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Safety of contrast flash-replenishment stress echocardiography in 500 patients with a chest pain episode of undetermined origin within the last 5 days

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Aims Safety concerns regarding the use of echo-contrast agents during baseline and SE in patients with recent chest pain have been raised. The purpose of the present study was to provide evidence regarding the safety of flash-replenishment contrast dipyridamole–atropine echocardiography (DASE) in such patients.

Methods and results Five hundred consecutive individuals who presented to the Emergency Department with chest pain, normal electrocardiograms (ECG) and troponin I were selected based on a less than 5 days interval between chest pain episode and performance of contrast flash-replenishment DASE. Analysis of myocardial perfusion with SonoVue© infusion after dipyridamole was routinely added on top of standard wall motion assessment during DASE. Adverse events (AEs) were reported according to standardized terminology and then compared with a historical control group in which contrast was not used. No deaths, myocardial infarctions, sustained arrhythmias, or any other life-threatening events were observed. Adverse events were not significantly different between the study group and the control group. In the selected subgroup of patients ($n = 149$) who underwent coronary angiography, accuracy of DASE with additional perfusion assessment was higher (88%, 95% C.I. 83–93%) than without (72%, 95% C.I. 65–79%).

Conclusion DASE with SonoVue© infusion for myocardial perfusion assessment was exceptionally safe even when routinely performed within the first 5 days following a chest pain episode of undetermined origin in subjects without ECG and troponin abnormalities.

Introduction

Stress echocardiography (SE) is an effective tool to exclude obstructive coronary artery disease (CAD) as the origin of the chest pain episode in patients in whom an acute coronary syndrome has been excluded by normal serial electrocardiograms (ECG) and cardiac enzymes. Stress echocardiography can additionally stratify the risk of future cardiac events in this particular subset of patients.[1,2]

The use of second generation echo-contrast media during SE not only widens the feasibility of the test due to better endocardial border visualization, but it can significantly increase diagnostic accuracy thanks to myocardial perfusion imaging (MPI).[3]

Scientific evidence of the excellent safety profile of SonoVue© during low mechanical index (MI) SE is accumulating, but still no safety data have been specifically collected in patients with recent chest pain, a setting in which the incremental sensitivity of MPI could be particularly helpful.[4–6]

The aim of the current study is to evaluate the safety of dipyridamole–atropine echocardiography (DASE) with low-MI, flash-replenishment assessment of myocardial perfusion by means of a continuous infusion of SonoVue© in a large number of patients in which the test was performed less than 5 days after the chest pain episode.

Methods

Patients

Our contrast SE database is made of consecutive patients who presented to the chest pain unit between November 2007 and August

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2008 and were prospectively selected for contrast DASE based on the following criteria.

Inclusion criteria: (i) stress test requested by the cardiology consultant for an episode of chest pain of undetermined origin, (ii) absence of new ECG ischaemic changes or raised cardiac enzymes in at least two serial measurements, (iii) low to intermediate pre-test risk of CAD, as estimated using a table of risk based on: age, gender, chest pain type, and number of risk factors (Diamond and Forrester criteria integrated by Duke database data).[7,8]

Exclusion criteria: (i) left ventricular ejection fraction $<30\%$, (ii) severe valvular disease, (iii) frequent or sustained ventricular arrhythmias or haemodynamic instability by any cause, (iv) active chest pain at the time of echocardiography, (v) anti-ischaemic medications in the last 24 h.

In the current safety analysis, only patients in whom DASE was performed within 5 days after their chest pain episode were considered.

The decision to proceed to coronary angiography after DASE was always left to the referring physician, based on clinical judgment (no per-protocol recommendations).

Patients gave a more specific informed consent when administration of SonoVue© fell less than 2 days after the chest pain episode, since this specific case could be interpreted as a relative contraindication in the 2008 European Medicines Agency (EMEA) recommendations for SonoVue© administration during SE; an informed consent was also required for SonoVue© administration between 2 days and 1 week after chest pain, since in this setting it could be felt contraindicated too, as per recommendations for use during baseline echocardiography.[9] All patients gave written informed consent to the study protocol, which was approved by the Institutional Review Board of our Hospital.

