

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*

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

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

KEYWORDS

Sonovue;
Anaphylactic shock;
Dobutamine stress echo

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.

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 in the right arm (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

* Corresponding author. Tel: +44 179 270 3195; fax: +44 179 270 3544.
E-mail address: adrian.ionescu@swansea-tr.wales.nhs.uk

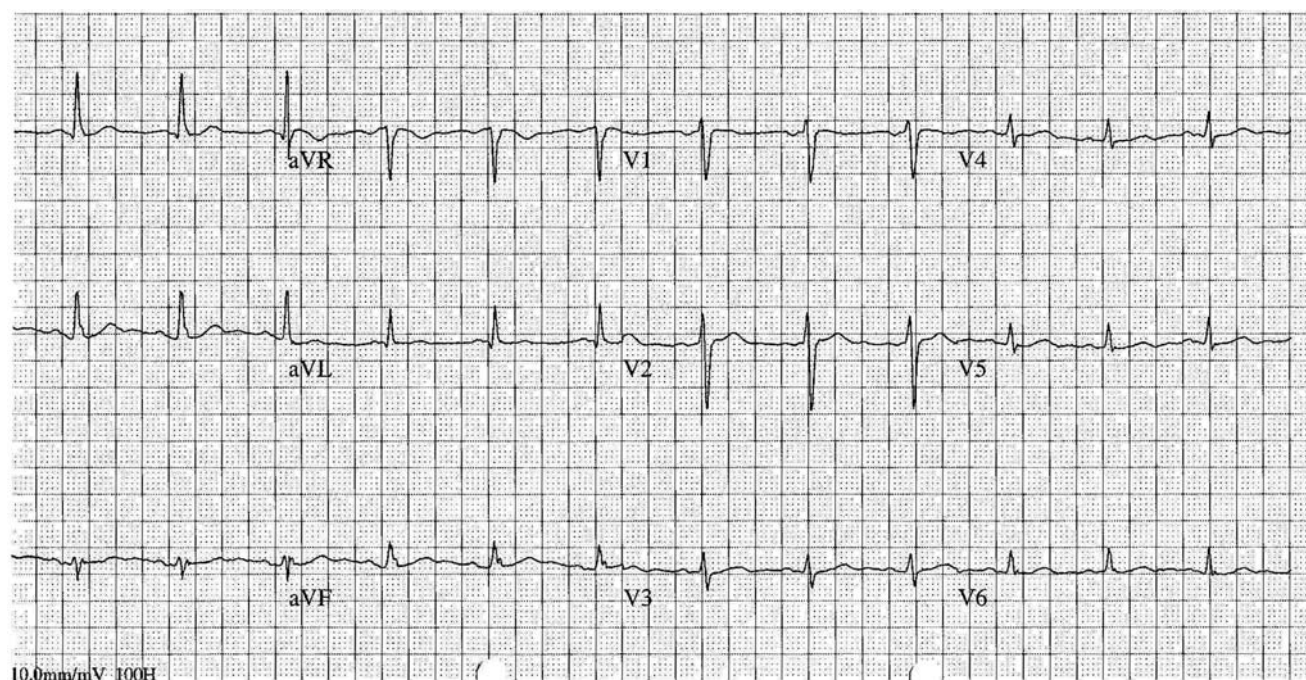


Figure 1

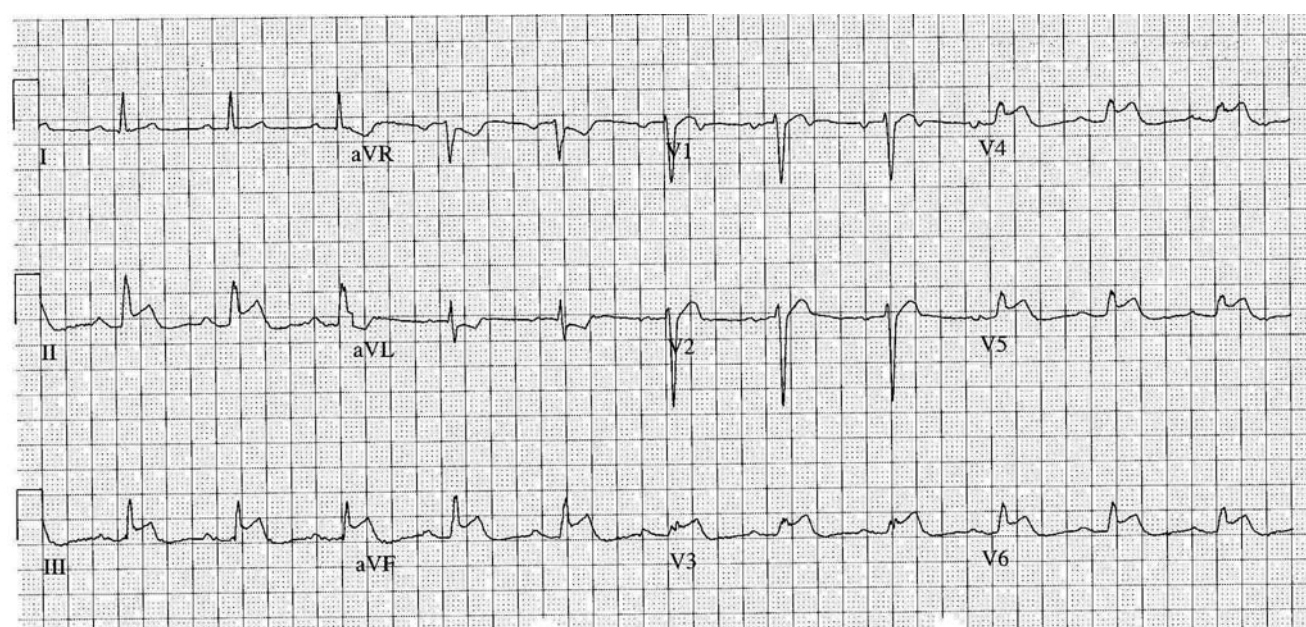


Figure 2

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 µmol/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 EMEA² 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 vital signs, electrocardiography, and pO_2 saturation for 30 min after administration.¹ This was prompted by the occurrence of four deaths occurring in a temporal relationship to the administration of Definity; however, it is important to place this in the context of a total of approximately 2 million doses of Definity administered since its introduction. Serious side effects have been reported to occur at a rate of 0.014% for Sonovue and ≤ 0.002 for Optison.⁵ This compares very favourably with the rates of adverse effects observed with other cardiology tests: exercise test has a risk of death or myocardial infarction of 1:2500, whereas cardiac catheterization carries a 1:500 risk of major cardiopulmonary and neurological events⁶ as well as with the risk of other contrast-enhanced non-invasive imaging tests.⁷

In May and June 2008, the FDA relaxed the contraindications to the use of contrast, which now include worsening or clinically unstable congestive heart failure, acute myocardial infarction or acute coronary syndromes, serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval, respiratory failure, severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension.¹

In a large, retrospective, multicentre experience with 42 408 patients, exposure to Definity or Optison carried no additional risk of death or myocardial infarction when compared with patients undergoing echocardiography without contrast agents.⁸ In a much larger registry of over 4 million patients exposed to contrast also had no increase in the risk of death compared with those not exposed.⁹

In a prospective series of 751 patients having DSE in Oxford, Sonovue or Optison was used in 419, and overall, 4% had side effects (excluding ectopic beats), with no difference between groups, no fatalities, and no myocardial infarctions.¹⁰ A Spanish group¹¹ reported a single case of possible anaphylaxis (out of 175 studies) when Sonovue was given at peak dobutamine dose only, and the Thoraxcentre group referred to a case of possible anaphylaxis with this

