DOI: 10.1111/echo.12149

New-Onset Seizure after Perflutren Microbubble Injection during Dobutamine Stress Echocardiography

Adriana Quiñones, M.D., Ricardo Benenstein, M.D., and Muhamed Saric, M.D., Ph.D.

Leon H. Charney Division of Cardiology, New York University Langone Medical Center, New York, New York

Intravenous microbubble contrast agents are frequently used during ultrasound imaging to improve endocardial border detection, enhance Doppler signals, differentiate thrombi from tumors or define vascular anatomy. Dobutamine stress echocardiography (DSE) with or without addition of atropine is a standard technique for evaluation of coronary artery disease. Noncontrast or contrast-enhanced DSE is generally considered a safe procedure. We report what appears to be the first case of new-onset seizure activity following perflutren microbubble contrast injection during dobutamine-atropine stress echocardiography. On the basis of this single occurrence, we are only able to demonstrate a temporal, but not a causal relationship between the administration of microbubble echo contrast and onset of seizure. We do not suggest withholding administration of microbubble contrast when clinically indicated. However, increased vigilance in monitoring for seizure development in patients receiving microbubble contrast seems warranted. (Echocardiography 2013;30:E95-E97)

Key words: dobutamine stress echocardiography, side effects, seizure, perflutren

Case Report:

A 58-year-old morbidly obese woman with diabetes mellitus, hypertension, and no known prior neurologic disorder was referred for dobutamine stress echocardiography (DSE) as a part of preoperative evaluation prior to gastric banding.

At rest, she was in sinus rhythm with a heart rate (HR) of 54 beats per minute (bpm); blood pressure (BP) was 130/61 mmHg and room air oxygen saturation was normal. Resting electrocardiogram (EKG) (Cardiac Assessment System for Exercise Testing, GE Healthcare, Freiburg, Germany) showed sinus bradycardia, poor R-wave progression, nonspecific ST/T wave abnormalities, and a corrected QT interval of 440 msec (normal 450–460 msec in women). There were no significant abnormalities on the resting transthoracic echocardiogram (HP Sonos 7500, Philips Medical Systems, Andover, MA, USA). However, left ventricular endocardial border delineation was suboptimal necessitating the use of intravenous perflutren microbubble contrast (Definity; Lantheus Medical Imaging, N. Billerica, MA, USA) throughout dobutamine stress testing. Per laboratory protocol, 1.3 mL of activated Definity is diluted with 8.7 mL of preservative-free saline in a 10 mL syringe (referred by manufacturer insert as the "diluted IV bolus" dosing option).

Dobutamine was infused intravenously at increasing doses to a maximum of 40 μg/kg per minute. At peak dobutamine dose, she also received 0.25 mg of atropine sulfate intravenously. She reached a peak HR of 127 bpm (78% of maximum age predicted HR) and a peak BP of 156/75 mmHg. The test was stopped at patient's request because medications made her feel "scared." She received between 1 mL and 1.5 mL of diluted intravenous boluses of Definity per stage, for a total of 5 mL of diluted Definity. There was neither EKG nor echocardiographic evidence of inducible ischemia. Left ventricular ejection fraction increased from 65% at rest to 75% at peak infusion. At peak dobutamine infusion, EKG revealed sinus tachycardia with peak HR of 127 bpm. There were occasional premature ventricular contractions, couplets, triplets, and short runs of up to four beats of nonsustained ventricular tachycardia. Ventricular ectopy resolved spontaneously within 1 minute of cessation of dobutamine infusion. Sinus tachycardia resolved within 9 minutes of cessation of dobutamine infusion. There were no sustained arrhythmias or arrhythmias beyond what is expected and often seen after infusion of dobutamine for stress testing.

Patient was alert and awake upon completion of DSE. About 10 minutes into recovery, she

Address for correspondence and reprint request: Muhamed Saric, M.D., Noninvasive Cardiology Laboratory, New York University Medical Center, 560 First Avenue, New York, NY 10016. Fax: (212)-263-8461;
E-mail: muhamed.saric@nyumc.org

became unresponsive and was noted to have intermittent myoclonic jerks of both shoulders as well as intermittent lip smacking. There were no focal neurological deficits.

