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Myocardial Contrast Echocardiography Yields Best Accuracy Using Quantitative Analysis of Digital Data from Pulse Inversion Technique: Comparison with Second Harmonic Imaging and Harmonic Power Doppler During Simultaneous Dipyridamole Stress SPECT Studies

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Aims: This prospective study assesses the (1) feasibility of quantifying ultrasound myocardial perfusion studies based on the densitometric analysis of digital data and the (2) comparison of pulse inversion, second harmonic and harmonic power Doppler modalities with SPECT.

Methods and Results: Twenty-three patients with suspected ischaemic heart disease had i.v. injections of Tc-Sestamibi and Optison® during a dipyridamole stress test for echocardiography in pulse inversion, second harmonic and harmonic power Doppler mode. Analysis was (a) visual by scoring and (b) quantitative by densitometry of digital data for background subtracted myocardial opacification (a.u.) and normalized contrast effect (%). In the nine control patients, myocardial opacification at stress was greater ($P \leq 0{\cdot}002$) than in the pathologic group (5·8 ± 3·3 vs 2·6 ± 2·5 a.u. in pulse inversion, 5·4 ± 2·1 vs 2·4 ± 1·8 in second harmonic and 7·1 ± 3·7 vs 4·9 ± 3·7 a.u. in harmonic power Doppler). In the pathologic group, normalized contrast effect decreased significantly during stress (23·7 ± 18·8 to 11·3 ± 10·8%, $P<0{\cdot}003$) only in pulse inversion. Kappa values for patient based diagnostic agreement with SPECT were 0·75 by pulse inversion, 0·62 by second harmonic and 0·52 by harmonic power Doppler for quantitative analysis, and 0·51, 0·37 and 0·35 respectively, for visual assessment.

Conclusion: Myocardial contrast echocardiography should be analysed using densitometry of digital data. The new technique pulse inversion demonstrates best agreement with SPECT data.
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Key Words: Myocardial perfusion imaging; contrast echocardiography; video signal; SPECT.

Introduction

An important task of myocardial perfusion imaging is to diagnose potential ischaemia in patients with coronary heart disease. Although validated in animal studies[1,2], standard fundamental echocardiography failed to demonstrate reproducible myocardial contrast effects after intravenous microbubble injections in man. This fact induced the more recent development of new imaging modalities which exploit non-linear bubble behaviour and result in improved signal to noise ratio. They are based on the following mechanisms: (1) microbubble resonance and subsequent induction of harmonic frequencies for second harmonic imaging[3,4], (2) microbubble destruction and induction of high energy complex frequency signals for power Doppler techniques[5] as loss of correlation on-line subtraction imaging[6]

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and, most recently (3) specific response to a negative vs a positive acoustic pressure wave for pulse inversion technique[7].

Due to the fast development and introduction of these myocardial perfusion imaging modalities, only second harmonic imaging[8,9] and power Doppler techniques have been evaluated individually[10,11] using high mechanical index and triggered imaging. To our knowledge, there is no such report on pulse inversion technique and no comparative evaluation of all three imaging modalities in man. Furthermore, traditional evaluation has been based on visual inspection of videotaped perfusion studies which implies two important limitations to diagnostic accuracy. One of them is the non-quantitative and subjective nature of analysis and the other is the use of video signals for analysis, which contain only 20–30 dB of information, whereas digital signals contain 50–60 dB of information. Most modern ultrasound systems, however, allow access to digital signals for analysis and archiving purposes.

The purpose of this prospective study was (1) to evaluate the feasibility of quantifying ultrasound myocardial perfusion studies based on the analysis of digital data, (2) to perform a comparative evaluation of pulse inversion, second harmonic and power Doppler techniques and (3) to study the diagnostic accuracy of these modalities using simultaneous single photon emission computed tomography (SPECT) as the reference method in patients with suspected coronary heart disease, subjected to a dipyridamole stress test for the assessment of significant coronary artery stenosis.

