Diagnosis of ischaemic heart disease by myocardial contrast echocardiography during supine bicycle stress

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Abstract

Introduction: Myocardial contrast echocardiography (MCE) is a new imaging modality for diagnosing ischaemic heart disease (IHD).

Aim: The aim of this study was to assess 1) the feasibility of MCE during supine bicycle stress and 2) the value of this method in the diagnosis of IHD.

Methods: Supine bicycle stress was performed in 44 consecutive patients (pts) referred for coronary angiography with an intermediate pre-test probability of IHD. MCE was carried out at peak stress and during recovery (once the heart rate returned to the pre-exercise value). During MCE an ultrasound contrast agent (Sonovue®) was administered intravenously in a continuous mode using an infusion pump (BR-INF 100, Bracco Research). The acquired images were qualitatively assessed for perfusion and wall motion abnormalities. The 18-segment division of the left ventricle was used in the analysis. Coronary angiography was performed in all pts within 15 days of the exercise test. A quantitative analysis of coronary artery stenoses was carried out using the CAAS system.

Results: MCE could not be performed in 2 pts due to technical difficulties. Coronary angiography revealed significant coronary artery stenosis in 25 pts. The sensitivity and specificity of MCE in the diagnosis of IHD were 92.0% and 82.4%, respectively. The positive and negative predictive values were found to be 88.5% and 87.5%, respectively, while the agreement between coronary angiography and MCE was 88.1% (κ=0.75).

Conclusions: MCE during supine bicycle stress and continuous intravenous administration of an ultrasound contrast agent is a feasible technique and allows accurate diagnosis of IHD in pts in whom the pre-test probability of the disease is intermediate.

Key words: myocardial contrast echocardiography, ischaemic heart disease, stress echocardiography

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Introduction

Myocardial contrast echocardiography (MCE) is a new technique allowing simultaneous real-time assessment of myocardial perfusion and function [1-4]. Previous clinical studies have shown that MCE performed during stress tests and after an intravenous bolus of an ultrasound contrast agent can accurately diagnose ischaemic heart disease (IHD) [5-8]. Recently, the development of a specialized infusion pump has made it possible to continuously administer a contrast agent at a constant concentration [9]. It seems likely that, when compared to a bolus, the continuous administration of contrast could improve perfusion image quality and reduce the number of visible artefacts [4,10]. The goals of this study were: 1) to assess the feasibility of MCE during supine bicycle stress and continuous intravenous infusion of an ultrasound contrast agent, and 2) to assess the value of this method in the diagnosis of IHD.

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Methods

Study population

The study was approved by the Ethics Committee of the University of Bonn. Forty-four consecutive patients referred for coronary angiography were included in the study. Patients with a high or low pre-test probability of IHD were excluded from the study [11]. Patients were not selected with respect to baseline echocardiographic image quality. Patients with absolute and/or relative contraindications to exercise tests were excluded from the study [12].

Supine bicycle stress

All patients underwent supine bicycle stress within a 15-day period prior to the scheduled coronary angiography. Each test was terminated in accordance with the AHA/ACC guidelines [12]. The initial workload was set at 50W and was subsequently increased in 25W increments every 2 minutes [12]. Stress MCE was carried out during the exercise when the peak stress was reached. Following the termination of exercise, each subject remained in the supine position on the cycle ergometer. Another MCE was performed when the subject's heart rate returned to the pre-exercise value.

Ultrasound contrast agent

During MCE an ultrasound transpulmonary contrast agent, Sonovue® (Bracco S.p.A., Milan, Italy), was administered in a continuous mode, using a purpose-built infusion pump (BR-INF 100, Bracco Research, Geneva, Switzerland) (fig. 1). Rotation of the syringe inside the pump ensured that the contrast agent was continuously stirred and maintained in suspension during infusion. The infusion began with automatic administration of a 1 ml bolus (over 15 s). The infusion rate was subsequently adjusted to attain a steady, homogeneous myocardial contrast opacification without attenuation and to ensure the complete destruction of contrast microbubbles within the myocardium by emitting high-power pulses (flash).

