Reviewer's report

Title: Clinical significance of retinal emboli during diagnostic and therapeutic cardiac catheterization

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Reviewer: James Wilentz

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All of the points below should be considered mandatory revisions if this is to be reconsidered for publication:

P1: How were the patients “selected?” You say “three-hundred selected patients,” but were they consecutive? If so over what range of time? Were there selection criteria for inclusion in the cohort reported here.

P2: Results-- The first sentence should be changed to read “There were 5 cases of retinal embolus before catheterization . . .”

P3: “Another study revealed a 10-fold increase in stroke among men with baseline retinal emboli within 3.4 years of follow-up (11).” You need to clarify what you mean to convey here. Is there an increase in stroke among a general medical follow-up group who have had a retinal embolus over those who have not? Or is it an increase in stroke after cardiac cath in the retinal embolus group?? I think it’s the former, but you have to state it. You could word it something like: Another study showed a 10 fold increase in the incidence of stroke among men followed a mean of 3.4 years after an index retinal embolus over the stroke incidence seen in a control group over the same period. Last sentence on P 3 the word ophthalmic is misspelled “Ophthalmic artery is the first branch of the internal carotid artery and emboli from the cardiovascular sources tend to directly go to the eye.” This should be changed to read: “The ophthalmic artery is the first major branch arising from the internal carotid artery and thus emboli from the heart and great vessels proximal to the carotid tend to directly go to the eye.

P4: The article you cite (11) for the incidence of retinal emboli following coronary surgery and carotid stenting is not about that but about the follow up of asymptomatic retinal emboli. I’m not sure where you got the figures on the incidence of retinal emboli after coronary surgery and carotid stenting, but there are ample references, and before you resubmit this paper I would request that you re-check your references for content throughout this paper, and also specifically review a few of the more modern references about the incidence of retinal embolization after carotid stenting (I’m an author on one in Cathet Cardiovasc Intervention 2002, and there are references from Dr. Vos in CardioVascular and Interventional Radiology; 2010 and AlMubarak J Endovasc Therapy 2001) which suggest that the rate is about 1.25% when utilizing modern
protection techniques but much higher without. Para 2: “Retinal emboli are partially obstructive and asymptomatic most of the time (9). But central retinal occlusion, although rare, is an emergency situation whose treatment remains highly uncertain and controversial (2).” should be changed to: “Retinal emboli are partially obstructive and asymptomatic most of the time (9); however, central retinal occlusion, although rare, is an emergency situation whose treatment remains highly uncertain and controversial (2).” It is not grammatical to start a sentence with “But.” Para 2: I am worried that you have cited references for findings that are not in the references. This makes me worried about the veracity of your entire report. You cite your reference number 15 to support the conclusion that after 97 min into a retinal embolus, thrombolysis is of no help. I have read reference number 15 [15. Law JC, Abrams GW, Kim RW, Elliot D, Garcia-Valenzuela E. Branch retinal artery occlusion. E Med. 2007; 9: 158-62. Available from: URL: http://emedicine.medscape.com/article/1223362-overview. Accessed January 30, 2009.] and I have not found any mention of the time period to successful retinal artery recanalization by thrombolytics. There is indeed a trial (and probably a lot more – I have not done the full search) of thrombolytics for RAE (retinal artery embolization) Schumacher M, Schmidt D, Jurkles B, Gall C, Wanke I, Schmoor C, Maier-Lenz H, Solymosi L, Brueckmann H, Neubauer AS, Wolf A, Feltgen N; EAGLE-Study Group. Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial. Ophthalmology. 2010 Jul;117(7):1367-75.e1. that suggests that there is no statistically significant difference between conservative medical treatment and thrombolysis by the local intra-arterial route. In this study the mean time to treatment was very long (11-13h) and I would not expect thrombolysis to be effective at that time. If you really do have a good reference for the use of thrombolytics in this entity, bring it on, because we need to see it. If not, my fears about the entire paper remain.

P5: Para 1 How much aortic stenosis? You need to say what the exclusion criteria really were. AS with a mean gradient greater than x? AS judged to be surgical based on echo criteria? Just tell us what the criteria were for exclusion. Para2 Why were patients with minor coronary disease excluded? You must redo the analysis with them included. This was a study of retinal embolization after cath, and those patients were cathed so I want you to tally how many had retinal emboli and do the analysis including them. It is even more awful for a patient who didn’t have the diagnosis for which the cath was indicated to suffer partial or total blindness as a complication. Also it would be important to know if there were really a difference in rates of retinal emboli between the true CAD patient and the patient presenting for cath who is found not to have severe CAD. Para 3 Could you comment on the wire exchange technique? Many of us feel that stroke is minimized when wire exchanges are performed rather than the catheters just pulled back around the aortic arch with their preformed shapes scraping the arch and the ostia of the neck vessels. How was the exchange done in your series if
this is ascertainable?