Vital signs were stable with HR of 78 bpm, BP of 130/61 and room air oxygen saturation of 100%. Finger stick glucose level was normal (99 mg/dL; normal 70–100 mg/dL). Onset of symptoms was approximately 15 minutes after the last dose of Definity.

A clinical diagnosis of typical temporal lobe seizure was established by the neurologist. She was given 1 mg of intravenous lorazepam. Duration of seizure activity was approximately 5 minutes before its termination by sedation. Her level of awareness improved, she started following commands and her myoclonic jerks and lip smacking resolved.

Urgent noncontrast computed tomography (CT) (Somatom, Siemens Healthcare, Erlangenm, Germany) of the head revealed mild to moderate microvascular changes, but no acute findings. Electroencephalogram (EEG) (Nicolet EEG, Natus Medical, Incorporated, San Carlos, CA, USA), performed shortly after head CT, demonstrated focal slowing in the left temporal region and a small number of left frontotemporal sharp waves, probably epileptiform. Magnetic resonance imaging (MRI) (Magnetom, Siemens) of the brain performed the following day showed focal gliosis and susceptibility changes within the posterior left temporal lobe, likely secondary to prior ischemia versus postcontusional etiology. There was no evidence of acute infarct. Mild hippocampal asymmetry and moderate microvascular disease were also noted.

Upon further questioning, she reported that 4 weeks prior to DSE, she suffered a fall with head trauma, which resulted in a brief episode of loss of consciousness, without associated nausea or vomiting. She thereafter developed left-sided headaches. Based on clinical, EEG and imaging findings, the diagnosis of complex partial seizure was made. She was started on levetiracetam and had no further seizures.

Discussion:

Dobutamine stress testing enhanced by addition of atropine is generally considered a safe procedure. The rate of major complication (such as myocardial infarction, ventricular arrhythmias, and death) been reported at approximately 0.25%.[1,2] To our knowledge, there are no published case reports of seizures during noncontrast dobutamine-atropine stress testing.

To enhance endocardial border delineation, intravenous echocardiographic contrast is frequently used during echocardiography. Ultrasound contrast agents are microbubbles with a thin, relatively permeable shell, filled with a high molecular weight gas, such as a perflutren. In the United States, there are 2 perflutren-containing echocardiographic contrast agents approved by the Food and Drug Administration (FDA): Optison, which has a shell derived from human serum albumin (GE Healthcare, Princeton, NJ, USA), and Definity, a lipid coated microbubble formed from a long chain lipid and an emulsifier, which is activated by agitation prior to use. Neither Optison nor Definity package insert specifically lists seizures as a known side effect of perflutren microbubble contrast use. The only approved indication is improvement of left ventricular endocardial border detection. Off-label use of perflutren microbubble contrast is prevalent and includes enhancement of Doppler signals, differentiation of thrombi from tumors and delineation of vascular anatomy during both cardiac and noncardiac ultrasound imaging.[3–6]

Single and multicenter retrospective analysis comparing noncontrast and contrast-enhanced echocardiography studies have shown no significant difference in the rate and type of adverse reactions.[7–9] A single center review of 16,025 patients who received intravenous echocardiographic contrast agents reported an overall rate of any adverse event of 0.12% and an incidence of serious adverse events of 0.031%. As part of this series, there is mention of only one patient with end-stage renal disease and known history of prior seizures, suffering a seizure 15–20 minutes following a DSE with echocardiographic contrast.[10] A multicenter, retrospective analysis, which included data on a total of 66,164 doses of Definity and 12,219 doses of Optison, reported an incidence of 0.01% severe adverse reactions, mainly anaphylactoid reactions. There were no cases of seizures in this report.[11]

FDA issued a black box warning in 2007, later revised in 2008, regarding possible serious side effects of microbubble contrast agents. The warning, however, did not include seizures or other neurologic complications.[12] Subsequently, the American Society of Echocardiography (ASE) released a consensus statement concluding that there is large body of evidence establishing the safety of approved microbubble contrast agents. Current contraindications to perflutren microbubble contrast use include known hypersensitivity to the products, right-to-left or bidirectional cardiac shunts.

