Delayed Cerebral Ischemia Following Arteriography

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SUMMARY Cerebral ischemic events associated with arteriography are usually attributed to catheter-induced emboli. We present three patients with cerebral ischemia occurring 6 to 48 hours post-arteriography. We suspected that alternate pathogenic mechanisms were in effect. To evaluate the possibility that sustained platelet activation occurs in association with arteriography, we measured the platelet-specific protein beta thromboglobulin (BTG) prior to and 24 hours following arteriography in two groups of patients. Group I had arteriography performed shortly after venipuncture, while Group II patients did not have arteriography between samples. Seven of eight Group I patients had an increase of BTG on day two, compared with two of eight group II patients (p < .05). When compared to Group II changes, Group I had a significant increase of BTG on day two (p < .05). We conclude that cerebral ischemic events associated with arteriography may occur on a delayed basis, and that platelet activation, manifested by increased BTG levels, may be one mechanism contributing to this phenomenon.

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CEREBRAL ISCHEMIC EVENTS represent a significant source of morbidity among patients undergoing arteriography for occlusive cerebral vascular disease.1 The pathogenesis of these complications is usually attributed to either thrombus formation on catheter tips with subsequent injection into the intracranial circulation, or dislodgement of atherosclerotic plaques by the catheter.1 These result in sudden neurological deficits, usually occurring while the patient is on the angiography table. We report three patients who experienced cerebral ischemic events beginning 6 to 48 hours following performance of arteriography. We suspected that alternate pathogenic mechanisms were in effect, and thus investigated the relationship between cerebral angiography and platelet activation. We present three patients with cerebral ischemia occurring 6 to 48 hours post-arteriography. We suspected that alternate pathogenic mechanisms were in effect. To evaluate the possibility that sustained platelet activation occurs in association with arteriography, we measured the platelet-specific protein beta thromboglobulin (BTG) prior to and 24 hours following arteriography in two groups of patients. Group I had arteriography performed shortly after venipuncture, while Group II patients did not have arteriography between samples. Seven of eight Group I patients had an increase of BTG on day two, compared with two of eight group II patients (p < .05). When compared to Group II changes, Group I had a significant increase of BTG on day two (p < .05). We conclude that cerebral ischemic events associated with arteriography may occur on a delayed basis, and that platelet activation, manifested by increased BTG levels, may be one mechanism contributing to this phenomenon.

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over a 12 hour period and were unassociated with hypotension or arrhythmia. She never experienced similar symptoms previously, and at follow-up, 19 months later, there was no recurrence of these symptoms.

Case 2

A 35 year old female was admitted for the acute onset of the inability to speak. The patient had a similar episode several months earlier, resolving over three days without treatment. She had a three year history of hypertension and was using oral contraceptives for six years. General physical examination revealed a blood pressure of 224/128. The cardiac exam was unremarkable. On neurological exam, the patient exhibited a moderate nonfluent aphasia, right central facial weakness, and a right pronator drift. Routine blood chemistries and hematological evaluation were unremarkable. Serum VDRL and FTA were positive. The cerebrospinal fluid, including serology, was normal. Echocardiography showed no evidence of mitral valve prolapse. A computerized tomographic (CT) scan showed a low density region in the left parietal lobe, without infarction. Her diagnosis was a left central Marcus-Gunn pupil. The mental status, sensory, and motor examinations were normal. Routine laboratory studies were unremarkable. Her diagnosis was a left central retinal artery occlusion, and she was discharged on anti-platelet medications. Follow-up at 20 months revealed no recurrence of symptoms.

Case 3

A 56 year old female underwent cardiac catheterization for evaluation of chest pain. The cardiac study revealed normal coronary arteries and normal left ventricular function. 48 hours following the procedure, the patient suddenly lost vision in the left eye. She had no previous neurological symptoms. The general physical exam was normal and there were no carotid bruits. Neurological examination revealed left optic disc pallor with light perception only, along with a left Marcus-Gunn pupil. The mental status, sensory, and motor examinations were normal. Routine laboratory studies were unremarkable. A CT scan showed no evidence of infarction. Her diagnosis was a left central retinal artery occlusion, and she was discharged on anti-platelet therapy. Follow-up 14 months later revealed no change in visual function, but no new symptoms.

