Adverse Response to Nifedipine in Unstable Angina Pectoris*

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A patient had accelerated attacks of chest pain associated with transient ST elevation or depression in the anterior leads. Coronary angiogram revealed severe multi-vessel disease. Anginal attacks with conspicuous ST depression were induced repeatedly by both oral and sublingual administration of nifedipine. Among various vasodilator drugs tested on this patient, dipyridamole and hydralazine induced anginal attacks. These observations suggest that anginal attacks induced by administration of nifedipine may be related to the augmentation of myocardial oxygen consumption due to increases in cardiac output and heart rate, the coronary steal phenomenon, or an increase in venous return accompanied by the subendocardial underperfusion.

Calcium antagonists represent an important, new class of antianginal drugs. The clinical application of these agents has verified their efficacy in the treatment of variant angina and their indications are now expanded to various types of angina including stable and unstable angina and even to acute myocardial infarction. The pharmacologic effect is proved to be due to an inhibition of calcium influx across the cell membrane. Nifedipine is the most potent coronary dilator among the drugs known as calcium antagonists by reducing coronary arteriolar resistance. Serious side effects such as hypotension or worsening angina are believed to be rare. We report a very unusual response to nifedipine in a patient with unstable angina pectoris.

**CASE REPORT**

A 68-year-old man was admitted to another hospital on July 4, 1980 because of accelerated attacks of anterior chest pain. He gave a ten-year history of angina of effort, with the progression to anginal attacks at rest in the last year. The symptoms became aggravated and refractory to medical therapy and he was transferred to Kobe University Hospital on July 11. On admission, the blood pressure was 130/90 mm Hg and the heart rate, 80/min. Physical examination was normal except for a systolic murmur (Levine 2/6) at the apex. Serial enzyme determinations were in the normal range throughout the hospitalization period. The cardiothoracic ratio on chest x-ray film was 0.5. The electrocardiogram during the pain-free period showed a complete right bundle branch block with the evidence of old inferior myocardial infarct and slight ST depression in $V_{6}$. The electrocardiogram during the pain-free period showed a complete right bundle branch block with the evidence of old inferior myocardial infarct and slight ST depression in $V_{4}$ (Fig 1A). Each episode was relieved by sublingual nitroglycerin. Handgrip test induced chest pain accompanied by transient myocardial ischemia which was demonstrated by ECG and $^{201}$Tl-myocardial scintigram, whereas the cold pressor test gave negative findings. He performed mild exercise, without any medications, by walking on level floor at a speed of 2 miles/hr for 8 min under careful monitoring. This procedure repeatedly induced chest pain associated with ischemic changes on the ECG. After the documentation of myocardial ischemia on the ECG during frequent episodes of spontaneous and exercise-induced chest pain, he was started on therapy with nifedipine, the vasolytic agent, for prophylaxis of anginal attacks.

About 20 minutes after the test oral administration of nifedipine (10 mg), severe chest pain developed lasting for 30 minutes. The electrocardiogram during the attack showed...

**Figure 1.** The ECG during the pain-free period (A), during the anginal attack on one occasion (B), and the other occasion (C).
that this adverse response is reproducible. Coronary arteriograms revealed that the patient had quadruple vessel disease, ie, 75 percent stenoses of the right coronary artery and the left main artery, 50 percent stenosis of the anterior descending artery, and 99 percent stenosis of the left circumflex artery. Collateral vessels were poorly developed. Left ventricular end-diastolic pressure was 37 mm Hg. Further studies have examined the effects of other vasodilator drugs (Table 1). Among various vasodilating agents, dipyridamole and hydralazine induced episodes of chest pain accompanied by electrocardiographic ischemic signs. The administration of di-propranolol, isosorbide dinitrate and molsidomine did not induce anginal attacks and showed beneficial effects on exercise tolerance.

