CORRESPONDENCE

Lack of Evidence that p-Synephrine is Responsible for STEMI

To the Editor:

I am writing with respect to the case report by Thomas and colleagues,[1] published in the *Texas Heart Institute Journal*, regarding ST-segment-elevation myocardial infarction (STEMI) in a young man who was taking the supplement Nutrex Lipo-6x®. I am not defending the product. The patient most assuredly experienced a cardiovascular event, which may or may not have been associated with the use of the supplement.

Nutrex Lipo-6x contains at least 7 alkaloids. Contrary to the discussion in the original article, one cannot, on the basis of standard structure-to-activity relationships, equate the pharmacokinetic and pharmacodynamic properties of p-synephrine with ephedrine, due to the major structural differences clearly pointed out by the authors. As a result of these stereochemical differences, p-synephrine exhibits little α-adrenergic receptor binding activity and has correspondingly limited cardiovascular effects. Therefore, it is impossible to conclude that one of these alkaloids, namely p-synephrine, was responsible for the event or was "the most likely culprit."

Of note, widely consumed juice from mandarin oranges grown in Placer County, California, contains as much as 158 mg p-synephrine per liter (U.S. Department of Agriculture). An 8-oz glass of this juice contains about twice the amount of synephrine as a serving of the product in question. Furthermore, more than 100 million doses of p-synephrine have been consumed without apparent ill effects. Thus, the margin of safety of p-synephrine greatly exceeds that of aspirin and acetaminophen, as well as all prescription weight-management drugs.

Rather than point an accusatory finger at synephrine in their title, the authors should have referred to a "multi-alkaloid-containing supplement." The other case reports cited by the authors also involved such products, and, as pointed out by the authors, there were confounding factors in conjunction with these reports. As a consequence, I contend that any assertion or suggestion that these effects are due to or associated with p-synephrine or *Citrus aurantium* is not justified.[2]

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References

1. Thomas JE, Munir JA, McIntyre PZ, Ferguson MA. STEMI in a 24-year-old man after use of a synephrine-containing dietary supplement: a case report and review of the literature. Tex Heart Inst J 2009;36(6):586-90.
2. Stohs SJ, Shara M. A review of the safety and efficacy of Citrus aurantium in weight management. In: Bagchi D, Preuss HG, editors. Obesity: epidemiology, pathophysiology, and prevention. Boca Raton (FL): CRC Press; 2007. p. 371-82.

This letter was referred to Dr. Thomas and colleagues, who reply in this manner:

We appreciate Dr. Stohs's interest in our case report of a young man with an ST-segment myocardial infarction that occurred after taking the ephedra-free supplement Nutrex Lipo-6x®.[1] This supplement contains several pharmaceutical components that are reported by the makers to burn fat. The alkaloid in question is synephrine. This compound is the replacement for ephedrine in most "ephedra-free" dietary weight-loss supplements. As described in the original article, although synephrine has structural differences from ephedrine, certain isomers of synephrine can still affect cardiovascular function.

The para isomer (p-synephrine) does have α-adrenergic effects but is believed to exert its primary effects on the β_3-adrenergic receptors—responsible for lipolysis and the removal and oxidation of fat from adipose tissues. The meta isomer (such as m-synephrine, phenylephrine, and neosynephrine) acts on the α_1, β_1, and β_2 receptors and therefore exerts more cardiovascular effects.[2,3] Furthermore, in small trials, dietary supplements containing synephrine have been shown to cause elevated blood pressure after exercise.[4]

As we indicated,[1] the dietary weight-loss supplement Nutrex Lipo-6x contains multiple stimulant compounds that may have contributed to our patient's myocardial infarction. Of the compounds discussed, synephrine is the one most widely reported to be associated with adverse cardiovascular events, including myocardial infarction, tachycardia, hypertension, and sudden cardiac death. We agree with Dr. Stohs that it is not possible to know with certainty the precise metabolic agent or synergistic interaction that caused the myocardial infarction in our patient. Nevertheless, given the known cardiovascular effects of synephrine, the results of trials indicating that synephrine-containing dietary supplements affect blood pressure, and the numerous case reports of adverse cardiovascular events with syneph-

rine-containing products, we believe that synephrine remains the most likely culprit in this case.

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1. Thomas JE, Munir JA, McIntyre PZ, Ferguson MA. STEMI in a 24-year-old man after use of a synephrine-containing dietary supplement: a case report and review of the literature. Tex Heart Inst J 2009;36(6):586-90.
2. Stohs SJ, Shara M. A review of the safety and efficacy of Citrus aurantium in weight management. In: Bagchi D, Preuss HG, editors. Obesity: epidemiology, pathophysiology, and prevention. Boca Raton (FL): CRC Press; 2007. p. 371-82.
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4. Haller CA, Duan M, Jacob P 3rd, Benowitz N. Human pharmacology of a performance-enhancing dietary supplement under resting and exercise conditions. Br J Clin Pharmacol 2008;65(6):833-40.

A Third Treatment Option for Entrapped Thrombus in Patent Foramen Ovale

To the Editor:

In the report published in your journal by Erkut and colleagues,[1] "Entrapped Thrombus in a Patent Foramen Ovale," two different therapies were suggested for entrapped or left-sided thrombus: thrombolytic and surgical treatment. We would like to report a third treatment option, which we successfully applied in a similar patient.

