Clinical Research

Cost-Effectiveness of Second-Generation Contrast Agents in Stress Echocardiography: Data From Greek Clinical Practice

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Introduction: The unsatisfactory imaging of the endocardial borders is the main limitation of dobutamine stress echocardiography (DSE). Second-generation echo-opaque contrast agents, such as Levovist and Optison, have been shown to improve the imaging of endocardial borders in both rest and stress echocardiographic studies. The aims of the present study were twofold: first, to determine to what extent the improvement in the quality of echocardiographic imaging with a contrast agent reduced the need for additional diagnostic examinations and, second, to investigate the cost-effectiveness of these agents.

Methods: A hundred and twenty two patients underwent DSE for the detection or evaluation of coronary artery disease. An examination was considered technically unsatisfactory when the endocardial border was not imaged either fully or partially in 2 or more neighbouring sections of the left ventricle. The patients with an unsatisfactory study were divided into 2 groups: patients in group A were administered Levovist, while patients in group B completed the study without Levovist administration. When the results of the DSE were unsatisfactory the patients were referred for a scintigraphic myocardial perfusion study. The cost of the Levovist and the scintigraphy were calculated on the basis of the price paid by the hospital and the government-approved charge, respectively.

Results: In 40 of the 132 patients (30%) the DSE study was considered technically unsatisfactory. Levovist was administered to 30 of those patients (group A) but not to the remaining 10 (group B). In 27 of the 30 patients in group A administration of Levovist improved imaging. During the following month, 8 patients from group B and 3 (10%) from group A underwent scintigraphy because of the unsatisfactory DSE. Calculation of the added cost in both groups of patients gave € 216 per patient for group B and € 95 per patient in group A, representing a saving of € 121 per patient through the use of Levovist.

Conclusion: The use of a contrast agent during DSE reduces the significant number of studies with lower diagnostic value and hence reduces the need for additional diagnostic examinations, achieving good cost-effectiveness.

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Two-dimensional echocardiography is the most commonly performed non-invasive examination in Europe. Its greatest limitation is unsatisfactory imaging, mainly of the endocardial borders, in obese patients, the elderly, and patients with pulmonary disease. Various review articles have reported that unsatisfactory studies represent up to 10-15% of the total.[1] In dobutamine stress echocardiography (DSE), where good imaging of the endocardial borders is an essential condition for a satisfactory study, this percentage can reach as high as 33%.[2] Second-generation echo-opaque contrast agents, such as Levovist and Optison, have been reported to improve imaging of the endocardial borders in both rest and DSE studies.[1]

The aims of the present study were twofold: first, to determine to what extent the improvement in the quality of echocardiographic imaging with a contrast agent reduced the need for additional diagnostic examinations and, second, to investigate the cost-effectiveness of these agents in DSE.

Material and methods

We studied 132 patients who underwent DSE for the detection or evaluation of coronary artery disease (CAD) during a period of one year. The dobutamine administration protocol included 5 stages with progressively increasing doses (5, 10, 20, 30, 40 μg/kg/min) and the addition of 1 mg atropine at the end of the infusion if the heart rate achieved was less than the submaximal expected rate. A Philips SONOS 5500 device with β-harmonic frequency capability (transmit-receive frequency: 1.8-3.6 MHz, mechanical index 1 to 1.4) was used for all the studies. The evaluation of left ventricular (LV) systolic wall thickening was based on 4 views: the parasternal long-axis view, the short axis and the apical 4- and 2-chamber views. The images were digitised and stored for the direct comparison of systolic LV wall thickening before, during and at peak dobutamine administration. A study was considered technically unsatisfactory (suboptimal), when the endocardial borders of 2 or more neighbouring LV wall segments, were not visualised either fully or partially in 1 or more echocardiographic views. If the endocardial border of a wall segment was not rendered satisfactorily in one view but was fully visualised in another, the study was considered to be satisfactory. The patients whose studies were unsatisfactory were administered half a vial of Levovist (4 g vial) at rest, in intravenous infusion at 2 ml/min of 300 mg/ml solution, the remainder at the same infusion rate at peak dobutamine stress.

The patients with an unsatisfactory study were divided into 2 groups: group A was comprised of the patients who received a contrast agent and group B of the patients who completed the DSE study without Levovist administration. The reason for not giving Levovist to the patients in group B was the unavailability of the contrast agent in the laboratory at the time of the study or the patient's refusal, in one case. The patients with an unsatisfactory study were referred for myocardial perfusion scintigraphy with Thallium-201or Technetium-99m. Patients whose DSE results failed to be diagnostic for reasons other than the unsatisfactory visualisation of endocardial segments (e.g. paradoxical reaction to dobutamine) were excluded from the study. The cost of the Levovist was determined from the price paid by the hospital (€ 67.47 per vial). The cost of the scintigraphic examination was based on the government-recommended charge (€ 270.58 for the rest and stress studies), allowing for the discount (discounted cost € 106.17) granted to those insured with the national Foundation of Social Security Services.

