Clinical usefulness of SonoVue contrast echocardiography: the Thoraxcentre experience

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Although other imaging techniques, such as magnetic resonance imaging and computer tomography, are becoming more and more important in cardiology, two-dimensional echocardiography is still the most used technique in clinical cardiology. Quantification of left ventricular function and dimensions is important because therapeutic strategies, for example implanting an ICD after myocardial infarction, are based on ejection fraction measurements. Because of the sometimes low quality of echocardiographic images we started to use an ultrasound contrast agent and in this article we describe our experiences with SonoVue, a second-generation contrast agent, over a three-year period in the Thoraxcentre. (*Neth Heart J* 2007;15:55-60.)

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Two-dimensional echocardiography is the main diagnostic technique for most cardiac diagnoses. Although considerable technical improvements have been achieved during the last decades, poor acoustic windows are still an important limiting factor of transthoracic echocardiography. Ultrasound contrast agents that traverse the pulmonary circulation and opacify the left cardiac chambers may overcome this limitation and have proven to be important for the assessment

of left ventricular (LV) border detection and function.^{1,2} An overview of the use of ultrasound contrast agents was published in this journal in 1998.^{3,4} SonoVue, a commercially available contrast agent, has been used in the Netherlands since 2001. In this article we report our SonoVue experience during a three-year period from 2002 to 2004.

Contrast agent

SonoVue (Bracco, Milan, Italy) is based on stabilised sulphur hexafluoride microbubbles surrounded by a phospholipid shell with a mean size of 2.5 μm .⁵ After mixing with saline, a manual process that takes less than one minute (figure 1), a suspension is obtained with SonoVue microbubbles in a concentration of 1 to 5 $\times 10^8$ per ml. This suspension should be injected intravenously in a straight access through a three-way stopcock (to avoid destruction of the microbubbles) as a bolus (0.5 ml with additional 0.25 ml injections when necessary) followed by saline injection or as a continuous infusion by a dedicated pump delivered by the Bracco company. In our institute we only use bolus injections. It should be emphasised that it is important to constantly shake the suspension to keep the microbubbles soluble. For virtually all indications 5 ml of SonoVue is sufficient; simple questions (LV ejection fraction) can often be answered with only half this volume in 15 minutes.

Echocardiography

Transthoracic echocardiography was performed with the Philips Sonos 5500 (Philips, Best, the Netherlands) system with a S3 transducer in the second harmonic contrast-imaging mode. Transmit/receive frequency was 1.6/3.2 MHz and the mechanical index was 0.4 for endocardial border detection and 0.1 for myocardial perfusion imaging. Mechanical index reflects the normalised energy to which a target (such as a microbubble) is exposed in an ultrasound field. Normally this index ranges from 0.1 to 2.0. For myocardial perfusion studies power modulation imaging was used. With this technique, differences in acoustic properties of microbubbles and tissue result in selective enhancement of microbubble-generated reflections

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Figure 1. SonoVue file including syringe and needle.

but suppression of reflections from cardiac tissues. To visualise myocardial contrast bubble replenishment with real-time power modulation imaging, at peak contrast intensity the microbubbles in the myocardium were first destroyed with flash imaging with high a mechanical index (1.6).

The basic assumption underlying power modulation imaging is that the reflective properties of cardiac

structures, unlike those of microbubbles, are mostly linear.⁶ Power modulation uses this assumption by transmitting repeated pulses of different intensities in the same direction (figure 2). Two consecutive pulses of identical shape but twofold difference in amplitude would result in identical reflections from the heart, other than the expected twofold difference in amplitude. The smaller pulse is then multiplied by 2 and subtracted from the larger one, resulting in a zero signal. When reflected by the nonlinear microbubbles, the same two pulses would differ from each other not only in amplitude but also in their shape. Amplifying the smaller pulse and subtracting it from the larger one would result in a nonzero signal. The amplitude of this signal is colour-coded and displayed in an overlay over the grey-scale image.

Real-time power modulation imaging was started after flash imaging with a high mechanical index (1.6) to destroy the microbubbles in the myocardium at peak contrast intensity in order to explore artefacts and to visualise myocardial contrast bubble replenishment.

Contrast applications

During the three-year period, 289 contrast studies were performed in 241 patients (48 patients underwent two studies because of a research protocol).⁷ As indicated in the next sections and in table 1, SonoVue was used for many different indications.

