement in three patients (patients 3, 14, and 20), aortic and mitral valve replacement in patient 24, removal of a calcified cardiac pseudotumour in patient 12, and right carotid endarterectomy in patient 16. Surgery was performed within two months of the initial funduscopic examination in five patients (patients 3, 12, 16, 20, and 24) and three years after the diagnosis of CRE in patient 14 because of echocardiographic evidence of disease progression. A seventh patient (patient 6) with asymptomatic CRE was advised two years later to have aortic and mitral valve replacement for moderate aortic stenosis and severe mitral stenosis but deferred intervention.

Medical management

Medical treatment, advised for 14 of the 18 patients who did not have surgery, consisted of aspirin in nine patients, warfarin in three patients, and combination treatment with aspirin and dipyridamole in two patients.

Follow up

No patient had documented recurrence of CRE. Eight patients in the group died of ischaemic bowel (patients 10 and 17), myocardial infarction (patients 2, 8, and 14), complications from stroke (patient 19), pulmonary oedema (patient 13), and an unknown cause (patient 7). Whether the cause of any of these events was cardioembolic is not known.

DISCUSSION

Our study shows that CRE may be the first clinical manifestation of otherwise unrecognised serious underlying cardiovascular pathology. More than a third of patients had calcific valvar stenosis and a fourth of patients underwent cardiovascular surgical intervention. The 9.3% prevalence of CRE among all patients with embolism to the eye in our study is similar to the 8.6% reported by Arruga and Sanders,[1] and none of our patients had evidence of multiple or bilateral CRE, also similar to their results. To our knowledge, only two cases of spontaneous bilateral and multiple CRE have been reported.[2 5] Temporal arterioles were the sites of CRE in most of our patients, similar to the findings in other series.[1 9]

Systemic calcium embolisation from calcified cardiac valves is not unusual and can have devastating clinical consequences, such as myocardial ischaemia or infarction[10–12] and cerebral infarction.[13–15] Holley and colleagues[16] reported that 31 of 165 patients (19%) with necropsy proven calcific aortic stenosis (85% moderate to severe) had pathological evidence of systemic calcium embolisation, but only one patient had CRE. Systemic calcium embolisation also has been observed after surgical valvar manipulation.[17 18]

We cannot comment on the most appropriate medical management of this condition given the small number of cases in the literature and lack of long term follow up of patients with CRE. In theory, antiplatelet agents and anti-coagulants should not have an effect on calcific emboli or prevent their recurrence, unless the embolism contained fibrin or platelet components. The risk of CRE may be related to the quantity of calcium present rather than lesion severity,[6 10 13] which has prompted some to recommend replacement of calcified cardiac valves in the event of CRE regardless of their haemodynamic severity or symptoms.[7]

Our study has limitations inherent in its retrospective design. A direct causal relation between calcified cardiac valves and CRE cannot be established. The prevalence of CRE may be underestimated because of referral bias and because patients with calcific valve stenosis did not routinely undergo funduscopic examination. Although none of the patients in our study had pathologically proven CRE, the findings on ophthalmoscopic examination were typical and have been well described in the literature.[1 19] Additionally, although all patients underwent standard two dimensional echocardiography, only 10 patients (42%) had concomitant carotid ultrasonography, angiography, or both. A carotid source of embolism cannot be ruled out definitively in the remaining patients. In a few patients, the severity of aortic valve stenosis was assessed visually but results with this method correlate well with those from direct surgical inspection.[20] Because only two patients underwent TOE, the association (if any) of significant calcific debris in the ascending aorta, aortic arch, or left atrium or its appendage to the presence of CRE could not be established.

Conclusion

CRE is an unusual but serious complication of calcific cardiac valve disease and may be the presenting feature of severe underlying cardiovascular disease in need of early surgical correction. Two dimensional echocardiography should be considered for all patients with CRE.