Whether the seizure episode in our patient was temporally or causally related to medications administered during her pharmacologic stress echocardiogram is uncertain. It is highly unlikely

that seizures were triggered by dobutamine or atropine use alone. Our case report raises the possibility that seizure activity may have been associated with the administration of microbubble ultrasound contrast agents in this patient with evidence of prior cerebral injury and possible predisposition to seizures.

The recent head injury could have predisposed the patient to develop seizures following administration of microbubble contrast. However, complex partial seizures are uncommon in the setting of trauma.[13] To our knowledge, this is the first case report of an association between perflutren microbubble contrast use and new-onset seizure activity at time of dobutamine-atropine stress echocardiography. On the basis of this single occurrence, we are only able to demonstrate a temporal, but not a causal relationship between the administration of Definity echo contrast and onset of seizure. We do not routinely code for history of seizure disorders in our echo database. However, given the high volume of our lab, it is likely that other patients with history of seizure disorder have received Definity with no ill effect. We do not plan to withhold administration of Definity contrast when clinically indicated. However, we will increase our vigilance in monitoring for seizure development in patients receiving Definity contrast.

References

1. Mathias W, Arruda A, Santos FC, et al: Safety of dobutamine atropine stress echocardiography: A prospective experience of 4033 consecutive studies. *J Am Soc Echocardiogr* 1999;12:785–791.
2. Varga A, Garcia MA, Picano E: Safety of stress echocardiography (from the International Stress Echo Complication Registry). *Am J Cardiol* 2006;98:541–543.
3. Mulvagh SL, Rakowski H, Vannan MA, et al: American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. *J Am Soc Echocardiogr* 2008;21:1180–1201.
4. Stoupakis G, Fuhrman MA, Dabu L, et al: The use of contrast echocardiography in the diagnosis of an unusual case of congestive heart failure: Achalasia. *Echocardiography* 2004;21:149–152.
5. Jang HJ, Kim TK, Burns PN, et al: Enhancement patterns of hepatocellular carcinoma at contrast-enhanced US: comparison with histologic differentiation. *Radiology* 2007;244:898–906.
6. Fleischer AC, Lyshchik A, Andreotti RF, et al: Advances in sonographic detection of ovarian cancer: Depiction of tumor neovascularity with microbubbles. *AJR Am J Roentgenol* 2010;194:343–348.
7. Shaikh K, Chang SM, Peterson L, et al: Safety of contrast administration for endocardial enhancement during stress echocardiography compared with noncontrast stress. *Am J Cardiol* 2008;102:1444–1450.
8. Dolan MS, Gala SS, Dodla S, et al: Safety and efficacy of commercially available ultrasound contrast agents for rest and stress echocardiography a multicenter experience. *J Am Coll Cardiol* 2009;53:32–38.
9. Abdelmoneim SS, Bernier M, Scott CG, et al: Safety of contrast agent use during stress echocardiography: A 4-year experience from a single-center cohort study of 26,774 patients. *JACC Cardiovasc Imaging* 2009;2:1048–1056.
10. Herzog C: Incidence of adverse events associated with use of perflutren contrast agents for echocardiography. *JAMA* 2008; 299:2023–2025.
11. Wei K, et al: The safety of definity and optison for ultrasound image enhancement: A retrospective analysis of 78,383 administered contrast doses. *J Am Soc Echocardiogr* 2008;21:1202–1206.
12. US Food and Drug Administration. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110260.htm (accessed August 15, 2011).
13. Lee ST, Lui TN: Early seizures after mild closed head injury. *J Neurosurg* 1992;76:435–439.