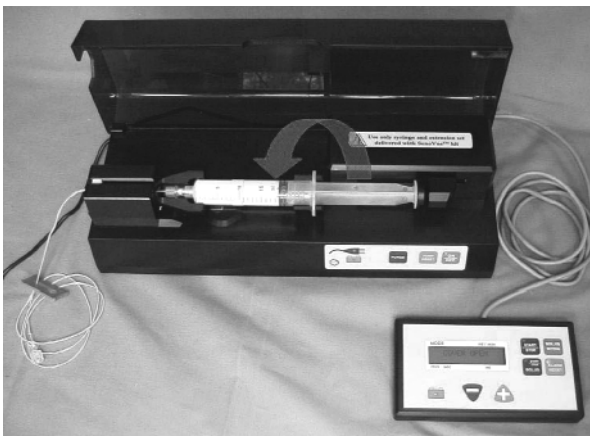

Figure 1. Infusion pump BR-INF 100 (Bracco Research, Geneva, Switzerland)

Echocardiographic image acquisition

MCE was performed using a Sonos 5500 ultrasound unit (Philips Medical Systems, Andover, MA, USA). The real-time power modulation imaging technique, which allows low power (mechanical index, MI=0.1) visualisation of contrast agent, was applied. An S3 ultraband transducer (1–3 MHz) was used. Instrument settings were predefined. The pulse repetition frequency was set at 3200 Hz. The focus was placed at the mitral valve level and the colour sector size was adjusted to cover the entire left ventricular myocardium. The resulting frame rate ranged from 11 to 14 Hz. Once a steady state of myocardial contrast opacification was reached, high power pulses were emitted to disrupt the contrast within the myocardium. It was provided by an automatic increase of the MI to 1.5 for the span of 5 frames. Afterwards, the MI automatically returned to 0.1, allowing visualisation of myocardial contrast replenishment (RP). During MCE the sequences of 15 consecutive cardiac cycles, encompassing steady state of myocardial contrast opacification, flash frames and RP, were recorded digitally. The acquisition was performed in all three apical views, both at peak stress and during recovery.

Interpretation of echocardiographic images

The 15-cardiac-cycle sequences registered during MCE were assessed off-line for segmental perfusion and/or wall motion abnormalities. Eighteen-segment division of the left ventricle (LV) was applied in the analysis [4]. Perfusion was analysed (at peak stress and during recovery) based on a relative (i.e. compared to the best-perfused myocardial segment) assessment of myocardial contrast opacification (1 – normal, 2 – reduced, 3 – none) and the RP rate (1 – normal, 2 – delayed, 3 – practically none) [4, 7]. The RP rate was assessed according to the number of cardiac cycles required to refill the myocardium with contrast. An LV segment was considered refilled when its enhancement returned to the level observed prior to contrast destruction. Contractility was assessed in terms of systolic wall thickening and/or inward movement of LV segments, according to the scale: 1 – normokinesia, 2 – hypokinesia, 3 – akinesia, 4 – dyskinesia. The examination result was considered positive if, at peak stress (in comparison to recovery), at least one LV segment displayed new or more severe disturbances in

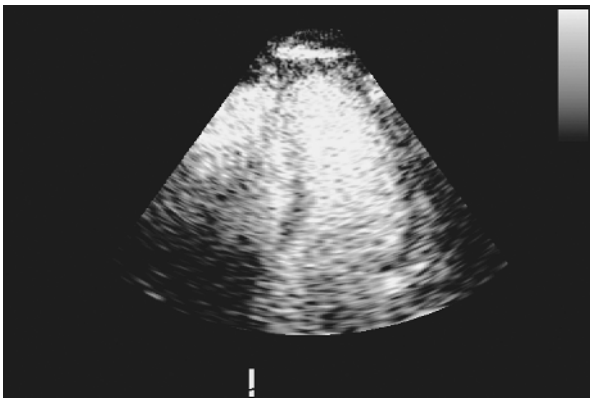

Figure 2. Peak stress myocardial contrast echocardiography in a 68 year old female with two-vessel disease (LAD – occluded, LCX – significantly stenosed) – apical four chamber view. The delayed myocardial contrast replenishment is seen in the apex and lateral wall. There were new wall motion abnormalities (akinesis) in the apex

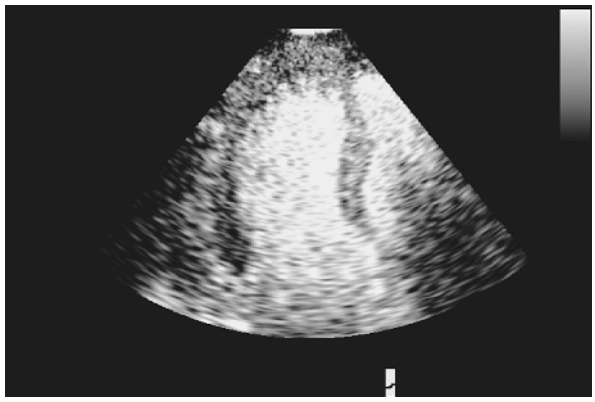

Figure 3. Peak stress myocardial contrast echocardiography in a 68 year old male with two-vessel disease (LAD and LCX significantly stenosed) – apical long axis view. The delayed myocardial contrast replenishment is seen in the posterior wall. No wall motion abnormalities were present.