Echocardiography

Stress protocol

Patients underwent standard DASE with adjunctive MPI between the end of dipyridamole infusion (0.84 mg/kg/10 min) and the beginning of atropine infusion 4 min later (Atropine up to 1.5 mg in 2 min). Aminophylline was routinely used to reverse dipyridamole effect. Consolidated endpoints and contraindications to DASE were used. Known allergy to sulfonamides, pregnancy, or lactation were considered contraindications to administration of echographic contrast media (SonoVue©—Bracco Imaging Italia srl, Milan, Italy). All patients entered a follow-up program.

Standard and myocardial contrast echocardiography

Patients underwent both WM and MPI studies using an iE33 echocardiograph with an S5 scan head (Philips Ultrasound, Bothell, Washington). Myocardial perfusion imaging was performed activating low-MI power-modulation imaging after the end of dipyridamole infusion, whereas WM acquisition was performed after atropine infusion, at peak heart rate. Flash-replenishment cine-loops in the three apical views were acquired, starting 1 min after the initiation of SonoVue© infusion (0.8–1.0 cc/min) and continuing through the end (4 min later using one vial of SonoVue©). A rotating infusion pump was used (BR-INF 100, Bracco SpA). After the 4 min dedicated to MPI, atropine was administered and SonoVue© infusion stopped. Left ventricular opacification generally persisted long enough to allow for peak WM imaging with the left ventricle still opacified; if not, the residual contrast in the pump tubing (0.8 cc) was infused at this time by means of a saline bolus. Myocardial perfusion imaging was performed acquiring both triggered and real-time flash-replenishment sequences at low MI (0.08–0.12). Real-time mode acquired images at 39 frames per second. High-MI 'flash' frames (eight frames, MI = 1.13) were delivered to destroy the microbubbles; on completion of the flash sequence, low-MI imaging automatically resumed. Myocardial contrast replenishment was visualized and images acquired through 10 cycles after.

Interpretation of WM and MPI has been described in detail elsewhere.[10] Briefly, regional WM was evaluated at baseline and at peak stress by a semi-quantitative assessment of wall motion score index with the 17-segment model of the left ventricle, as according to recommendations of the American Society of Echocardiography.[11] Test positivity was defined as the occurrence in at least one segment of either a new dyssynergy or worsening of rest dyssynergy.

Normal perfusion after dipyridamole was assigned, if myocardium was fully replenished 1.5–2 s after the end of flash impulse; perfusion was defined abnormal, if myocardium was not replenished after this time, but later filled from subepicardium to subendocardium.

Quantitative coronary angiography

Only coronary angiographies performed within 60 days after DASE were considered. Quantitative coronary angiography (QCA) was performed by an experienced cardiologist (A.S.), unaware of the results of echocardiography. Any visually evident stenosis was measured using a hand-held electronic caliper (Tesa S.A., Renes, Switzerland) operated with custom-developed PC software.[12] Coronary artery disease was defined as $>50\%$ luminal diameter stenosis in one or more major coronary arteries.

A true positive SE result was defined as a WM/MPI abnormality matching the perfusion territory of a $>50\%$ stenosis diagnosed at QCA.

Safety evaluation

Adverse events were recorded during and immediately after DASE by the physician performing the test, and after 24 h by contacting the patient. The final assessment of the recorded AEs was based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events v3.0 (CTCAE) as previously described.[4,13,14] Selectively in patients in whom DASE was performed less than 2 days after the chest pain episode, troponin I was measured 6 h after the stress study, for additional safety monitoring. Any unfavourable or unintended sign or symptom occurring during the echocardiographic stress study or in the next 24 h, which might or might not be related to the procedure, was considered as AE. Adverse event severity was graded using a five-grade scale: mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), and death caused by AE (Grade 5). The presence of arrhythmias was specifically determined by reviewing all the following sources: (i) 12-lead ECG acquired at each stage of the stress protocol, (ii) all the digitally stored flash-replenishment clips, and (iii) real-time ECG on the echo monitor during the test. Hypotension was defined as a fall of systolic blood pressure below 80 mmHg or a reduction >40 mmHg from baseline. Chest pain observed after a positive study was not considered an AE, since it is an expected consequence of a stress protocol, as long as it did not persist after the end of the test.