Methods

Patients

The protocol of this study was approved by the Institutional Review Board of the Karolinska Hospital in Stockholm. Following informed consent, 23 ambulatory patients who had been referred for the scintigraphic evaluation of suspected or known coronary heart disease participated in this study (14 men, mean age 59 ± 9 years, mean weight 76 ± 14 kg, mean height 171 ± 8 cm). All patients were in sinus rhythm and unselected with regard to the ultrasound image quality. Three patients had a history of inferior myocardial infarction and one had had coronary arteriovenous bypass grafting. Exclusion criteria were pregnancy, unstable angina, obstructive airways disease and hypersensitivity to blood products and albumin. Coronary angiography was not necessary for inclusion into this study. It was, however, performed on clinical indication in eight patients.

Imaging methods for stress test are used only in patients with an intermediate probability of reversible ischaemia. Thus, the meaningfulness of any new diagnostic method should be tested in this particular risk group. Accordingly, we ascribed to the control group individuals with normal perfusion by SPECT (n=9) as compared to the patients with stress induced perfusion defects (n=14) in the sector equivalent to the echocardiographic four-chamber view.

Stress Test

An intravenous infusion of dipyridamole (Dupont/Merck) was maintained over 6 min to a total dose of 0·84 mg/kg if the echocardiographic monitoring after 4 min at the dose of 0·56 mg/kg dipyridamole had confirmed unchanged regional left ventricular function. End points were as in standard stress echocardiography. If required, intravenous theophylline was given as an antidote. Myocardial contrast ultrasound images were taken before and after the infusion of dipyridamole together with recordings of blood pressure, heart rate and a 12-lead ECG.

SPECT

^{99m}Tc-Sestamibi (450 MBq) was injected 3 min after the infusion of dipyridamole.

Imaging was performed 1 h post injection with a dual headed gamma camera (SMV DST-XL) equipped with high resolution low energy parallel hole collimators. Thirty-two projections were acquired through 180° degrees using a 90° detector geometry. Reconstruction was performed without attenuation correction, using filtered back projection. For evaluation, a polar map (bull's eye) was generated from short axis sections with a nominal thickness of 11 mm. Each map was scaled to the maximum within the myocardial volume. The only reference area used for evaluation was a sector about the posterior/lateral to septal anterior/septal diagonal which corresponded to the orientation of the ultrasound images. Thus, the segmentation into the basal and the apical part of these walls corresponded to the localization of the four left ventricular segments analysed in the ultrasound images. Subjective assessment of myocardial perfusion in this sector was made independently from the complete polar map by two experienced observers kept unaware of the patients' clinical and echocardiographic data. A four point scale was used: 0= no perfusion defect, 1= mild defect, 2=moderate and 3=severe perfusion defect. The spatial extent and localization and, thus, the stenosed vessel, were also identified. Inter- and intra-observer variability from resting as well as stress images was established after 4 months in 10 randomly selected patients.

Myocardial Contrast Echocardiography

The contrast agent, Optison® (Mallinckrodt), is a suspension of perfluoropropane filled albumin microspheres with a mean concentration of $5–8 \times 10^8$

microspheres/mL and a mean diameter of 2·0–4·5 μm[12]. The time needed to switch from one to two more different imaging modalities both at rest and at stress would have far exceeded the time available with an intravenous infusion of Optison for the recording of different trigger intervals during steady state. Therefore, it was necessary to use bolus injections (0·3 ml) followed by a flush of 5 ml saline for each imaging modality at the trigger rate of one frame per two cardiac cycles. Experience has shown that this trigger rate allows good discrimination between normal and reduced myocardial perfusion in endsystolic images during stress.

Patients were studied in the left lateral semicubitus position. A commercially available ultrasound system (ATL HDI 5000) was used with a broad band transducer (1·77 MHz) to image the four-chamber view in a randomized sequence of the following three imaging modalities: (1) second harmonic imaging, (2) harmonic power Doppler and (3) pulse inversion technique.