contractility (defined as a worsened contractility score) and/or perfusion (defined as a decrease in myocardial contrast opacification score and/or RP rate). MCE results were compared to coronary angiography findings.

Coronary angiography

Coronary angiography was performed in all patients within 15 days of the exercise test. Any visualised coronary artery lesions were quantitatively assessed using the CAAS system (CAAS II, QCA V 4.1, Pie Medical Imaging B.V., Maastricht, Netherlands). Atherosclerotic plaques were considered haemodynamically significant if they reduced the vessel lumen diameter by at least 50%.

Statistical analysis

Quantitative data were presented as mean ± standard deviation; qualitative data were presented as prevalence (%). Qualitative variables were compared using the chi-squared test. Correlations between coronary angiography and MCE were assessed using the κ coefficient. Values of κ <0.4, ≥0.4, ≥0.6 and ≥0.8 indicated poor, fair, good, and very good agreement, respectively. Values of p <0.05 were considered statistically significant.

Results

Study group

Out of the total of 44 patients included in the study, MCE was successfully performed in 42 patients (12 female and 30 male). The mean age was 57.3±10.2 years. The 2 patients in whom MCE could not be evaluated due to technical difficulties were excluded from further analysis. Tables I and II present the clinical and echocardiographic characteristics of the study group. Patients did not suspend medication use prior to the exercise test. Twenty-four (57.1%) patients were on beta-adrenergic blocking agents, 22 (52.4%) on angiotensin-converting enzyme inhibitors, 8 (19.0%) on calcium-channel blocking agents, 6 (14.3%) on nitrates, 24 (57.1%) on statins and 1 (2.4%) on digitalis.

Table I. Clinical characteristics of study group

Parameter	n (%)
Cigarette smoking	19 (45.2)
Hypercholesterolaemia	36 (85.7)
Hypertension	24 (57.1)
Diabetes mellitus	3 (7.1)
Family history of IHD	23 (54.8)
BMI ≥25 [kg/m^2]	20 (47.6)
Angina pectoris	26 (61.9)
CCS class 1	8 (19.0)
CCS class 2	16 (38.1)
CCS class 3	2 (4.8)
Exertional dyspnea	18 (42.9)
NYHA class 1	7 (16.7)
NYHA class 2	21 (50.0)
ST segment depression at rest	2 (4.8)

BMI – body mass index, IHD – ischemic heart disease, CCS – Canadian Cardiovascular Society classification system, NYHA – New York Heart Association classification system.

Table II. Echocardiographic characteristics

Parameter	Mean ± SD	Range
LV ejection fraction [%]	60.4±7.7	41–74
End diastolic volume of LV [ml]	107.9±26.1	67–188
End systolic volume of LV [ml]	43.3±15.7	20–99
End diastolic diameter of LV [cm]	4.4±0.9	2.67–6.14

LV – left ventricle, SD – standard deviation

Table III. Supine bicycle stress characteristics

Parameter	Mean ± SD	Range
Heart rate at rest [beats/min]	72±10	54–98
Double product at rest [mmHg x beats/min]	9393±1972	5561–13838
Heart rate at peak stress [beats/min]	126±18	90–158
Double product at peak stress [mmHg x beats/min]	25 201±5753	15 330–42 772
% age predicted maximum heart rate	78±11%	56–98%
Achieved workload [W]	99±32	50–175
% age predicted workload	114±44%	56–250%

SD – standard deviation

Exercise test

Table III presents the characteristics of the supine bicycle test. Fifteen (35.7%) patients demonstrated new or more severe wall motion abnormalities at peak stress (in comparison with recovery). Ten (23.8%) patients reached 85% of the age-adjusted maximum heart rate without new or more severe LV wall motion abnormalities. Sixteen (38.1%) patients' exercise tests were terminated prior to reaching the predicted heart rate due to fatigue (10 of them reached the target age-adjusted workload), 1 (2.4%) patient's due to dyspnoea. No patients reported chest pain during the exercise test.