Calculation of cost-effectiveness

Analysis of cost-effectiveness (CE) is a way of comparing various clinical tests and treatments. In its most usual form a new strategy is compared with the one that is currently used. The cost-effectiveness relation may be defined as the difference between the cost of one test or treatment (x) and that of another (y), divided by the additional benefit that arises from the use of test or treatment x rather than y.[1] Mathematically, this relation is expressed by the equation $CE = (C_x - C_y) / (B_x - B_y)$, where C and B represent the costs and benefits of the two tests or treatments. If B_x and B_y are similar only the nominator $C_x - C_y$ is used as a measure of the cost reduction that may be expected from choice of test or treatment y over x when both are equally effective. Thus, in the present study this difference, $C_x - C_y$ was used to express the expected financial benefit per patient from choosing DSE with a contrast agent rather than scintigraphy in cases where DSE alone is not diagnostic.

Results

In 40 of the 132 patients (30%) the study was considered technically unsatisfactory based on recordings at rest. The reason for the unsatisfactory imaging was obesity in 13 patients, coexistent chronic obstructive pulmonary disease in 10, skeletal chest abnormalities in 8 and previous heart surgery in 9. The wall segments where the endocardium was poorly visualised were the apical wall (63%), lateral (mainly basal and median, 30%) and the inferior wall (7%). In 30 of these patients (75%, group A) Levovist was administered, whereas in the remaining 10 (25%, group B) no contrast agent was given. The clinical characteristics of the patients are shown in table 1. There was no qualitative or quantitative difference between the 2 groups in regard to the endocardial wall segments that were not visualised satisfactorily. In 27 of the 30 patients in group A the administration of Levovist resulted in an improvement in the visualisation of the endocardial bor-

Table 1. Patients' clinical characteristics.

Parameter	Group A (n=30)	Group B (n=10)
Mean age (range)	66 (40-79)	61 (49-75)
Men - women	21-9	9-1
History of MI	60%	50%
Known CAD	75%	70%
CHF	26%	30%
Hypertension	22%	30%
Diabetes mellitus	20%	20%
COPD	15%	20%

MI: myocardial infarction, CAD: coronary artery disease, CHF: chronic heart failure, COPD: chronic obstructive pulmonary disease.

ders that could not be distinguished in the resting study before Levovist was given (Figure 1), using the Power Doppler technique, which enables better and longer-lasting imaging of the LV cavity.

During the following month, 8 patients from group B (80%) underwent myocardial perfusion scintigraphy, as did the 3 patients from group A (10%) whose DSE study remained unsatisfactory even after Levovist administration, because of attenuation artefacts. In all 3 of the latter patients it was the lateral LV wall that could not be visualised. The percentages of tests positive for ischaemia (or for the existence of viable myocardium) and of negative DSE studies for the whole patient population were 52% and 48%, respectively. The addition of a contrast agent raised the percentage of technically satisfactory studies from 70% to 90% (Figure 1).

The above findings indicate that 80% of patients with an unsatisfactory DSE study would normally have been referred for scintigraphy for the investigation of CAD. If those patients are given a second-generation contrast agent (Levovist) this percentage is reduced to 10%. If Levovist is given to 100 patients with an unsatisfactory DSE study the added cost is € 6,747 (100 × € 67.47). If 10% of these patients also require scintigraphy it is necessary to add a further € 2,706 (10 × € 270.58). Therefore, the total added cost is € 9,453, or around € 95 per patient. If Levovist is not given to the same 100 patients, 80 of those will subsequently undergo scintigraphy giving an added cost of € 21,650 (80 × € 270.58) or around € 216 per patient. Thus, the use of Levovist results in a cost reduction of approximately € 121 per patient. Similarly, if the same calculations are carried out using the discounted charge for scintigraphy (see above), the cost reduction becomes substantially lower at just € 7 per patient; this is still, however, a saving.