**Discussion**

The patient presented here had crescendo-type anginal attacks. During the attack, the ECG showed ST elevation on one occasion and at all other times ST depression. It is uncertain whether coronary spasm may play a role as the mechanism of episodes of chest pain in patients with unstable angina.1

In this patient with multivessel disease, anginal attacks were induced repeatedly by both oral and sublingual administration of nifedipine.

Similar cases have been reported briefly by Jariwalla et al2 and Keidar et al.3 In most of these cases, the reproducibility of ischemic chest pain and electrocardiographic evidence of ST-segment alteration were lacking.

To clarify the mechanism of an adverse response to nifedipine, various vasodilator drugs were tested with hemodynamic observations on this patient. Several explanations should be discussed from these results.

**Figure 2.** The ECG during an episode of chest pain induced by nifedipine administration.

![ECG during an episode of chest pain induced by nifedipine administration](image)

Conspicuous ST depression in V4, (Fig 2) similar to findings during spontaneous attacks. Both sublingual and oral administrations of nifedipine 10 mg provoked the same symptoms accompanied by electrocardiographic changes two more times except earlier onset of chest pain occurring seven minutes after sublingual administration, confirming

**Table 1—Comparison of the Effects of Various Vasodilator Drugs on the Hemodynamics and Provocation of an Anginal Attack**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>mAP Before (mm Hg)</th>
<th>mAP After (mm Hg)</th>
<th>%</th>
<th>mAP Before (mm Hg)</th>
<th>mAP After (mm Hg)</th>
<th>%</th>
<th>HR Before (/min)</th>
<th>HR After (/min)</th>
<th>%c</th>
<th>DP ÷ c</th>
<th>Chest Pain</th>
<th>ECG Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine (10 mg sublingual)</td>
<td>142/92</td>
<td>134/84</td>
<td>-7.3</td>
<td>79</td>
<td>85</td>
<td>+7.5</td>
<td>1.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10 mg oral)</td>
<td>152/86</td>
<td>130/80</td>
<td>-10.5</td>
<td>74</td>
<td>84</td>
<td>+13.5</td>
<td>+1.6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>Dipyridamole (0.6 mg/kg iv)</td>
<td>150/90</td>
<td>150/90</td>
<td>0</td>
<td>74</td>
<td>82</td>
<td>+10.8</td>
<td>+10.8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminophylline (4 mg/kg iv)</td>
<td>160/90</td>
<td>+3</td>
<td>81</td>
<td>+9.5</td>
<td>0</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine (10 mg/kg iv)</td>
<td>132/78</td>
<td>122/78</td>
<td>-3.4</td>
<td>84</td>
<td>92</td>
<td>+9.5</td>
<td>+1.2</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td></td>
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<tr>
<td>Isosorbide dinitrate (5 mg sublingual) + exercise</td>
<td>140/80</td>
<td>122/80</td>
<td>-6.0</td>
<td>69</td>
<td>74</td>
<td>+7.2</td>
<td>-6.5</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molsidomine (2 mg sublingual) + exercise</td>
<td>144/86</td>
<td>132/84</td>
<td>-5.0</td>
<td>80</td>
<td>86</td>
<td>+7.5</td>
<td>-2.1</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Propranolol (0.1 mg/kg iv) + exercise</td>
<td>150/90</td>
<td>150/90</td>
<td>0</td>
<td>81</td>
<td>70</td>
<td>-13.6</td>
<td>-13.6</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Prostaglandin E1 (2.5 r/min iv)</td>
<td>142/88</td>
<td>132/76</td>
<td>-10.7</td>
<td>81</td>
<td>89</td>
<td>+9.9</td>
<td>+2.1</td>
<td>-</td>
<td>-</td>
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The figures indicate the values immediately before the onset or disappearance of chest pain compared with those before administration. mAP = mean blood pressure; HR = heart rate; DP = double product. + indicates occurrence of an anginal attack, and - shows no anginal attack.
One explanation for the induction of an anginal attack may be that nifedipine alters systemic hemodynamics, i.e., increases in cardiac output and heart rate resulting in augmentation of myocardial oxygen consumption. In contrast, the other agent with similar effects such as PGE, did not induce myocardial ischemia.