A 68-year-old woman presented at our emergency clinic with dyspnea, palpitations, acute-onset chest pain, and left-leg swelling. She had a history of chronic obstructive pulmonary disease and chronic atrial fibrillation. Doppler ultrasonography of the lower extremities revealed deep-vein thrombosis in the left leg. Transthoracic echocardiography showed normal systolic function, right atrial and right ventricular enlargement, and grade-2 tricuspid regurgitation. The pulmonary artery systolic pressure was estimated to be 55 mmHg. There was a mobile, multilobular mass in the left atrium, attached to the interatrial septum. For better delineation of the mass and atria, we performed transesophageal echocardiography (TEE): 2- and 3-dimensional TEE showed a 4 × 5-cm multilobular, homogeneously echogenic mobile mass attached to patent foramen ovale (Figs. 1 and 2). These findings were confirmed by TEE with contrast medium. No mass was seen on the right atrial side. It is likely that a thrombus from the right side dislodged, because the patient was diagnosed with pulmonary embolism by use of clinical and laboratory tests. We treated the patient with unfractionated heparin bolus and infusion, monitored with regular aPTT follow-up tests. Two days later, transthoracic echocardiography showed that the thrombus on the left side had disappeared (Fig. 3). The patient was discharged from the hospital on warfarin therapy.

It is possible that the interatrial septal mass was not seen on follow-up echocardiography because it had embolized to a peripheral location in the interim—this is always a risk. However, we do not believe that this occurred in our patient, because of her improved clinical picture. In the report by Erkut and colleagues,[1] two different therapies were suggested.[2,3] We recommend that

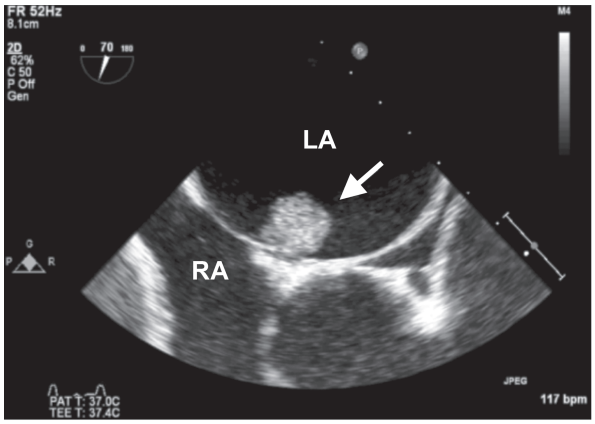

Fig. 1 *Two-dimensional transesophageal echocardiography shows thrombus (arrow) attached to the interatrial septum.*

LA = left atrium; RA = right atrium

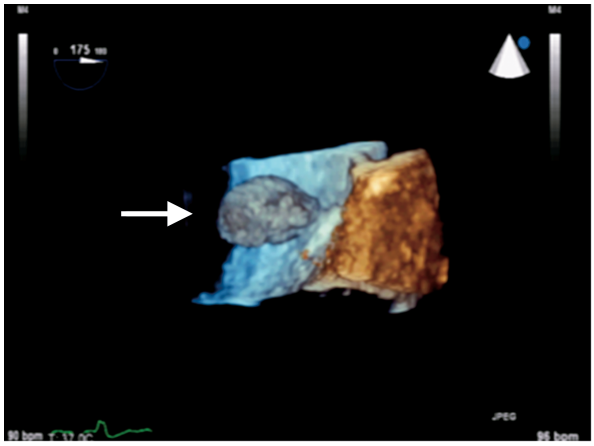

Fig. 2 *Three-dimensional transesophageal echocardiography shows a 4 × 5-cm multilobular, homogeneously echogenic mobile mass (arrow).*

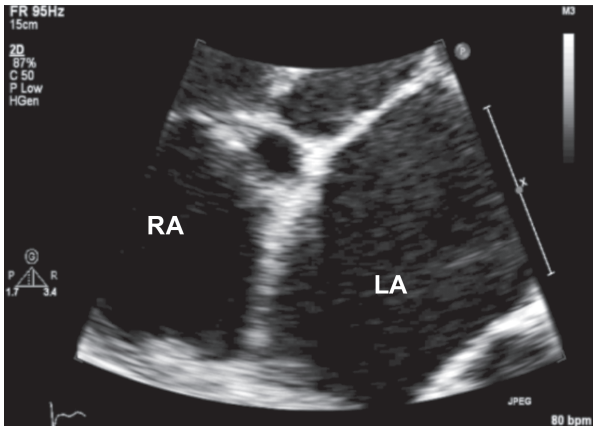

Fig. 3 *Two days after the institution of unfractionated heparin therapy, transthoracic echocardiography shows no thrombus on the left side.*

LA = left atrium; RA = right atrium

heparin infusion be considered as a third therapeutic option, depending on the urgency of the clinical situation.

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1. Erkut B, Sevimli S, Ates A, Erdem AF, Dogan N, Kantarci M. Entrapped thrombus in a patent foramen ovale: complicated by pulmonary embolism without paradoxical embolism. Tex Heart Inst J 2008;35(3):371-2.
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This letter was referred to Dr. Erkut, who replies in this manner:

I have read the letter, "A Third Treatment Option for Entrapped Thrombus in Patent Foramen Ovale" by Karabay and colleagues. They suggest the use of heparin as a third therapy for entrapped cardiac thrombi. I congratulate them on their successful application of this treatment.

Alternative treatment methods must be considered individually in patients with entrapped thrombi, in accordance with the situation of the patient and the thrombi. When surgical removal seems too hazardous or inconvenient—especially in elderly patients—the use of heparin and oral anticoagulants with echocardiographic follow-up may be the best choice.

Anticoagulation and thrombolytic therapy during medical treatment can lead to secondary complications such as embolization, that can threaten the life of the patient; however, there is no report of such a complication after surgery.

In brief, I agree that heparin therapy should be given to high-risk elderly surgical patients and to those for whom thrombolytic therapy would not be suitable.

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