agent, but it is not clear whether this occurred during dobutamine co-administration¹²; 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.¹³ In an update of their experience with Sonovue in 2009, the Thoraxcentre 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.¹⁴

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,¹⁵ 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

1. <http://www.fda.gov/cder/drug/infopage/microbubble/default.htm> accessed online 19 January 2009.
2. The European Agency for the Evaluation of Medicinal Products. Public statement on Sonovue. New contraindication in patients with heart disease. Restriction of use to non-cardiac imaging. London, 19 May 2004, EMEA/CMPM/212/04.
3. Main ML, Goldman JH, Grayburn PA. Thinking outside the 'box'—the ultrasound contrast controversy. *J Am Coll Cardiol* 2007;**50**:2434–7.
4. Grayburn PA. 'Product safety' compromises patient safety (an unjustified black box warning on ultrasound contrast agents by the Food and Drug Administration). *Am J Cardiol* 2008;**101**:892–3.
5. Van Camp G, Droogmans S, Cosyns B. Bio-effects of contrast ultrasound agents in daily clinical practice: fact or fiction? *Eur Heart J* 2007;**28**:1190–2.
6. Lindner JL, Wei K. Action or over-reaction? *J Am Coll Cardiol* 2008;**1**:109–10.
7. Dijkman PA, Visser CA, Kamp O. Adverse reactions to ultrasound contrast agents: is the risk worth the benefit? *Eur J Echocardiogr* 2005;**6**:363–6.
8. Dolan MS, Gala SS, Dodla S *et al.* Safety and efficacy of commercially available ultrasound contrast agents for rest and stress echocardiography. *J Am Coll Cardiol* 2009;**53**:32–8.
9. Main ML, Ryan AC, Davis TE, Albano MP, Kusnetzky LL, Hibberd M. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent (multicenter registry results in 4,300,966 consecutive patients). *Am J Cardiol* 2008;**102**:1742–6.
10. Timperley J, Mitchell ARJ, Thibault H, Mirza IH, Becher H. Safety of contrast Dobutamine stress echocardiography: a single center experience. *J Am Soc Echocardiogr* 2005;**18**:163–7.
11. Calvo D, de la Hera JM, Lee D.-H. Contrast echocardiography and clinical safety. *Rev Esp Cardiol* 2006;**59**:397–401.

12. de Groot MC, van Zwieten-Boot BJ, van Grootheest AC. Severe adverse reactions after the use of sulphur hexafluoride (SonoVue) as an ultrasonographic agent. *Ned Tijdschr Geneesk* 2004;**148**:1887–8.
13. Galema TW, Geleijnse ML, Vletter WB, de Laat L, Michels M, ten Cate FJ. Clinical usefulness of SonoVue contrast echocardiography: the Thorax-centre experience. *Neth Heart J* 2007;**15**:55–60.
14. Geleijnse ML, Nemes A, Vletter WB, Michels M, Soliman O II, Caliskan K *et al*. Adverse reactions after the use of sulphur hexafluoride (SonoVue) echo contrast agent. *J Cardiovasc Med* 2009;**10**:75–7.
15. Mulvagh SL, Vannan M, Abdelmoneim SS *et al*. ASE consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography. *J Am Soc Echocardiogr* 2008;**20**:1179–1201.