Safety was evaluated in the study group and compared with a control group of DASE studies without the use of contrast performed in our laboratory either during the study period or in the preceding year in patients with a chest pain to DASE interval less than 5 days.

Statistical analysis

Continuous variables were presented as mean and standard deviation and were compared using the Student *t*-test. Categorical variables were examined with a χ^2 test when appropriate (expected frequency >5); otherwise a Fisher exact test was used. Sensitivity, specificity, and accuracy were calculated using standard definitions and were presented with 95% confidence intervals (CI). Differences between sensitivity, specificity and accuracy using WM or WM + MPI were analysed using McNemar's test. A value of $P < 0.05$ (two sided) was considered significant. Statistical analysis was performed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline and dipyridamole–atropine echocardiography characteristics

In the study period, a total of 617 patients admitted to the chest pain unit underwent contrast DASE for their chest pain episode; out of them only the first 500 patients in whom the test was performed less than 5 days after the index chest pain episode were selected for current safety study. In 117 patients, the test was instead performed more than 5 days after their chest pain episode and consequently they were excluded from current analysis. Baseline characteristics of the 500 patients selected, together with subgroup comparison based on the presence/absence of AEs are shown in *Table 1*.

Mean age was 67, half of patients (54%) were males, one-third (34%) had a previous myocardial infarction or PCI, and three of four (77%) had two or more traditional risk factors for CAD. In 95 patients, the test was performed less than 48 h after their chest pain episode and in 405 patients after more than 2 days but still less than 5 days.

Safety of contrast dipyridamole–atropine echocardiography

The only statistically significant difference in baseline and DASE characteristics between patients with and without AEs was a higher prevalence of male gender in patients with AEs (*Table 1*).

Table 2 reports all AEs in the study group, according to standardized terminology and definitions.[14] No fatalities,

Table 1 Baseline clinical and stress echocardiography characteristics

	All study patients	Patients without AEs	Patients with AEs	*P*-value
Patients, *n*	500	446	54	–
Age, mean(±1SD), y	67 (10)	67 (10)	68 (9)	ns
Men, *n* (%)	268 (54)	232 (52)	36 (67)	<0.05
Risk factors ≥2, *n* (%)	384 (77)	338 (76)	46 (85)	ns
Prior myocardial infarction/PCI, *n* (%)	168 (34)	147 (33)	21 (39)	ns
Baseline LVEF <50%, *n* (%)	131 (26)	119 (27)	12 (22)	ns
Abnormal WM, *n* (%)	75 (15)	67 (15)	8 (14)	ns
Abnormal MPI, *n* (%)	119 (24)	106 (24)	13 (24)	ns
Peak RPP mean(±1SD)	15 437 (3517)	15 474 (3676)	15 402 (4201)	ns

PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; WM, wall motion; MPI, myocardial perfusion imaging; RPP, rate-pressure product. Headache and xerostomia were not considered AEs for the purpose of this table.

Table 2 Severity and frequency of observed adverse events in the study group, based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events v3.0.[13]

AE category	AE	Grade	Frequency, *n* (%)
Constitutional			
	Fatigue	1/2	2 (0.4)
Cardiac arrhythmias	*Supraventricular arrhythmias*		
	Supraventricular premature beats (PACs)	1	8 (1.6)
	Atrial fibrillation/flutter	1/2	2 (0.4)
	Supraventricular tachycardia	1/2	2 (0.4)
	Vasovagal episode (No LOC)	2	9 (1.8)
	Ventricular arrhythmias		
	Ventricular premature beats (PVCs)	1/2	28 (5.6)
	Non-sustained ventricular tachycardia	1	1 (0.2)
	Second-degree AV block	1/2	1 (0.2)
	LBBB	1/2	1 (0.2)
Cardiac general			
	Troponin I elevation[a]	–	0
	Hypotension	1/2	4 (0.8)
Gastrointestinal			
	Xerostomia	1	97 (19)
	Vomiting	1	1 (0.2)
Pain			
	Headache	1	214 (43)
	Pain at injection site	1	1 (0.2)

AE, adverse event; LOC, loss of consciousness; PACs, premature supraventricular complexes; PVCs, premature ventricular complexes; AV, atrio-ventricular; LBBB, left bundle branch block. Grades correspond to: mild (1), moderate (2), severe (3), life-threatening (4), death (5).

