# Transient Neurological Events During Dipyridamole Stress Test: An Arterial Steal Phenomenon?

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Dipyridamole-associated adverse neurological side effects have not been extensively described. We present two cases of dipyridamole-associated transient motor neurological events with no evidence of residual neurological deficits detected clinically or by head CT. The patients showed no evidence of significant extracranial (internal carotid) artery disease. We propose the presence of a regional cerebral perfusion disturbance due to an intracranial vascular steal phenomenon as the mechanism for the above side effects of dipyridamole.

**Key Words:** dipyridamole; exercise; neurological manifestations

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Dipyridamole stress myocardial imaging is a widely used and successful technique for diagnosing and evaluating coronary artery disease. Neurological adverse effects of intravenous dipyridamole have not been extensively described despite multiple studies involving more than 15,000 patients to date (*1–6*). Headache and dizziness have been reported to occur in approximately 12% of these patients. However, there have been only two prior case reports of serious neurological adverse effects of dipyridamole (one cerebral vascular accident and one transient ischemic attack) (*7,8*). Serious neurological effects are conceivable because of the resultant hemodynamic effect of an intravenous dipyridamole infusion.

We present two cases of transient motor neurological deficits associated with dipyridamole and discuss the intracerebral vascular steal phenomenon as a possible pathophysiological mechanism.

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## CASE REPORTS

### Patient One

A 74-yr-old caucasian male with noninsulin-dependent diabetes mellitus was referred for dipyridamole $^{201}$Tl scintigraphy with the diagnosis of pericarditis to evaluate potential coronary artery disease. He had a history of right Bell's palsy 40 yr prior and a transient right oculomotor (third) nerve paralysis 8 yr prior. Two years prior, both a head CT and an MRI scan were performed. The head CT revealed very mild generalized atrophy. The MRI revealed a few nonspecific, very small foci of prolonged T2 relaxation time. Since then, he had been neurologically asymptomatic without aspirin or anticoagulant therapy.

The cardiovascular examination was unremarkable: blood pressure of 102/60 mmHg, heart rate of 52 beats/min (sinus rhythm) and no carotid bruits. Myocardial perfusion was evaluated by dipyridamole $^{201}$Tl test. Dipyridamole (0.56 mg/kg undiluted) was injected via an antecubital vein over 4 min under ECG and blood pressure cuff monitoring. Isometric handgrip exercise was then performed for the following 3 min. The patient was instructed to grip a plastic bag containing 500 ml of normal saline for approximately 30 sec followed by a 5-sec rest period for a total of 3 min. After exercise, blood pressure was 115/70 mmHg and heart rate 62 beats/min. A 1-min intravenous infusion of 125 mg of aminophylline was given for mild chest pain 3 min postexercise. Blood pressure and heart rate did not change. Five minutes later, the patient complained of speech difficulty and lower extremity weakness; dysarthria and right leg paresis were present on neurological examination. Aspirin (100 mg) was given orally immediately and 1.0 liter of intravenous normal saline was administered over the following hour.

Twelve hours later, his neurologic deficit resolved. A subsequent continuous-wave Doppler scan was normal for both internal carotid arteries. A real-time B-mode scan revealed small (<0.5 mm) bilateral carotid plaques. The follow-up head CT scan again showed very mild generalized atrophy. A recurrent episode of transient left oculomotor (third) nerve paralysis occurred 12 mo later. Otherwise, he has been asymptomatic on a 28-mo follow-up examination.