Coronary angiography

Haemodynamically significant atherosclerotic plaques (defined as lesions narrowing the arterial lumen by at least 50%) were demonstrated in 25 patients (13 – single-vessel IHD, 12 – multi-vessel IHD). Eighteen patients were found to have significant lesions in the left anterior descending branch of the left coronary artery, 12 in the circumflex branch of the left coronary artery, 8 in the right coronary artery and 1 in the main left coronary artery.

Feasibility of MCE

Out of the 44 study participants, only 2 could not have MCE assessed due to technical difficulties. In one case, contrast could not be infused during the recovery stage due to occlusion of the intravenous line; in the other, RP during recovery could not be evaluated due to an acquisition error. These patients (see above) were excluded from further analysis. 756 (18x42) LV segments were ultimately analysed. When compared to myocardial contrast opacification, RP could be evaluated less frequently at peak stress (660 *vs* 629 segments, $p < 0.05$) and at similar frequency during recovery (618 vs. 606 segments, $p = 0.47$). Furthermore, peak stress and recovery perfusion could be compared in 580 segments, whereas wall motion could be compared in 675 segments ($p < 0.05$).

Diagnostic value

The sensitivity and specificity of MCE during supine bicycle stress in the diagnosis of coronary artery stenosis confirmed by angiography were demonstrated to be 92.0% and 82.4%, respectively. The positive predictive value of the method in the diagnosis of IHD was found to be 88.5%, while the negative predictive value was 87.5%. The concordance between quantitative coronary angiography and MCE was 88.1%. Using the kappa statistics, the agreement in the detection of IHD was good ($\kappa = 0.75$).

Discussion

Feasibility

The study demonstrates that MCE during supine bicycle stress and continuous infusion of an ultrasound contrast agent allows the simultaneous assessment of myocardial perfusion and contractility. During examination, myocardial perfusion in individual LV segments could be assessed with respect to both myocardial contrast opacification and RP. It has been suggested that the RP rate may be superior to myocardial contrast opacification in the diagnosis of significant coronary artery stenosis. [4]. This has been confirmed in previous experimental studies which quantitatively assessed myocardial perfusion [13-15]. The RP in individual LV segments is, however, more difficult to visualise than myocardial contrast opacification, since it requires the acquisition of consecutive cardiac cycles in the same scanplane [2, 10]. Our results support this statement, showing that RP was successfully assessed in fewer segments than myocardial contrast opacification. This difference was statistically significant only at stress, when it is more difficult to maintain the scanplane due to the patient's or transducer movements.

The contractility analysis could be performed for significantly more segments than the perfusion analysis. This can be attributed to the fact that imaging artefacts made it more difficult to assess myocardial perfusion than function. These artefacts were particularly frequently related to the basal segments

and anterior and lateral walls, i.e. regions in which perfusion imaging is difficult due to ultrasound beam attenuation [4, 16, 17]. As a result, assessment of the perfusion and function of these LV regions should be conducted especially carefully [4].

Diagnostic value

Previous studies have shown that MCE allows accurate detection of perfusion defects in patients with significant coronary artery stenosis [5-8]. The best agreement with coronary angiography was reached when the results of LV segmental perfusion and function analysis were combined. [6]. Our results confirm these findings, demonstrating that real-time power modulation imaging allows an accurate diagnosis of IHD. The concordance between coronary angiography and the combined assessment of LV perfusion and function was similar to that demonstrated by Shimoni et al. [6], who found that the agreement between coronary angiography and harmonic accelerated (low MI) intermittent imaging after a bolus injection of contrast was 86% (κ=0.71), with a sensitivity and specificity of 86% and 88%, respectively. In comparison to that study, it is noteworthy that despite a lower pre-test probability of IHD our examination was found to have a higher sensitivity.

There are several plausible explanations. First of all, the detection of perfusion defects using a power modulation technique may be easier than by harmonic imaging, due to the higher signal to noise ratio [4]. Secondly, when compared to bolus administration, continuous contrast infusion may ensure better imaging quality with fewer visible artefacts [18]. Thirdly, continuous infusion allows the assessment of the RP rate, which – according to experimental studies – appears to detect myocardial ischaemia more accurately than myocardial contrast opacification [4, 13-15]. Finally, the difference in sensitivity may be related to different stress protocols applied in the two studies. In the study of Shimoni et al. [6], the subgroup of patients that underwent post-treadmill exercise echocardiography could lower the sensitivity and affect the final results of the study [19].