P6: The contrast medium is tradenamed “Omnipaque” not “Omniopaque.” Also there are differences in anticoagulant status between different contrast agents. The non-ionic non-osmolar agents are felt to be more thrombogenic, and some labs use heparin added to the contrast media when these are used. (Many refs available on this including Aguejouf O, Doutremepuich F, Azougagh Oualane F. and Doutremepuich C. Thrombogenicity of ionic and nonionic contrast media tested in a laser induced rat thrombosis model. Thrombosis Research 1995; 77, 259-269)

P7: It sounds really sloppy to present numbers that don’t add up. You have 408 recruited patients. You state that only 300 patients came back for their post-cath eye exam. Then you go on to state that “Twenty patients had normal angiograms or mild coronary artery disease, and the others refused further cooperation. Therefore, this report is based on statistical analysis of the data for 300 patients (mean age 59.36 ± 7.86 years, 156 men and 144 women).” Things are just not adding up. Where are the 20 who had normal or mild CAD angios? Are they in the 300 who came back and were they then excluded from statistical analysis? Where are the others [who] refused further cooperation? Are they in the group that didn’t come back or are they excluded for other things gone wrong? Para 3 re the risk factors, all you can really conclude is that you do not have the statistical power to prove there is not a difference in the groups for any of the discriminants chosen for presentation in tables 1 and 2. You could also state that there may well be a trend to a greater incidence of retinal embolization in the presence of hypertension, but that is not statistically proven by these data.

P8: para2-3 There is something very wrong in the visual field testing. You have a patient complaining of a large blind spot in the right eye, and she has a large retinal embolus seen on retinal exam and yet the results of all the visual field measurements were negative. Perhaps they were tested too long after cath. In my report and clinical experience, significant retinal emboli early after cath where the patient is complaining about a blind spot are nearly always accompanied by a visual field defect. It would have been lock tight if you had performed fluorescein retinal angiography with the ophthalmoscopy as is recommended in cases of retinal embolization. This would have been the key to looking for emboli that stop blood flow which is shown absolutely clearly in a fluorescein retinal angio. That is the key difference between an asymptomatic small embolus and a large one that stops flow and infarcts a section of the retina. Para 4 You cannot say “revealed a slight but non-significant difference” when the p value is .477. What that means is that there was a 50% likelihood that this “difference” could have happened just by chance. You must say that “Although we observed, in this small series, a slightly larger proportion of retinal emboli in those patients undergoing therapeutic catheterization that in those undergoing diagnostic catheterization only, this difference was not significant.”

P12: You cannot at all say that “operator expertise” was strongly associated with the appearance of new retinal emboli. You did not measure operator expertise or did not present those measurements. If you are considering that procedure time
is a surrogate for operator expertise, you might be right, but you might not. It is an invalid conclusion from the data. Even on the data point of procedure time the data is insignificant p=0.188 is not p < .05.

P14 line 9 “analyzed the incidence of retinal emboli after coronary catheterization after.” should read: after coronary catheterization” and omit the second “after.”

P15 If this is to be published at all, the first sentence should be changed to read: “The rate of retinal embolization after therapeutic cardiac catheterization appeared to be slightly higher than after diagnostic angiography; however, this was not statistically significant.” The second sentence should read: “We suspect that further manipulation of the aortic root might increase the risk of embolism; however, further research will be needed to test this hypothesis.” You cannot start a sentence with the word “However” in formal English if it means “nevertheless” or “but.” If it means “in any way,” you may start the sentence with “However” as in “However you might play that piece, I just don’t care for it.” See Strunk and White’s Elements of Style, which is an invaluable reference for anyone trying to write properly in English. I would change the third sentence: “With respect to evaluations of retinal emboli after cardiac catheterization, identifying the source of the lesion requires a much longer time and more facilities such as transesophageal echocardiography and color Doppler study of the cerebral vessels. Despite potential material limitations, the long-term significance of retinal emboli in these patients warrants further investigation.” To read: “Retinal emboli occurring post cardiac catheterization warrant a careful vascular workup including a search for the source of the emboli in the aortic arch, the great vessels and the chambers of the heart itself. Vascular ultrasound, transesophageal echocardiography and potentially CTA or MRA can be extremely useful in this regard. We did not have the capacity to perform these studies in this cohort.”

Finally in the Conclusion sentence you should change it to say: “Our findings in a selected cohort of patients imply that cardiac catheterization is safe and feasible with respect to the retina. Retinal emboli are generally clinically silent especially when small and peripheral and may not produce any visual sequelae. Age and hypertension were independent predictors of retinal emboli in this study.”

Overall the statistical methods are not specified in the least other than saying the for categorical variables a chi-squared test was done. What about the non-categorical variables like age stent length procedure time, fluoro time etc etc. Also you say that a p of 0.05 is considered the threshold for significance as is standard but you go on to say that things are significant with p values of .477. What are we to think?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited
**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests