Bubble trouble: anaphylactic shock, threatened myocardial infarction, and transient renal failure after intravenous echo contrast for left ventricular cavity opacification preceding dobutamine stress echo

Adrian Ionescu*

Morriston Cardiac Centre, Morriston, Swansea SA6 6NL, Wales, UK

Received 23 January 2009; accepted after revision 9 May 2009; online publish-ahead-of-print 13 June 2009

Echo contrast agents are widely used and safe but can rarely produce serious side effects. This—to the author’s knowledge—is the first detailed published case report of a patient who had a severe and complex sequence of adverse reactions within 3 min of having an intravenous infusion of Sonovue initiated, and where the causal connection between Sonovue and the adverse reaction is not diluted by potential side effects from dobutamine.

KEYWORDS
Sonovue; Anaphylactic shock; Dobutamine stress echo

Left ventricular opacification with transpulmonary intravenous contrast agents (‘echo contrast’) is widely used to enhance diagnostic accuracy and to reduce observer-related variability during rest and stress echocardiography. Ultrasonic contrast has been repeatedly on the ‘radar’ of regulatory bodies such as the FDA1 in the USA or EMEA2 in Europe, on a background of vocal reaction from various segments of the echocardiographic community.3,4

The aim of this paper is to present the clinical case of a patient who developed a rare but dramatic sequence of reversible complications from exposure to Sonovue, and to offer a brief review of the relevant literature.

Case report

A 55-year-old obese man with a history of type 2 diabetes mellitus on insulin and Metformin, documented three-vessel coronary artery disease and angioplasty to a diagonal branch of his LAD 6 weeks earlier, was referred for elective dobutamine stress echo (DSE).

The patient had been angina-free since his angioplasty 6 weeks earlier. His resting observations and ECG (Figure 1) before DSE were normal. There was no history of allergy. His systemic arterial pressure was 138/72 mmHg (sitting).

Apical images of the left ventricle were obtained using harmonic imaging. The endocardial border definition was very poor (see Supplementary data, Film 1), so an infusion of sulphur hexafluoride (Sonovue, Bracco Imaging, Plan-les-Ouates, Geneva, Switzerland) via a VuJect pump (Bracco) at a rate of 0.8 mL/min was started. The apical four-, two-, and three-chamber views were obtained after cavity opacification, using a mechanical index of 0.3, with marked improvement of the endocardial border definition compared with earlier, and demonstrating normal left ventricular systolic function (see Supplementary data, Film 2).

Three minutes after the start of the Sonovue infusion, and without any other drug or infusion having been given, the patient reported paresthesias over his face and head, and then severe dizziness, after which he became unresponsive. The Sonovue infusion was discontinued and the line disconnected. He developed sinus bradycardia (30 b.p.m.), and his systemic arterial pressure was 60 mmHg systolic. Atropine 600 μg was given i.v. resulting in restored normal heart rate, but the blood pressure remained low; 200 mg of hydrocortisone and 10 mg of chlorpheniramine were given i.v. and a ‘free-running’ infusion of normal saline was started. At this point, the patient had a tonic–clonic fit and received 5 mg of Midazolam i.v. A faintly erythematous blanching rash was now visible on the patient’s chest and abdomen.

Systolic blood pressure remained 50–60 mmHg, and the adrenaline syringe was opened, when we noted ST segment elevation in leads 2, 3, aVF, and V1-V3 (Figure 2). To avoid
worsening myocardial ischaemia, we decided to give i.v. boluses of 100 μg of phenylephrine (a 'pure' arterial vasoconstrictor) rather than adrenaline, and after three boluses, his blood pressure increased to 90 mmHg systolic. He complained of chest pain, and intra-aortic balloon counter-pulsation was considered briefly; however, within 5 min, the ECG normalized and the chest pain subsided. The patient was transferred to the CCU, where an erythematous rash associated with mild oedema became visible around his eyes and on his torso. His systolic blood pressure dropped again to 70 mmHg but this time, there was no chest pain or ECG changes. Intravenous saline was continued, and an infusion of phenylephrine was started and titrated to maintain a systolic pressure above 100 mmHg. The phenylephrine could be discontinued 4 h later and his blood pressure and other vital signs and ECG remained stable; the rash disappeared.

Cardiac troponin T was measured 12 h later and was normal (<0.03 ng/mL). Serum creatinine, which had been normal at the time of his angioplasty 6 weeks earlier, was now elevated at 164 mmol/L. He had, however, a good diuresis overnight and was allowed to go home next morning in a
stable clinical condition. The creatinine level had come back to normal 24 h later. Another DSE was not attempted.

**Discussion**

In Europe, Sonovue is the only transpulmonary agent available for heart chamber opacification during echocardiography. In the USA, Definity and Optison are approved for this indication.

In May 2004, the use of Sonovue for echocardiography was temporarily suspended in Europe by the EMEA following ‘3 fatal cases in patients at high underlying risk for fatal cardiac complications’, which occurred after exposure to the agent. This suspension was withdrawn 1 year later, but an expanded list of contraindications to the use of Sonovue was inserted in the product information sheet: ‘recent acute coronary syndrome, clinically unstable cardiac disease (evolving/ongoing acute myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery interventions or other factors suggesting clinical instability’.

In the USA, the FDA changed labelling requirements for ultrasound contrast agents in September 2007 to include a ‘Black Box’ warning and the recommendation to monitor ultrasound contrast agents in September 2007 to include a clinical instability’. Sonovue was inserted in the product information sheet: an expanded list of contraindications to the use of cardiac complications’, which occurred after exposure to ‘3 fatal cases in patients at high underlying risk for fatal infarctions. A Spanish group reported a single case of possible anaphylaxis (out of 175 studies) when Sonovue was given at peak dobutamine dose only, and the Thoraccentre group referred to a case of possible anaphylaxis with this agent, but it is not clear whether this occurred during dobutamine co-administration; the ‘case report’ consists of four sentences in a review paper. Another Dutch review paper from 2004 mentions three anaphylactic reactions in the Netherlands, but the clinical details are sketchy. In an update of their experience with Sonovue in 2009, the Thoraccentre reports that during 352 consecutive cardiac Sonovue studies, seven patients (2.0%) experienced adverse effects. Four patients (1.1%) had mild allergic reactions [], and three patients (0.9%) experienced a severe allergic reaction resulting in (nonfatal) shock, a much higher incidence than that reported in the post-marketing surveillance studies.

During DSE, it may be impossible to distinguish between the side effects of the dobutamine and those of the contrast agent. In the case presented here, the causal link between the contrast agent and the side effects is established without doubt, and it highlights the fact that, like any other substance given to patients for diagnostic or treatment purposes, Sonovue can cause life-threatening reactions.

In conclusion, echocardiographic contrast agents, which are indispensable for the accurate interpretation of DSE, are among the safest pharmacological agents known in medicine. Side effects are usually minor and self-limiting, but severe, life-threatening anaphylactic shock can rarely occur. It is essential that these agents be administered only in a safe environment where full resuscitation facilities are available.

**Supplementary data**

Supplementary data are available at *European Journal of Echocardiography* online.

**References**