Figure 2. Upper panel shows myocardial reflection and lower panel microbubble reflection in power modulation mode (also see text for explanation). From: Mor-Avi V, et al. *Circulation* 2001;104:352-7.

Table 1. Overview of SonoVue contrast echocardiography applications.

Application	Patients	Reference
Research – completed		
- Myocardial perfusion after acute myocardial infarction	96	5
- Right ventricular visualisation in congenital heart disease	20	16
Research – ongoing		
- LV ejection fraction interobserver variability*	96	
- LV ejection fraction versus nuclear imaging	29	
- 3D stress echocardiography	14	
- Noncompaction cardiomyopathy	34	
- Arrhythmogenic right ventricular cardiomyopathy	8	
- Percutaneous transluminal septal myocardial ablation	43	
Routine use		
- Left ventricular ejection fraction	50	
- Dobutamine stress echocardiography	25	
- Differentiation of extra- and intra-cardiac structures	12	

*The same patients as in reference 5.

LV ejection fraction

As seen in figure 3, echo contrast improves endocardial border detection and therefore makes LV wall motion analysis⁸ and LV ejection fraction assessment^{9,10} more reliable. This improvement is reflected by an increase in intra- and inter-observer agreement of LV ejection fraction and volumes.^{9,10} In a recently completed study in our centre, LV ejection fraction inter-observer variability decreased from 16.9% with

second harmonic imaging to 7.0% with contrast imaging (unpublished data). Currently, we are using contrast for LV ejection fraction in several research protocols and in routine patients in whom accurate assessment of LV ejection fraction is necessary because of potential changes in clinical decision-making. Well-known examples of this latter include initiation of chemotherapy and implantation of an internal cardiac defibrillator.¹¹

Figure 3. Visualisation of endocardial border in four- and three-chamber images without (upper images) and with (lower images) contrast.

Figure 4. Intertrabecular recesses filling with contrast (*) and apical mobile thrombus in a patient with noncompaction cardiomyopathy.

Myocardial perfusion

Contrast myocardial perfusion reflects total myocardial capillary blood volume. One of the most promising applications of this new modality is in patients with acute myocardial infarction. We and others have shown that intact myocardial perfusion of infarcted myocardium assessed by contrast echocardiography can predict functional recovery in time.^{12,13} In addition, contrast echocardiography contributes to a better measurement of interventricular septal thickness and the combination of wall thickness >11 mm in the infarct region and intact perfusion is an excellent predictor of functional improvement.⁷

Another application of myocardial perfusion is in patients with hypertrophic cardiomyopathy undergoing percutaneous transluminal septal myocardial ablation. During this procedure a localised chemical septal myocardial infarction is induced by injection of ethanol into one or more septal branches. By infusion of echo contrast the specific septal branch that supplies

that part of the hypertrophied septum believed to produce LV outflow tract obstruction can be easily identified. In at least 10% of the procedures the echo contrast images change the selection of the septal branch.^{14,15}

Noncompaction cardiomyopathy

Noncompaction cardiomyopathy is a relatively rare congenital, unclassified cardiomyopathy that is characterised by excessively prominent trabecular meshwork and deep intertrabecular recesses, best evidenced by colour Doppler flow.¹⁶ Currently, we are studying the value of contrast echocardiography in these noncompaction patients. As seen in figure 4, we have described one patient in the literature in whom flow in the intertrabecular recesses could only be detected with the use of SonoVue contrast.¹⁷

Right ventricular function and morphology

Echocardiographic visualisation of the right ventricle remains a true challenge for the clinician. More reliable

Figure 5. Endocardial border detection of right ventricle without (left) and with contrast (right).

assessment of right ventricular dimension and function may be particularly useful in patients with congenital heart disease. In one study we demonstrated that in particular in the near-field images right ventricular contrast imaging gives a significantly better visibility of the endocardial border (figure 5).¹⁸ In addition, better identification of right ventricular trabeculation was possible, which may be important in the differentiation of right ventricular hypertrophy from marked trabeculation.

