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Safety of contrast-enhanced echocardiography within 24 h after acute myocardial infarction

Gaetano Nucifora[1,2†], Nina Ajmone Marsan[1†], Hans-Marc J. Siebelink[1], Jacob M. van Werkhoven[1], Joanne D. Schuijf[1], Martin J. Schalij[1], Don Poldermans[3], Eduard R. Holman[1], and Jeroen J. Bax[1*]

[1]*Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, The Netherlands;* [2]*Department of Cardiology, University Hospital 'Santa Maria della Misericordia', Udine, Italy; and* [3]*Department of Cardiology, ThoraxCenter Rotterdam, Rotterdam, The Netherlands*

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KEYWORDS
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Aims Contrast-enhanced echocardiography is widely used to enhance left ventricular (LV) endocardial border delineation in stable patients with known or suspected coronary artery disease. In patients with acute myocardial infarction, accurate assessment of LV function and size is important, but data on the safety of contrast-enhanced echocardiography in the early stage of myocardial infarction (within 24 h) are lacking. In the current study, the experience on the safety of contrast-enhanced echocardiography within 24 h of acute myocardial infarction is reported.
Methods and results A total of 115 consecutive patients (58 $\pm$ 11 years; 77% male) admitted to the coronary care unit for ST-elevation acute myocardial infarction underwent clinically indicated contrast-enhanced echocardiography within 24 h of hospital admission to assess LV size and function. Perflutren (Luminity®, Bristol-Myers Squibb Pharma, Bruxelles, Belgium) was used as contrast agent. Safety was determined evaluating vital signs, physical examination, ECG, and adverse events. On contrast-enhanced echocardiography, the mean LV ejection fraction was 44 $\pm$ 11%, and 56% of patients had an LV ejection fraction $\leq$45%. Administration of echo contrast did not induce any significant change in vital signs, physical examination, and ECG. Major adverse events were not observed whereas minor events occurred in 4% of patients (hypersensitivity at the injection site in three and transient back pain in two).
Conclusion These data provide evidence on the safety of contrast-enhanced echocardiography in the first 24 h of myocardial infarction; larger patient cohorts are needed to confirm these findings.

Introduction

Contrast-enhanced echocardiography is widely used to provide cardiac chamber opacification and to improve left ventricular (LV) endocardial border delineation in patients with known or suspected coronary artery disease,[1] but data on the safety of contrast-enhanced echocardiography in patients in the first 24 h after acute myocardial infarction are lacking. It is, however, particularly important in this subset of patients to have accurate information on LV function and LV dimensions, both for therapeutic and prognostic reasons. In this article, we report the experience on the safety of contrast-enhanced echocardiography with Perflutren (Luminity®, Bristol-Myers Squibb Pharma, Bruxelles, Belgium) performed the first day after acute myocardial infarction.

Methods

Study population

Over a 6 months period, a total of 115 consecutive patients admitted to the coronary care unit for ST-elevation acute myocardial infarction underwent urgent coronary angiography and primary percutaneous coronary intervention. Contrast-enhanced echocardiography was clinically performed in the coronary care unit within 24 h of patients' admission to optimally evaluate LV dimensions, LV regional and global function and to exclude LV thrombus formation and mechanical complications of infarction.

Contrast-enhanced echocardiography

Patients were imaged in the left lateral decubitus position with a commercially available system (Vivid 7 Dimension, GE Healthcare,

* Corresponding author. Tel: +31 715262020; fax: +31 715266809.
E-mail address: j.j.bax@lumc.nl
† The first two authors contributed equally to this article and are shared first authors.

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Horten, Norway) equipped with an M3S phased array transducer (3.5 MHz).

Luminity® was used as contrast agent. Each patient received an infusion of 1.3 mL of echo contrast diluted in 50 mL of 0.9% NaCl solution through a 20 gauge intravenous catheter in a proximal forearm vein. Infusion rate was initially set at 4.0 mL/min and then titrated to achieve optimal LV cavity enhancement without attenuation artefacts.[2] Contrast-enhanced echocardiography was performed using harmonic imaging at low mechanical index (0.26). Images were obtained in the standard four-, two-, and three-chamber apical views, and care was taken to record the images at a phase when the contrast agent flow was relatively stable with absent or minimal swirling in the apex. Left ventricular end-diastolic (EDV) and end-systolic (ESV) volumes were measured according to the Simpson's biplane method[3] and LV ejection fraction was calculated as $[(EDV-ESV)/EDV] \times 100$. Qualitative assessment of the regional wall motion was performed according to the 16-segment model of the American Society of Echocardiography, and the global wall motion score index was calculated for each patient.[3] The three LV apical views were also systematically checked for the presence of LV thrombi and mechanical complications of infarction.

Safety monitoring

The safety of contrast-enhanced echocardiography was assessed by evaluating the vital signs (blood pressure and heart rate), physical examination, ECG, and occurrence of adverse events. Vital signs were assessed 10 min before the administration of echo contrast and repeated after 2, 15, 30, and 60 min. Physical examination was performed before and after contrast-enhanced echocardiography and daily until discharge. Furthermore, during hospitalization, all patients had continuous 12-lead ECG monitoring for the occurrence of arrhythmias and ischaemia and an additional standard single-lead ECG was monitored during the examination. All patients were evaluated for the occurrence of adverse events during echo contrast administration and the following days of hospitalization. The investigators characterized the intensity of potential adverse events.