### Patient Two

A 64-yr-old normotensive, nondiabetic caucasian male, had a myocardial infarction and subsequent coronary artery bypass grafting 15 yr prior and had compensated congestive heart failure (LVEF 35%). He had no history of neurological disease. Baseline cardiovascular examination was normal: no carotid bruits, blood

pressure of 105/70 mmHg, and heart rate of 53 beats/min (sinus rhythm). A routine intravenous dipyridamole $^{201}$Tl test was performed as described above for Patient 1. During isometric handgrip exercise, Patient 2 complained of right lower extremity paresthesias. He then developed a right lower extremity motor weakness, more pronounced distally. Handgrip exercise was stopped. His blood pressure was then 105/60 mmHg and his heart rate was 78 beats/min. A 1-min intravenous infusion of 125 mg of aminophylline was administered 2.5 min after exercise cessation but did not lead to any change in his neurological status. One liter of normal saline solution was then given during the following 30-min image acquisition time.

After imaging was completed, the neurological findings persisted but resolved 36 hr after the study. Two days later, the symptoms and signs returned and persisted for 10 hr. After the symptoms disappeared, a neurological examination was normal. Pentoxifylline therapy was started. A subsequent head CT scan was unremarkable as was a continuous-wave Doppler scan for both internal carotid arteries. A real-time B-mode scan revealed small plaques in the right internal carotid artery (<0.5 mm) and small-medium nonhemodynamically significant plaques in the left internal carotid artery. This patient remained neurologically asymptomatic on a 15-mo follow-up examination.

## DISCUSSION

The two above-presented patients experienced transient motor neurological deficits immediately following an intravenous dipyridamole infusion. To the best of our knowledge, only two other cases of serious neurological complication associated with dipyridamole infusion have been reported. Pounds et al. described the occurrence of a transient ischemic attack 25 min postdipyridamole injection (*7*). This 25-min delay in symptoms does not contradict the temporal linkage of events since the physiologic dipyridamole effect may persist 30 min postinfusion (*1,9*). Whiting et al. reported a cerebrovascular accident 6.5 min after intravenous administration of a dipyridamole dose (0.56 mg/kg) (*8*); a cerebral angiogram revealed bilateral carotid stenoses (>70% luminal narrowing) with good antegrade flow and a normal intracerebral circulation.

Dipyridamole is a phosphodiesterase inhibitor which increases endogenous levels of the potent vasodilator adenosine (*9*). The peak vasodilatory effect of intravenous dipyridamole occurs 6 min following initiation of a 4-min infusion (standard dose, 0.56 mg/kg) (*1,9*). Systemic hemodynamic effects of dipyridamole include an approximate 5% decrease in systolic arterial pressure and a reflex increase in heart rate of 10–20 beats/min (*1*). The study of cerebral and systemic circulatory effects of dipyridamole and adenosine-induced arterial hypotension in the canine model has shown that cerebral blood flow decreases by 28% and cerebral vascular resistance decreases by 53% (*10*); blood flow reduction was most noted in the cerebral cortex. However, in a rabbit model, dipyridamole (with a 0.25 mg/kg intravenous bolus) provoked generalized cerebral blood flow augmentation (*11*). Additional evidence in animal models supporting an active role for dipyridamole or adenosine in cerebral vasodilatory autoregulation may be found in the presence of adenosine receptors in both the cerebral cortex and cerebral microvasculature and in adenosine's transportability across the blood-brain barrier (*12*).

The mechanism of dipyridamole's adverse neurological side effects remains unclear. One possible explanation is the production of a neurological deficit due to a direct toxic effect on the nervous system. Alternatively, this deficit may be a result of cerebral perfusion disturbances associated with the systemic hemodynamic actions, as well as the local cerebrovascular effects of dipyridamole (*1,2,10,12*). A regional reduction in cerebral blood flow may be caused by either a generalized decrease in cerebral blood flow (watershed phenomenon) or a vascular steal phenomenon. A vascular steal phenomenon may occur in any vascular bed when one portion of the bed is supplied by a patent artery and the adjacent portion is supplied by a severely stenosed artery in the setting of a generalized vasodilatation.