[a]Troponin was measured only in the 95 patients with a chest pain to stress echocardiography interval less than 2 days.

myocardial infarction, or acute coronary syndromes were recorded during the stress study or in the next 24 h. Elevation of cardiac troponin I to a level higher than the normal cut-off was never observed in the subgroup of 95 patients in whom it was measured after the test (only the ones studied less than 48 h after their chest pain episode).

Common side effects (observed at a frequency of >1%) were: mild headache (43%) and dry mouth (19%), well-known dipyridamole/atropine effects, premature ventricular complexes (PVCs) (5.6%), vasovagal reactions without loss of consciousness (1.8%), and supraventricular premature beats (1.6%).

Uncommon AEs (observed at a frequency of 0.1–1%) were: hypotension (0.8%), atrial fibrillation/flutter (0.4%), supraventricular tachycardia (0.4%), fatigue (0.4%), non-sustained ventricular tachycardia (0.2%), second-degree AV block (0.2%), left bundle branch block (0.2%), vomiting (0.2%), and pain at injection site (0.2%). There were no cases of minor or life-threatening allergic reactions.

All AEs were self-limiting or promptly resolving (Grade 1 or 2) after aminophylline administrationor with atropine administration in case of vagal reactions.

The episode of non-sustained ventricular tachycardia was a brief five-beat run that could only be recorded, because the patient was still monitored with telemetry; this event took place 90 min after the test, with the patient completely asymptomatic and its causal link with the study procedure is at least uncertain; however, we included it in AEs report, due to the time association. The few cases of test-related atrial fibrillation, supraventricular tachycardia, or conduction abnormalities were self-terminating or terminated after aminophylline infusion. All vagal episodes were without loss of consciousness and they always took place during or immediately after dipyridamole infusion; such mild episodes are often encountered during standard dipyridamole-echocardiography, probably triggered by drug-induced hypotension.

Similarly, the single episode of second-degree AV block took place after the infusion of dipyridamole, in a patient with a baseline PQ interval 200 ms, which was not considered an absolute contraindication to the use of dipyridamole; the same patient underwent implantation of a permanent pacemaker 2 months after the test for the development of a complete AV block, confirming the underlying disease of the conduction system.

Table 3 compares AEs in the less than 2 days subgroup with the more than 2 days subgroup; male gender prevalence and the rate–pressure product resulted significantly higher in the more than 2 days subgroup, but AEs were not significantly different.

Table 4 reports the incidence of AEs in the study group compared with a same size control group in which contrast was not used. Adverse events were not significantly different between the two groups. Mean age and history of prior myocardial infarction were significantly lower in the control group, possibly reflecting the a priori selection of patients with better acoustic windows when not taking advantage of contrast use.

Diagnostic accuracy of dipyridamole—atropine echocardiography/MPI

Among the 149 patients for whom angiographic data were available, 80 (68%) had significant obstructive CAD on

Table 3 Comparison of clinical, stress echocardiography characteristics, and adverse events between patients who were subjected to contrast stress-echo less or more than 2 days after chest pain in the study group

Baseline and stress data	<2 Days after chest pain	>2 Days after chest pain	*P*-value
Patients, *n*	95	405	—
Age, mean(±1SD), y	68 (9)	67 (10)	ns
Men, *n* (%)	39 (41)	229 (46)	<0.05
Risk factors ≥2, *n* (%)	77 (81)	307 (76)	ns
Prior myocardial infarction/PCI, *n* (%)	25 (26)	143 (35)	ns
Baseline LVEF <50%, *n* (%)	21 (22)	110 (27)	ns
Abnormal WM, *n* (%)	15 (16)	59 (15)	ns
Abnormal MPI, *n* (%)	25 (26)	94 (23)	ns
Peak RPP mean(±1SD)	14 744 (3589)	15 639 (3751)	$P < 0.05$
Adverse events, *n* (%)			
Headache	38 (40)	176 (43)	ns
Xerostomia	20 (21)	77 (19)	ns
Vasovagal reaction	3 (3.1)	6 (1.48)	ns
PVCs	4 (4.2)	24 (5.9)	ns
Non-sustained VT	1 (1)	0 (0)	ns
PACs	0 (0)	8 (2)	ns
Supraventricular tachycardia	0 (0)	2 (0.5)	ns
Atrial fibrillation/flutter	0 (0)	2 (0.5)	ns
Second-degree AV block	0 (0)	1 (0.2)	ns
LBBB	0 (0)	1 (0.2)	ns
Hypotension	0 (0)	4 (1)	ns
Vomiting	0 (0)	1 (0.2)	ns
Fatigue	0 (0)	2 (0.5)	ns
Pain at injection site	0 (0)	1 (0.2)	ns

All tests were performed less than 5 days after chest pain episode. Abbreviations as in *Tables 1 and 2*.