Table 1 Clinical and echocardiographic characteristics of the patient population ($n = 115$)

Age (years)	58 ± 11
Gender (male/female)	88/27
Diabetes, *n* (%)	10 (9)
Family history of coronary artery disease, *n* (%)	48 (42)
Hypercholesterolaemia, *n* (%)	18 (16)
Hypertension, *n* (%)	40 (35)
Current or previous smoking, *n* (%)	73 (63)
Previous myocardial infarction, *n* (%)	11 (10)
Previous myocardial revascularization, *n* (%)	7 (6)
Body mass index (kg/m^2)	27 ± 4
Anterior myocardial infarction, *n* (%)	47 (41)
Infarct-related artery, *n* (%)	
Left anterior descending coronary artery	48 (42)
Left circumflex coronary artery	16 (14)
Right coronary artery	51 (44)
Multi-vessel disease, *n* (%)	39 (34)
Left ventricular end-diastolic volume (mL)	97 ± 25
Left ventricular end-systolic volume (mL)	54 ± 19
Left ventricular ejection fraction (%)	44 ± 11
$<35\%$, *n* (%)	24 (21)
35–45%, *n* (%)	40 (35)
$>45\%$, *n* (%)	51 (44)
Wall motion score index	1.9 ± 0.4

Statistical analysis

Continuous variables are expressed as mean and standard deviation. Categorical data are presented as absolute numbers and percentages.

Results

Study population

Clinical characteristics of the patients are summarized in *Table 1*. Mean age of the patients was 58 ± 11 years; 88 (77%) were male. The infarct-related artery was the left anterior descending coronary artery in 48 (42%) patients and obstructive multi-vessel disease (i.e. more than one vessel with a luminal narrowing $\geq 70\%$) was present in 39 (34%) patients.

Contrast-enhanced echocardiography

The mean infusion rate of echo contrast during echocardiography was 3.0 ± 0.6 mL/min and the total infusion dose was on average 16 μL/kg. As shown in *Table 1*, the mean LV ejection fraction was $44 \pm 11\%$, and 64 (56%) patients had an LV ejection fraction $\leq 45\%$. In all the patients, contrast-enhanced echocardiography excluded the presence of LV thrombi and mechanical complications of infarction, including seven patients in whom an apical thrombus was suspected based on non-enhanced 2D echocardiography.

Safety monitoring

Administration of echo contrast did not induce any significant change in vital signs, physical examination, and ECG. No death, acute myocardial infarction or other cardiovascular events occurred during the echocardiographic examination or the remaining hospitalization period. The only adverse events observed were transient hypersensitivity at the injection site (in three patients) and transient back pain (in two patients); all these adverse events were rated as mild in intensity and required no treatment.

Discussion

Echocardiography is readily available, can be quickly performed at bedside, and is frequently the primary test to evaluate LV size and function in patients with known or suspected coronary artery disease.[3] In patients with suboptimal acoustic windows, intravenous echo contrast is administered to improve endocardial border delineation and to increase accuracy and reproducibility of regional and global LV function assessment.[4–6] Contrast-enhanced echocardiography may be particularly important in patients presenting with acute myocardial infarction. Urgent and repeated echocardiographic examinations are indeed crucial in these patients, in order to evaluate regional and global LV function and to exclude LV thrombi and mechanical complications of infarction.[7–9] Contrast-enhanced echocardiography, providing more accurate and reproducible data, when compared with non-enhanced echocardiography, is therefore more reliable for the following therapeutic decision-making.[10] Moreover, potential alternative diagnostic imaging techniques (i.e. transoesophageal echocardiography, radionuclide ventriculography, and cardiac magnetic resonance) are more invasive or expensive.[10]

Luminity® is a second-generation contrast agent that comprises a perfluoropropane microbubble coated with a particularly flexible bilipid shell.[11] This contrast agent has a microvascular rheology similar to that of the red blood cells, with a transient and haemodynamically insignificant microbubble entrapment in the pulmonary microcirculation.[12] Moreover, it does not require cellular uptake, and the fluorocarbon gas is filtered out by the lungs within minutes.[12] Preclinical and clinical studies demonstrated a high safety index of this echo contrast agent in animal models, healthy humans, and patients with suspected cardiac disease.[4,13] Post-marketing surveillance data confirmed these results, with a very low reported risk of major events (1:10 000 risk of serious cardiopulmonary events and 1:500 000 risk of death).[14,15] Although a clear relationship of these events with contrast injection has not been proven, non-immunoglobulin E-mediated or anaphylactoid reactions from local complement activation, as well as sudden increase of pulmonary artery pressure in patients with impaired pulmonary function, have been proposed as potential explanatory mechanisms.[14]

Overall, the safety profile of Luminity® seems to be quite similar to that reported for another commercially available hexafluoride-based agent (SonoVue®, Bracco, Milan, Italy).[11,16]

Therefore, substantial safety data already exist for the use of Luminity® in stable patients with known or suspected cardiac disease,[4,17] but safety data on its use in patients within 24 h of acute myocardial infarction are lacking. In the current clinical report, administration of Luminity® shortly after acute myocardial infarction (within 24 h) was safe and well tolerated, even in the presence of LV dysfunction. No significant changes in vital signs, physical examination, and ECG were observed, whereas possible transient increase of serum cardiac biomarkers indicating microdamage to cardiomyocytes could not be detected due to the confounding effect of the recent acute myocardial infarction. No major adverse events were observed and minor adverse events occurred in 4% of patients and were mild in intensity and required no treatment. These findings were quite similar to that reported by previous clinical studies (minor events in 6.8% of 1558 patients).[17] In particular, in the present case series no patient referred headache (the most common side effect of Luminity®), whereas three and two patients, respectively, complained hypersensitivity at the injection site and transient back pain.

In conclusion, the current data provide evidence on the safety of using Luminity® in the acute phase of myocardial infarction, even if these findings need further confirmation in larger cohorts of patients. In this specific clinical setting, the risk/benefit ratio associated with the use of this echo contrast agent seems to be particularly favourable, considering the provided advantages for the diagnostic process and the therapeutic management.

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