Methods

Two groups of patients with signs and/or symptoms of occlusive cerebral vascular disease were selected for the experimental study. Plasma was collected from these patients for BTG assay on two consecutive days at an interval of approximately 24 hours. Group I had selective carotid arteriography performed on day one of the study, shortly after collection of the plasma sample. Group II did not have arteriography between plasma samples.

Plasma samples were collected using a modification of the method of Files et al. A solution of 1 ml acid-citrate-dextrose (ACD, NIH Formula A), 80 ul aspirin (180 mg ASA/ml ethanol), and 10 ul PGE_1, (100 pg PGE, /ml ethanol) was prepared just prior to venipuncture. The solution was drawn into a syringe, which was then placed on ice. Using a 21-gauge "buttery," 4 ml of blood was drawn directly into the syringe without the use of a tourniquet. The syringe was then inverted 10 times, placed on ice for 5 to 30 minutes, and centrifuged at 10,000 g for 30 minutes. Aliquots of approximately 100 ul were then stored at −20°C until assayed. Plasma BTG levels were determined using a commercially available radioimmunoassay (Amersham), with serial plasma samples from each individual patient evaluated on the same assay. Normal adult BTG levels (n = 21) were 9.5 ± 1.7 ng/ml (mean ± SEM).

All Group I patients were studied with selective carotid arteriography using Conray-60 (iothalamate). Aortic arch studies at the same sitting were performed using Renograffin-76 (diatrizoate). To evaluate the possibility that altered renal function or the stress of the procedure contributed to BTG changes, all Group I patients had blood drawn for determination of BUN, creatinine, and cortisol (by radioimmunoassay) prior to, and one day following, arteriography. Patients were carefully evaluated for the presence of ecchymosis at the site of femoral puncture. Statistical studies were performed using unpaired t-tests and chi-square analysis.

Results

There were eight patients in both Group I (arteriography) and Group II (non-arteriography). Group I consisted of six males and two females, with an average age of 49.1 years. There were no clinical events associated with arteriography. In Group II, there were five males, three females and an average age of 55.8 years (table I). Seven of eight patients in each group had ischemic events within two weeks, while one patient in each group had a stable deficit. Three of the Group II patients had cerebral arteriography performed at least 3 months prior to, or following, the serial plasma samples. The reasons for not performing arteriography on the remaining five Group II patients were: posterior circulation ischemia (two patients), extensive neurological deficits (two patients), and presumed small vessel disease (one patient). No patient had evidence of polycythemia, thrombocytosis, or renal failure.

Among Group I patients, BTG levels on day one were 19.1 ± 8.1 ng/ml (mean ± SEM) and on day two were 22.5 ± 8.4 ng/ml. Among Group II patients, BTG levels on day one were 19.8 ± 1.8 ng/ml, while on day two the levels were 17.0 ± 2.2 ng/ml. The mean difference (day two minus day one) was significantly greater for Group I patients when compared to Group II patients (p < .05). Seven of eight Group I
patients had an increase on day two, compared to only two of eight Group II patients (p < .05). BTG levels for the three case report patients, with plasma collected two to nine months following the arteriographic episodes, were within normal limits.