The second explanation may relate to the possibility that nifedipine induces an anginal attack by coronary steal mechanism in patients with multiple coronary stenoses. In this patient we were able to induce the attack by injecting dipyridamole which might be associated with coronary steal phenomenon, i.e., the diversion of blood flow from ischemic to nonischemic areas by the disproportional decrease in driving pressure for collateral channels. The steal is believed to be related to greater dilation of small coronary arteries in nonischemic areas. The alternative explanation for a coronary steal is the diversion of blood flow from subendocardium to subepicardium in regions supplied by severely stenosed coronary artery.

Lastly, the possibility should also be considered that nifedipine, hydralazine and dipyridamole mainly dilate systemic resistance vessels (arterioles) resulting in an increase in venous return. The elevation in left ventricular filling pressure may deteriorate subendocardial underperfusion in the area supplied by the stenosed coronary artery. This deleterious effect of vasodilators is suggested by an experimental study. In contrast, the vasodilatory effects of isosorbide dinitrate, molsidomine and PGE, are principally on the systemic capacitance vessels (veins) resulting in a reduction in preload with a diminished ventricular wall tension. This report represents an isolated instance, but if more such cases are recognized, caution should be required in using the calcium antagonist, nifedipine, in patients with unstable angina pectoris compromised by severe multivessel disease.

REFERENCES


Can Pulmonary Barotrauma Cause Cerebral Air Embolism in a Non-Diver?*

C. Gresham Bayne, CDR, MC, USN; and Terrie Wurzbacher, LCDR, MC, USN

It is generally assumed that only the diver exiting a compressed air environment is at risk for the complications of systemic air embolism following pulmonary barotrauma. We present a case of sudden death following a swimming pool dive, with evidence supporting a diagnosis of fatal systemic air embolism.

Each year in the United States there are some 7,000 drownings, most of which occur in young, healthy men, in and around pools or other swimming areas. Many of these fatalities are associated with a lucid interval between surfacing and subsequent collapse. In addition to these post-immersion syndromes, divers are at risk from an event called "shallow water blackout" whereby a scuba diver swimming at or near the surface suddenly convulses or loses consciousness and sinks to the bottom. Another form of "shallow water blackout" occurs when breathhold divers attempting a distance swim lose consciousness and drown, presumably from hypoxia.

As early as 1906, the possibility of air embolism as a cause of drowning was presented, but no documentation has appeared. We believe the following case supports the clinical entity of fatal systemic air embolism in a free swimmer.

CASE REPORT

A 21-year-old white man with no diving history was swimming in a crowded military pool. The history given independently by his two friends and an observer who, by chance, happened to be the chief pharmacist of our hospital, is that he tried to swim across the 25 yard pool underwater at the six foot depth. Failing on the second try, he stood up and immediately had the onset of headache, dizziness and "tingling all over." Helped out of the pool by his friends, he complained of nausea, severe dizziness and was quoted as saying "my lungs are hurting." No history of true vertigo, cough or shortness of breath could be obtained from the observers. After five minutes, he was helped to the dressing room, sat down and continued to complain of nausea and dizziness. After vomiting once, he said he felt better, but immediately had a grand mal seizure lasting about five minutes. Lifeguards trained in cardiopulmonary resuscitation, (CPR), reported he was pulseless and apneic after the seizure ended spontaneously. CPR was begun immediately with paramedics on-scene in 15 minutes.

*From the Emergency Medicine Service, and the Clinical Investigation Center, Naval Regional Medical Center, San Diego. Supported in part by the Bureau of Medicine and Surgery Clinical Investigation Program, Protocol No. 0-16-1445. The opinions or assertions expressed herein are those of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy or the naval service at large.

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