Coronary vascular steal phenomenon associated with dipyridamole has been well substantiated by clinical, angiographic and laboratory data (*13–15*). The fall in the distal coronary blood flow is associated with a redistribution of blood from endocardial to epicardial layers (*14*). The presence of well-demonstrated "good" coronary collateral vessels and the increase in rate-pressure product after dipyridamole infusion are the only significant predictors of dipyridamole-induced ischemic ST segment depression and may further substantiate the phenomenon of coronary steal (*15*). Such a phenomenon is conceivable in noncardiac vascular beds and in particular cerebrovascular. Therefore, abnormal neurological effects may theoretically occur in the context of extracranial and intracranial vascular pathology.

Our two patients demonstrated no evidence of significant extracranial vascular disease as assessed by both continuous wave Doppler and real time B-mode scanning. These two techniques, when combined, result in a high diagnostic accuracy, comparable to that of angiography (*16*). Therefore, for our two patients, the dipyridamole-associated motor neurological deficit does not seem to occur in the setting of extracranial vascular disease. Interestingly, there were 96 patients who comprised a subgroup out of 882 patients who underwent this study (according to the protocol detailed for Patients 1 and 2) at Hadassah University Hospital between 1990 and 1993. They had angiographically documented (luminal stenosis ≥70%; 65% unilateral disease, 35% bilateral) and perioperatively verified atherosclerotic internal carotid artery disease. None of these 96 patients experienced motor neurological adverse effects during intravenous dipyridamole plus handgrip exercise $^{201}$Tl testing.

As for intracranial vascular pathology, the presence of an occult cerebral arterial narrowing with vasodilation in the adjacent vessel resulting in a cerebral vascular steal phenomenon may explain the neurological events observed in our two patients. These two patients had no CT

and Patient 1 showed no MRI evidence of focal brain disease. Although the MRI and CT findings in Patient 1 are commonly seen in older patients, they may also indicate mild intracranial cerebrovascular disease. Furthermore, if disease is present, it would support the existence of an arterial narrowing and a possible steal phenomenon.

The pathophysiological discussion should also address the possible effects of handgrip exercise and aminophylline on cerebral circulation. Moderate isometric handgrip exercise may immediately raise systemic systolic blood pressure by 20–40 mmHg (*17*) by heart rate and cardiac output elevation and later by increased peripheral vascular resistance (*18*). When observing the combined effects of dipyridamole infusion followed by isometric handgrip exercise, systemic arterial pressure may rise rather than fall (*2*) as was the case for Patient 1, or remain almost unchanged, as for Patient 2. However, handgrip exercise is known to induce a focal cerebral blood flow increase in the corresponding cortical motor area (*19*) which may be more relevant to the hypothesis of a vascular steal phenomenon.

Both patients received intravenous aminophylline to reverse the dipyridamole effect. Patient 1 received aminophylline 6 min after the end of dipyridamole infusion and Patient 2 received it to ameliorate his acute neurological deficit. Aminophylline is an adenosine antagonist and therefore reverses the physiological changes attributed to dipyridamole. Aminophylline is also known to increase cerebral vascular resistance with an accompanying decrease in cerebral blood flow (*20*). Therefore, aminophylline may have precipitated (Patient 1) or aggravated (Patient 2) the neurological deficits of the above two patients. However, even if the intravenous aminophylline reversed dipyridamole's hemodynamic effect immediately, the lack of an immediate resolution of the neurological deficit is not surprising: transient ischemic insults to the cerebral tissue may result in prolonged neurological deficits. An unanswered issue concerns the transient recurrence of Patient 2's neurological symptoms 2 days following his initial event.

## CONCLUSION

We have presented two cases of transient motor neurological deficits temporally related to a stress protocol including intravenous dipyridamole infusion and isometric handgrip exercise. There have been only two prior cases reported thus far in the literature. Although the mechanism of the neurological adverse effects is not elucidated, extracranial internal carotid disease did not appear to be a risk factor. We, therefore, suggest that a transient regional cerebral blood flow disturbance occurred which may have been related to an intracranial cerebral vascular steal phenomenon. However, additional adverse effects of aminophylline may not be excluded.

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