Among Group I patients, there were no ecchymoses noted over femoral puncture sites. There were no significant increases of BUN (17.4 ± 2.7 mg/dl day one vs 17.0 ± 3.2 mg/dl day two, mean ± SD), creatinine (1.3 ± 0.3 mg/dl day one vs 1.2 ± 0.3 mg/dl day two), or cortisol (10.9 ± 2.6 mg/dl day one vs 7.6 ± 1.3 mg/dl day two). All but two Group I patients were fully anticoagulated with heparin prior to and shortly after arteriography or were taking aspirin. The patients receiving heparin or aspirin (n = 6) had a mean BTG increase of 2.8 ng/ml, while the patients taking neither medication had a mean increase of 5.0 ng/ml. Patients with unilateral carotid injections (n = 4), bilateral carotid injections (n = 3), bilateral carotid injections (n = 1) had increases of 1.4 ± 0.3 ng/ml (mean ± standard deviation), 1.2 ± 0.5 ng/ml, and 5.0 ng/ml, respectively. In contrast, the control group showed smaller changes with a mean BTG decrease. One explanation for the diminished BTG for the control group lies in the fact that all but one patient had recent cerebral ischemic episodes. Diminishing platelet activation is known to occur following such episodes, and may account for the reduction in BTG seen here.

There are several possible mechanisms for platelet activation in association with arteriography. Measurable changes in BTG might result from arterial thrombosis following femoral puncture or platelet aggregation and thrombus formation on arterial catheters during arteriography. Contrast-induced hemorrhological changes, consisting of increased blood viscosity and reduced erythrocyte aggregation and deformability, could induce altered platelet function. Additionally, interactions between platelet membrane and contrast agents might occur, similar to those between erythrocyte membranes and these ionic, hypertonic contrast agents might occur, similar to those between erythrocyte membranes and contrast agents.

### Table 1: Clinical and BTG Data

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*C1 = unilateral selective carotid, C2 = bilateral selective carotid, A = arch study. †A = aspirin, H = heparin, O = no anticoagulants or antiplatelet agents.

### Discussion

Our case reports document episodes of cerebral ischemia occurring 6 to 48 hours following arteriography. Two patients had previously experienced cerebral ischemic episodes, while one was likely at risk for cerebral ischemia due to symptoms of myocardial ischemia. Nevertheless, it is of note that all three patients had new symptoms following arteriography, without recurrence at follow-up of 14–20 months. Thus, it seems reasonable to speculate that these symptoms were related to the arteriograms.

It is not immediately apparent what the mechanism might be for delayed cerebral ischemia following arteriography. Catheter-induced embolism or spasm would appear to be unlikely, due to the delay in onset of these episodes. Contrast media may cause marked alteration of the blood-brain barrier, with neurological symptoms usually consisting of cortical blindness. Postarteriographic CT scans in these patients may show extensive contrast enhancement. While our patients did not have such CT scans, the strikingly focal, delayed nature of their symptoms suggest an alternate mechanism.

Our experimental study indicates that increased platelet activation occurs in some patients 24 hours after cerebral arteriography. This supports the findings of Gawel et al, who, using an earlier collection procedure for BTG, described increased platelet activation following cerebral arteriography. In our study, the changes in platelet activation were demonstrated with a mean BTG increase of 3.4 ng/ml for Group I patients. In contrast, the control group showed smaller changes with a mean BTG decrease. One explanation for the diminished BTG for the control group lies in the fact that all but one patient had recent cerebral ischemic episodes. Diminishing platelet activation is known to occur following such episodes, and may account for the reduction in BTG seen here.
contrast agents, resulting in altered platelet function.

Elevations of BTG may represent a risk factor for stroke among patients with transient cerebral ischemia. The elevations in our study were smaller than those noted to be a significant risk for stroke. However, some trends seen in this study include the tendency for larger increases in platelet activation to occur in patients with more extensive arteriographic procedures and among those not taking anticoagulants or anti-platelet agents. While these trends clearly need to be studied in a larger patient population, they raise the possibility of the existence of a subset of arteriogram patients with increased levels of platelet activation comparable to those demonstrated to be at risk for stroke.

Based on the current study, we believe that ischemic episodes occurring within 48 hours following arteriography may be considered as possible complications of the procedure. The underlying mechanism for such episodes is unclear, but may include increased platelet activation superimposed on pre-existing vascular disease. Further studies are needed to determine how this increased platelet activation is modified by the extent of the arteriographic procedure and the administration of anticoagulant or antiplatelet medications.

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References

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