More recently, we started a research protocol in patients with a suspicion of arrhythmogenic right ventricular cardiomyopathy. According to existing guidelines echocardiography should be part of the diagnostic work-up. For the diagnosis of arrhythmogenic right ventricular cardiomyopathy visualisation of the right ventricle is important, but often difficult in routine echocardiography. We are currently examining whether contrast echocardiography can help in the visualisation of right ventricular aneurysms, (segmental) right ventricular dilatation and (regional) right ventricular hypokinesia, all criteria for the diagnosis of this cardiac disease.¹⁹

Stress echocardiography

The use of echo contrast improves interobserver agreement and diagnostic accuracy of dobutamine stress echocardiography, in particular in patients with sub-optimal image quality.^{8,20,21} The limited use of contrast in stress echocardiography in our centre is mainly due to the confidence of the observer during the described time period in its interpretation quality and to a lesser extent SonoVue costs. Because 3D real-time stress echocardiography suffers from a significant decrease in image quality compared with conventional 2D imaging we are convinced that contrast may play an even more important role in this new stress modality. At the moment the role of contrast in 3D real-time stress echocardiography is one of our main research interests.

Differentiation of extra- and intracardiac structures

Contrast echocardiography may also be helpful in the identification of cavities of unknown origin. Since newer contrast agents such as SonoVue pass the pulmonary circulation, the microbubbles can reach all intracardiac cavities. If opacification with SonoVue is limited to the cardiac chambers, the cavity of interest (figure 6) has no luminal connection to a cardiac chamber and is thus diagnosed as located extracardiacally.

Left ventricular thrombus detection

LV thrombus detection may have important implications with regard to the use of anticoagulant therapy. With conventional echocardiography it is sometimes difficult to image well-defined apical details. As seen in figure 4, besides the noncompaction cardiomyopathy, contrast echocardiography may also be of great help in the correct interpretation of the presence or absence of an apical LV thrombus.

Safety

During the described three-year study period, two of the 241 patients (1%) experienced mild hypotension, sinus tachycardia and skin flushing most likely caused by an allergic reaction to SonoVue. Both patients had received SonoVue for the second time and were successfully treated with intravenous clemastine and hydrocortisone. Before this study period we used SonoVue in a role-in phase in a patient to enhance endocardial border detection with dobutamine-stress echocardiography. He developed extensive skin erythema and anaphylactic shock with a decrease in blood pressure from 150/70 to 70/30 mmHg. After intravenously administered clemastine, hydrocortisone and volume, the patient rapidly recovered and was discharged the next day. This adverse event was reported to the European Medicines Agency (EMA). In 2004 several serious side effects with SonoVue were also reported by others²² and in a postmarketing

Figure 6. Patient with echinococcus cyst; contrast image shows no connection with left ventricle.

analysis of 157,838 SonoVue studies 19 cases of severe (0.0012%) and three cases of fatal adverse events (0.002%) were described (<http://www.emea.eu.int/humandocs/Humans/EPAR/sonovue/sonovue.htm>). All three patients with a fatal outcome had severe coronary artery disease and their clinical situation was far from stable. The allergic reactions may have been caused by the sulphur hexafluoride gas or the shell component polyethylene glycol (macrogel 4000).^{23,24} Subsequently, in May 2004 the EMEA recommended not to use SonoVue as an ultrasound agent in cardiology. After a review of the cases by the Committee for Human Medicinal Products in November 2004 the recommendations changed and the use of SonoVue was again allowed in cardiac ultrasound. However, SonoVue is still contraindicated in patients with recent unstable cardiac symptoms, a recent (<7 days) coronary intervention, class III and IV heart failure or serious arrhythmias. An allergic reaction should always be anticipated and antiallergic drugs should be available in addition to standard resuscitation equipment. It is also recommended to keep the patient under medical supervision during and for at least 30 minutes following the infusion of SonoVue.

Limitations of SonoVue contrast

As described before, SonoVue may have important side effects, which makes the attendance of a physician mandatory. Contrast echocardiography needs a different pre-setting of the echo machine (mechanical index, second harmonic imaging). Another limitation for the widespread use of SonoVue is costs because there is only a small reimbursement for contrast echocardiography.