Discussion

DSE has become established as a precise method for the diagnosis of CAD and for the assessment of myocardial viability.[3] One fundamental problem facing stress echocardiography is the significant number of unsatisfactory studies, in which it is not possible to visualise all segments of the myocardium. This percentage, according to various studies, exceeds 30%

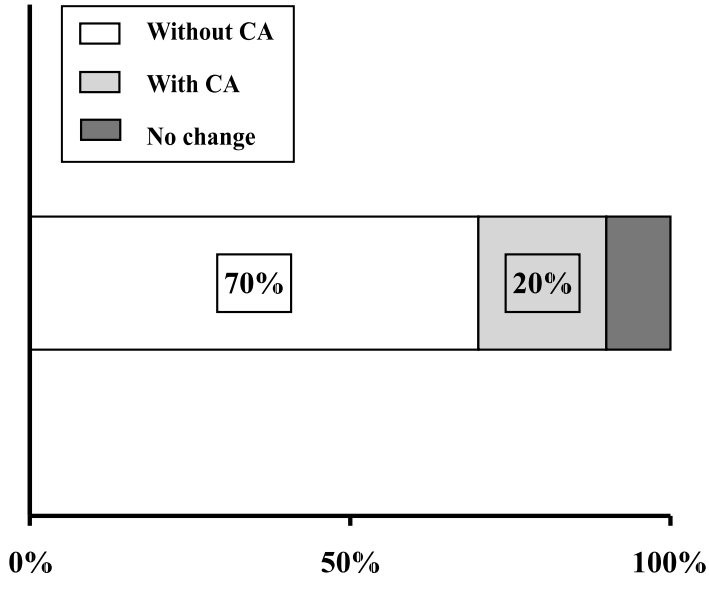

Figure 1. Improvement in imaging of the endocardial borders following administration of a contrast agent (CA) during a dobutamine stress echocardiographic study in relation to the percentage of patients given a contrast agent.

of the total DSE examinations.[2] The use of contrast agents in daily clinical practice is still limited, even though their effectiveness, as well as their good cost-effectiveness in the evaluation of LV function, has been well proven.[4,5] One recent study found that contrast agents are used systematically in no more than 7%-8% of transthoracic and stress echocardiographic examinations, while in the case of DSE this percentage rises to 15%.[4] The most likely reason for this is that the improvement in the diagnostic and prognostic accuracy resulting from the addition of contrast agents to the basic echocardiographic examination has not been confirmed by large studies.

The present study shows that in a significant number of patients (30%) undergoing DSE the examination is not diagnostic because of unsatisfactory imaging of some segments of the endocardium. This percentage agrees with the findings of other studies in the literature. The administration of Levovist, half a vial at rest and the remainder at peak dobutamine stress, resulted in satisfactory imaging of the endocardial borders in 90% of the patients with unsatisfactory imaging during the examination at rest. The main reason why Levovist was not given to the patients in group B was that it was not available in the laboratory at the time of the examination. All the patients in group A who, in spite of the Levovist administration, still had an unsatisfactory study, as well as 80% of the patients in group B, underwent myocardial perfusion scintigraphy, which was recommended by the treating physician (not by the echocardiographer) in accordance with usual clinical practice. None of the patients in group A in whom Levovist administration resulted in a satisfactory DSE study needed to be referred for scintigraphy.

Our findings indicate that the use of Levovist during DSE, by reducing the need for a subsequent scintigraphic examination, resulted in a saving of € 121 per patient, even though the administration of a contrast agent during DSE increases the cost of the study. It should also be noted that the cost of scintigraphy was calculated based on the charge for a simple (rest and stress) study and not the charge for a viability study (reinjection), which is 35%-43% higher depending on the patient's health insurance provider. Furthermore, our calculations took no account of gated SPECT, which is also used for the assessment of LV function and whose chargeable cost has not yet been specified by the insurance providers in this country.

According to many studies in the literature the diagnostic accuracy of DSE is similar to that of myocardial perfusion scintigraphy,[1,6,7] with DSE having better specificity.[6] On the basis of this datum, the 2 methods may be considered to have similar effectiveness, so that the cost-effectiveness relation may be expressed simply as the difference between the costs of the examinations, although the extra trouble to patients who undergo a scintigraphic examination should also be taken into account.

Other studies in the USA, where the costs of DSE and scintigraphy are substantially higher than they are in Greece, reached the same conclusion, with around double the cost reduction that we found in our study.[8]

The absence of angiographic confirmation of CAD in patients where regional LV dysfunction was found could be considered as a limitation of the present study. Also, because of the study's retrospective nature, the patients were not randomised to one group or another.

In conclusion, our findings show that the use of contrast agents during a DSE study reduces the significant percentage of studies with low diagnostic value and also reduces the need for additional diagnostic examinations, thus achieving good cost-effectiveness. Given their low cost and ease of use, newer contrast agents that can be used not only for imaging the endocardial borders, but also for studying myocardial perfusion, may prove to be equally cost-effective.

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