We are not aware of any other study that has attempted to determine the accuracy of MCE in patients with an intermediate pre-test probability of IHD, for whom, according to Bayes' theorem, the diagnostic value of the method should be the greatest [20]. Porter et al. [7] performed coronary angiography on patients with an intermediate pre-test risk of IHD and reversible perfusion defects, discovering significant (i.e. ≥50%) atherosclerotic lesions in 75% of patients. Our study showed a higher positive predictive value. In the study of Porter et al. [7], however, the combined assessment of perfusion and wall motion was not performed and perfusion was not evaluated in terms of RP.

Methodological limitations

Our study examined a relatively small group of patients and our findings must, therefore, be confirmed in a larger group. Myocardial perfusion was assessed qualitatively, while a quantitative evaluation would allow more accurate detection of ischaemia [8]. It is noteworthy that qualitative analysis has not yet been standardised and the evaluation of perfusion may be influenced by the presence of wall motion abnormalities [6]. A qualitative assessment does, however, accurately detect ischaemia [5-8] and, being a less time-consuming method, it may be more useful in clinical practice [8]. The fact that MCE was not compared with myocardial perfusion scintigraphy – the only validated method of myocardial perfusion analysis – is a further limitation. Coronary angiography does not allow a functional assessment of the visualised arterial stenoses.

Conclusions

1. Myocardial contrast echocardiography during supine bicycle stress and continuous intravenous infusion of an ultrasound contrast agent is a feasible technique allowing simultaneous real-time visualisation of LV myocardial perfusion and function.
2. This method allows an accurate diagnosis of ischaemic heart disease in patients with intermediate pre-test probability of the disease.

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Rozpoznawanie choroby niedokrwiennej serca przy użyciu perfuzyjnej echokardiografii kontrastowej w czasie próby wysiłkowej na ergometrze rowerowym w pozycji leżącej

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Streszczenie

Wstęp: Perfuzyjna echokardiografia kontrastowa (ECHO/K) jest nową techniką umożliwiającą diagnostykę choroby niedokrwiennej serca (IHD).

Cel: Ocena możliwości wykonania ECHO/K w czasie próby wysiłkowej na ergometrze rowerowym oraz ocena wartości diagnostycznej tej metody w rozpoznawaniu IHD.

Metody: 44 kolejnych chorych, którzy byli kierowani na planową koronarografię i u których przedtestowe prawdopodobieństwo IHD było umiarkowane, poddano próbie wysiłkowej na ergometrze rowerowym w pozycji leżącej. ECHO/K wykonywano na szczycie wysiłku oraz w fazie odpoczynku, gdy tylko częstość rytmu serca osiągnęła wartość sprzed próby wysiłkowej. W trakcie ECHO/K stosowano ciągły wlew ultrasonograficznego środka kontrastowego (Sonovue®) podawanego za pomocą pompy infuzyjnej (BR-INF 100, Bracco Research). Otrzymane obrazy oceniano jakościowo pod kątem zaburzeń perfuzji oraz kurczliwości mięśnia sercowego. Do analizy wykorzystano podział mięśnia lewej komory na 18 segmentów. W ciągu 15 dni od próby wysiłkowej u wszystkich pTS wykonano koronarografię. Ocenę ilościową uwidocznionych zwężeń tętnic wieńcowych dokonano za pomocą programu CAAS.

Wyniki: U 2 chorych nie można było ocenić ECHO/K z przyczyn technicznych. Badanie koronarograficzne ujawniło obecność istotnych zwężeń tętnic wieńcowych u 25 z nich. Czułość i swoistość ECHO/K w rozpoznawaniu IHD wynosiła odpowiednio 92,0% i 82,4%. Dodatnia i ujemna wartość predykcyjna przyjęły wartości 88,5% i 87,5%, a zgodność pomiędzy wynikami koronarografii i ECHO/K 88,1% (κ=0,75).

Wnioski: ECHO/K wykonywana w czasie próby wysiłkowej na ergometrze rowerowym przy ciągłym wlewie ultrasonograficznego środka kontrastowego jest techniką możliwą do wykonania. Metoda ta umożliwia trafne rozpoznawanie IHD u chorych, u których przedtestowe prawdopodobieństwo choroby jest umiarkowane.

Słowa kluczowe: perfuzyjna echokardiografia kontrastowa, choroba niedokrwienna serca, echokardiografia obciążeniowa

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