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IMAGES IN CARDIOLOGY

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Left sided unilateral pulmonary oedema

A 74 year old man was admitted with chest pain of 12 hours duration accompanied in the preceding hours by severe dyspnoea. On auscultation of the chest, crackles were noted all over the left lung, as well as an apical pansystolic murmur radiating to the left axilla. The baseline ECG revealed significant ST segment depression in the precordial leads with raised concentrations of creatine kinase and creatine kinase-MB fraction. Chest *x* ray showed extensive haziness in the left lung field (panel A). Echocardiography revealed inferior akinesis, a reduced global left ventricular ejection fraction, and a large eccentric mitral regurgitation jet reaching the left pulmonary veins (panels B and C). Urgent coronary angiography was not done (time window). High dose parenteral furosemide and glyceryl trinitrate treatment resulted in rapid improvement of symptoms and the resolution of left sided haziness on chest *x* ray by the next day. Coronary angiography later revealed severe three vessel disease with an occluded circumflex artery.

Asymmetric *x* ray findings usually have a pulmonological origin. However, if the murmur of mitral regurgitation is heard, unilateral pulmonary oedema caused by papillary muscle dysfunction and an eccentric regurgitation jet should be considered; transoesophageal echocardiography and rapid response to diuretics are the two most useful clues to making the diagnosis.

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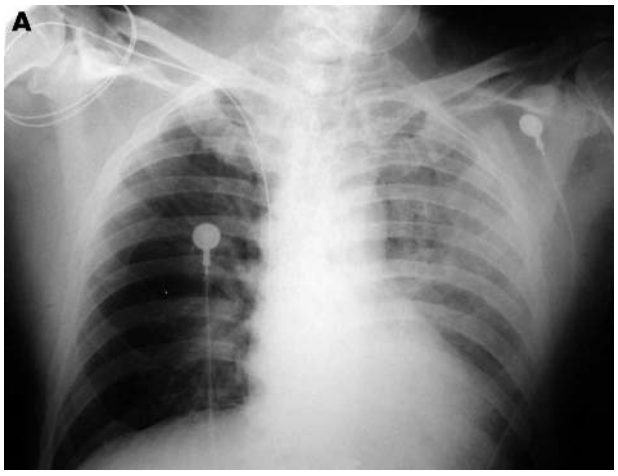
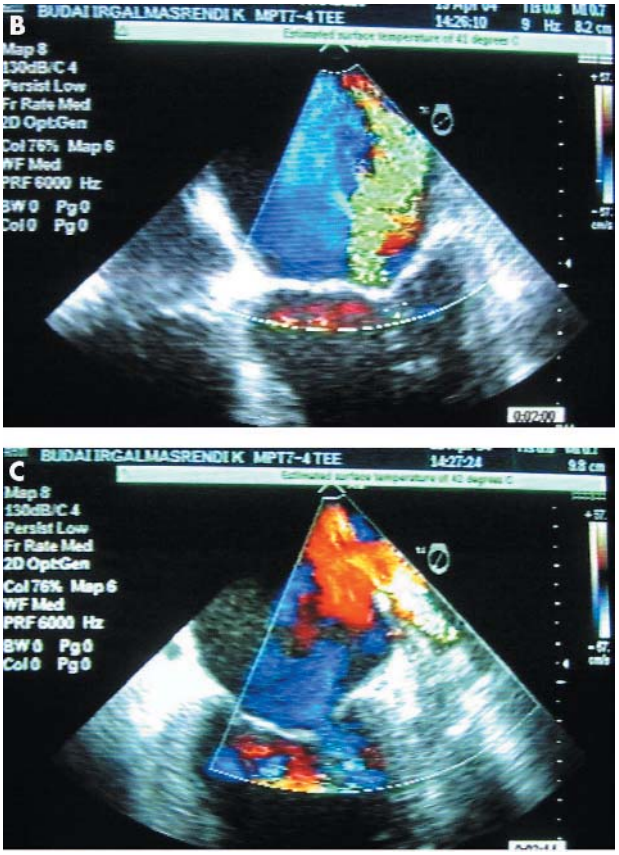


Anteroposterior chest *x* ray performed on the hour of admission revealing the presence of left sided pulmonary oedema. (A temporary pacemaker lead was inserted from the right subclavian vein because of transient complete atrioventricular block on admission.)



Transoesophageal echocardiography documented a retrograde jet towards the left pulmonary veins.