Conclusion

When detailed morphological and/or quantitative information of the heart is needed echo contrast agents such as SonoVue may provide better and more reliable results. Imaging of myocardial perfusion will be a main area for future applications, but in our opinion it is not applicable for routine practice at this moment. Costs and safety issues will most likely determine the clinical future of SonoVue. ■

References

- Hundley WG, Kizilbash AM, Afridi I, Franco F, Peshock RM, Grayburn PA. Administration of an intravenous perfluorocarbon contrast agent improves echocardiographic determination of left ventricular volumes and ejection fraction: comparison with cine magnetic resonance imaging. *J Am Coll Cardiol* 1998;**32**:1426-32.
- Kasprzak JD, Paelinck B, Ten Cate FJ, et al. Comparison of native and contrast-enhanced harmonic echocardiography for visualization of left ventricular endocardial border. *Am J Cardiol* 1999;**83**:211-7.
- Sieswerda GT, Kamp O, Visser CA. The use of contrast agents in echocardiography. Part I: History, Principles and Developments in Agents and Ultrasound Technology. *Neth Heart J* 1998;**5**:583-8.
- Sieswerda GT, Kamp O, Visser CA. The use of contrast agents in echocardiography. Part II: clinical indications and experimental applications. *Neth Heart J* 1998;**5**:648-57.
- Schneider M. SonoVue, a new ultrasound contrast agent. *Eur Radiol* 1999;**9**(Suppl 3):S347-8.
- Mor-Avi V, Caiani EG, Collins KA, Korcarz CE, Bednarsz JE, Lang RM. Combined assessment of myocardial perfusion and regional left ventricular function by analysis of contrast-enhanced power modulation images. *Circulation* 2001;**104**:352-7.
- Biagini E, Galema TW, Schinkel AF, Vletter WB, Roelandt JR, Ten Cate FJ. Myocardial wall thickness predicts recovery of contractile function after primary coronary intervention for acute myocardial infarction. *J Am Coll Cardiol* 2004;**43**:1489-93.
- Dolan MS, Riad K, El-Shafei A, et al. Effect of intravenous contrast for left ventricular opacification and border definition on sensitivity and specificity of dobutamine stress echocardiography compared with coronary angiography in technically difficult patients. *Am Heart J* 2001;**142**:908-15.
- Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. *J Am Coll Cardiol* 2004;**44**:1030-5.
- Thomson HL, Basmadjian AJ, Rainbird AJ, et al. Contrast echocardiography improves the accuracy and reproducibility of left ventricular remodeling measurements: a prospective, randomly assigned, blinded study. *J Am Coll Cardiol* 2001;**38**:867-75.
- Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933-40.
- Rocchi G, Kasprzak JD, Galema TW, de Jong N, Ten Cate FJ. Usefulness of power Doppler contrast echocardiography to identify reperfusion after acute myocardial infarction. *Am J Cardiol* 2001;**87**:278-82.
- Sieswerda GT, Klein LJ, Kamp O, et al. Quantitative evaluation of myocardial perfusion in patients with revascularized myocardial infarction: comparison between intravenous myocardial contrast echocardiography and 99mTc-sestamibi single photon emission computed tomography. *Eur J Echocardiogr* 2004;**5**:41-50.
- Faber L, Seggewiss H, Gleichmann U. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: results with respect to intraprocedural myocardial contrast echocardiography. *Circulation* 1998;**98**:2415-21.
- Faber L, Seggewiss H, Welge D, et al. Echo-guided percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy: 7 years of experience. *Eur J Echocardiogr* 2004;**5**:347-55.
- Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart* 2001;**86**:666-71.
- de Laat LE, Galema TW, Krenning BJ, Roelandt JR. Diagnosis of non-compaction cardiomyopathy with contrast echocardiography. *Int J Cardiol* 2004;**94**:127-8.
- van den Bosch AE, Meijboom FJ, McGhie JS, Roos-Hesselink JW, Ten Cate FJ, Roelandt JR. Enhanced visualisation of the right ventricle by contrast echocardiography in congenital heart disease. *Eur J Echocardiogr* 2004;**5**:104-10.
- McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J* 1994;**71**:215-8.
- Mathias W, Jr. Arruda AL, Andrade JL, Filho OC, Porter TR. Endocardial border delineation during dobutamine infusion using contrast echocardiography. *Echocardiography* 2002;**19**:109-14.
- Ten Cate FJ. Usefulness of ultrasound contrast for image enhancement during stress echocardiography. *Echocardiography* 2002;**19**(7 Pt 2):621-5.
- de Groot MC, van Zwieten-Boot BJ, van Grootheest AC. [Severe adverse reactions after the use of sulphur hexafluoride (SonoVue) as an ultrasonographic contrast agent]. *Ned Tijdschr Geneesk* 2004;**148**:1887-8.
- Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. *Contact Dermatitis* 1978;**4**:135-8.
- Dewachter P, Mouton-Faivre C. Anaphylaxis to macrogol 4000 after a parenteral corticoid injection. *Allergy* 2005;**60**:705-6.