Table 4 Adverse events in the study group compared with the control group

	Study group (SonoVue)	Control group (no SonoVue)	*P*-value
Patients, *n*	500	500	–
Age, mean(±1SD), y	67 (10)	64 (9)	<0.01
Men, *n* (%)	268 (54)	259 (52)	ns
Risk factors ≥2, *n* (%)	384 (77)	359 (72)	ns
Prior myocardial infarction/PCI, *n* (%)	168 (34)	137 (27)	<0.05
Baseline LVEF <50%, *n* (%)	131 (26)	107 (21)	ns
Abnormal WM, *n* (%)	74 (15)	63 (13)	ns
Abnormal MPI, *n* (%)	119 (24)	–	ns
Peak RPP mean(±1SD)	15 437 (3517)	15 604 (3656)	ns
Adverse events, *n* (%)			
Headache	214 (40)	220 (43)	ns
Xerostomia	97 (21)	93 (19)	ns
Vasovagal reaction	9 (3.1)	5 (1.48)	ns
PVCs	28 (4.2)	24 (5.9)	ns
Non-sustained VT	1 (1)	2 (0)	ns
PACs	8 (0)	10 (2)	ns
Supraventricular tachycardia	2 (0)	3 (0.5)	ns
Atrial fibrillation/flutter	2 (0)	1 (0.5)	ns
Second-degree AV block	1 (0)	0 (0.2)	ns
LBBB	1 (0)	0 (0.2)	ns
Hypotension	4 (0)	5 (1)	ns
Vomiting	1 (0)	1 (0.2)	ns
Fatigue	2 (0)	1 (0.5)	ns
Pain at injection site	1 (0)	1 (0.2)	ns

Table 5 Diagnostic parameters of contrast dipyridamole–atropine echocardiography to detect angiographically significant (>50%) coronary artery disease on a patient basis in subjects who underwent coronary angiography ($n = 149$)

	Wall motion	Wall motion + perfusion
Sensitivity (95% CI)	67/101; 66% (61–70%)	98/101; 97% (93%–99%)*
Specificity (95% CI)	40/48; 83% (73–91%)	33/48; 69% (60%–73%)**
Accuracy (95% CI)	107/149; 72% (65–77%)	131/149; 88% (83%–91%)*

Results are number; percent of patients (corresponding 95% confidence intervals).
*$P < 0.001$ compared with wall motion criteria.
**$P < 0.05$ compared with wall motion criteria.

angiography (>50% stenosis). Sensitivity was increased ($P < 0.001$) and specificity decreased ($P < 0.05$) by the addition of MPI to standalone WM. The total diagnostic accuracy was anyway increased by the addition of MPI (88%) compared with standalone WM without MPI assessment (72%) and that increase was highly statistically significant ($P < 0.001$). *Table 5* summarizes the main diagnostic parameters of DASE with and without additional MPI in the angiographic group.

Discussion

DASE with SonoVue© for perfusion assessment was exceptionally safe in subjects with recent chest pain (defined as less than 5 days before) in whom an acute coronary syndrome was excluded by serial ECG and troponin measurements.

No study related deaths, myocardial infarctions, sustained arrhythmias or other severe AEs were encountered. Moreover, there were no differences in AEs when the study group was compared with a historical control group in which DASE was performed without contrast use. The clinical safety of contrast flash-replenishment SE has been recently demonstrated in a single-centre study in which more than 5000 patients underwent dobutamine–atropine echocardiography, a stress protocol slightly more prone to AEs than DASE.[4,15]

Complying with European Medicines Agency recommendations

The European marketing authorization for SonoVue©, revised in 2008 by the EMEA, warns that for what it concerns baseline echocardiography 'SonoVue is contraindicated for use in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or ongoing myocardial infarction, *typical angina at rest within last 7 days*' while concerning SE '... if SonoVue© is to be used in conjunction with stress-echocardiography, patients must have a stable condition verified by absence of chest pain or ECG modifications during the *two preceding days* ...'.[9] In our centre, the EMEA statement has been interpreted as a warning not to use SonoVue© in unstable patients or in patients with recent chest pain of clearly established cardiac origin. Consequently, we perform contrast DASE in those chest pain unit patients (no matter if within 2 days or 1 week after the episode) in whom the following conditions are verified: (i) stable patients admitted to the chest pain unit for chest pain of undetermined origin and asymptomatic at the time of testing, (ii)

absence of ECG/enzyme abnormalities, serially tested in the chest pain unit. When all of these conditions are satisfied patients can be defined stable and there is no proof that their chest pain is of cardiac origin.

Novelty of our findings

Our study is the first to assess the safety of SonoVue© during flash-replenishment DASE, and the first in which contrast DASE has been selectively applied to patients with recent chest pain, a subset normally considered at higher risk for AEs related to SonoVue©. No severe (Grade 3) or life-threatening (Grade 4), or deadly (Grade 5) AEs were observed.

A peculiarity of our study is that contrast was per-protocol infused only after dipyridamole, without a baseline infusion, so that for some mild AEs (such as PACs or PVCs) which started before contrast infusion and did not lead to test interruption, it is reasonable to exclude a causative role of SonoVue©. Ultrasound contrast agents have long been used to enhance ultrasonographic imaging of various organs and in several settings with very good safety profile.[16]

Concern has been recently expressed over the safety of microbubble contrast agents when used in echocardiographic applications. High-MI imaging (MI $>$ 1.0–1.1) during contrast infusion might truly potentially trigger isolated PVCs, at least when imaging is triggered at endsystole, whereas discordant data exist regarding the possibility of microcirculatory damage during real-life ultrasound imaging in humans.[17–20] The potential mechanism leading to AEs during high-MI imaging would probably be mediated by a process called cavitation, which is proportional to the delivered acoustic energy, at least beyond a definite threshold.[20] This is why it is fundamental to differentiate between entirely high-MI imaging and entirely low-MI imaging or hybrid flash-replenishment imaging (as used in our study). To date, convincing safety data in adequately large SE samples have been produced only for entirely low-MI or, more recently, for dobutamine–atropine flash-replenishment imaging.[4,5]

Flash-replenishment combines the advantages of low-MI imaging (real-time imaging, less mechanical energy delivered) with the opportunity to dynamically assess myocardial perfusion by microbubbles replenishment of the microvascular bed. However, the use of high-MI impulses (in our study eight frames at an MI $\leq$ 1.13) for flashing, even for as brief periods of time as $\sim$0.2 s (eight frames at a frame rate = 39 Hz), might result in increased incidence of AEs compared with totally low-MI techniques. On the contrary, no flash-related AEs were observed in our study, similar to the recently published study using dobutamine–atropine.[4]

We followed the recent proposal to use a standardized terminology for AEs reporting (CTCAE v3.0) and by so doing, we took advantage of the standardized definitions of severity for each type of AE.[4,14]

Study limitations

Even if safety studies may require wider samples, the absence of any life-threatening event in 500 consecutive contrast studies (in a study population thought at high risk for contrast-related AEs), compared with the published AEs expected rate during DASE without contrast (1/600), and the absence of any difference with the control group are very reassuring.[21] The control group was carefully selected and analysed for AEs following the same criteria and methods used for the study group; anyway it had to be built retrospectively. This obviously deviates from the ideal design for prospective comparison between an intervention and a control group, with some baseline characteristics resulting imperfectly matched. Regarding the evaluation of the diagnostic parameters of contrast DASE, it should be noted that in most such diagnostic studies pre- and post-referral bias exist, since the result of the test is heavily taken into account in deciding whether or not to proceed to coronary angiography.

These factors may lead to under or over-estimation of sensitivity, specificity, and accuracy.

Our results pertain to stable chest pain patients without ECG or biomarker abnormalities; these results may not be able to be extrapolated to unstable or higher risk patients.

Conflict of interest: none declared.

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