In (1), second harmonic imaging, a filter is applied to the reflected ultrasound signals in order to selectively use the signals with harmonic frequencies (3·3 MHz) for image construction. In (2), harmonic power Doppler technique, a sequence of 4–8 short ultrasound bursts is emitted during each frame. Comparison of these signals allows the detection of fast movements or microbubble destruction as on-line subtraction. The intensity of these Doppler signals which is independent of velocity, direction and the angle of incidence is displayed in a colour coded map. The additional use of the harmonic frequency range reduces motion artefacts and clutter. In (3), pulse inversion technique, ultrasound signals are displayed in grey scale within the harmonic frequency range. This is achieved not by filtering but by adding the reflected signals from two successive ultrasound bursts with inverted phases of the acoustic pressure wave which induce different patterns of signal reflection from microbubbles as opposed to tissue resulting in a harmonic pattern for bubbles and, theoretically, into cancellation for tissue.

The mechanical index was set high (1·1–1·3), the timing of the trigger at the top of the T wave and the focus was placed at the level of the mitral annulus. The dynamic range was 60 dB and the overall gain low enough to display the pre-contrast myocardium as a dark grey structure. In harmonic power Doppler, pulse repetition frequency was set at 1500 Hz, wall filter at medium and Doppler gain increased up to the level where pre-contrast images do not yet display colour artefacts. This setting of the ultrasound system was maintained throughout the study.

Analysis

The digital data were downloaded into a personal computer and analysed off-line using dedicated software (HDI lab version 1·77) by an experienced echocardiographer (HB) who was unaware of the patients' clinical and SPECT data. Signal intensity was measured by densitometry and expressed in arbitrary units related to reflectivity (a.u.) in four myocardial transmural regions of interest (the basal and the apical segments of the septal and lateral left ventricular wall) and in the right and left ventricular cavity. These regions were carefully aligned so that endo- and pericardial structures were not included. Time intensity curves were generated from all regions of interest to facilitate the selection of the optimal frames for calculating the peak contrast effect: the basal septum should no longer demonstrate blooming artefacts from the right ventricular cavity and the basal lateral wall should display maximal signal intensity after contrast attenuation effects had disappeared. Pre-contrast and peak myocardial signal intensities were averaged from four consecutive frames to calculate myocardial opacification as background subtracted signal intensity (ΔSI). To enable comparison of rest and stress contrast effects (CE), myocardial opacification was normalized for the signal intensity of the left ventricular blood pool (SI_{LV}) and expressed in percent ($CE = 100 \times \Delta SI / SI_{LV}$). The stress induced change of the contrast effect was defined as CE stress − CE rest (%). The perfusion pattern was interpreted as normal if myocardial opacification during stress, was >4 a.u. or 2–4 a.u. associated with normal contrast effect >40%. To facilitate a segment based evaluative comparison of the three ultrasound modalities, a control group and a pathologic group were selected as follows: the control group consisted of all segments (n=36) of the patients with normal SPECT stress test and the pathologic group contained the segment with the least tracer uptake from each patient with an abnormal SPECT study (n=14).

Densitometric analysis in the three imaging modalities of five randomly selected patients was performed by two experienced investigators (HB and AH) for inter-observer variability and repeated by the first investigator after 4 months for intra-observer variability.

In addition to densitometry, visual assessment was performed by two independent observers who were unaware of the patients' clinical and scintigraphic data. The dedicated analysis software (HDI lab version 1·77) was used to display rest and stress studies side by side to evaluate whether a stress induced contrast defect was discernible in any myocardial segment. The confidence of this interpretation was noted as score: 1=limited, 2=moderate and 3=good and 0= analysis not possible. Differences of opinion were resolved by consensus.

Statistical Methods

Data are expressed as mean ± standard deviation in text and tables and as boxplots of percentiles in the graphs. The Student *t*-test for paired observations was used for sequential changes in myocardial signal intensity and the unpaired Student *t*-test with non-even distribution for comparison of the control with the pathologic group.

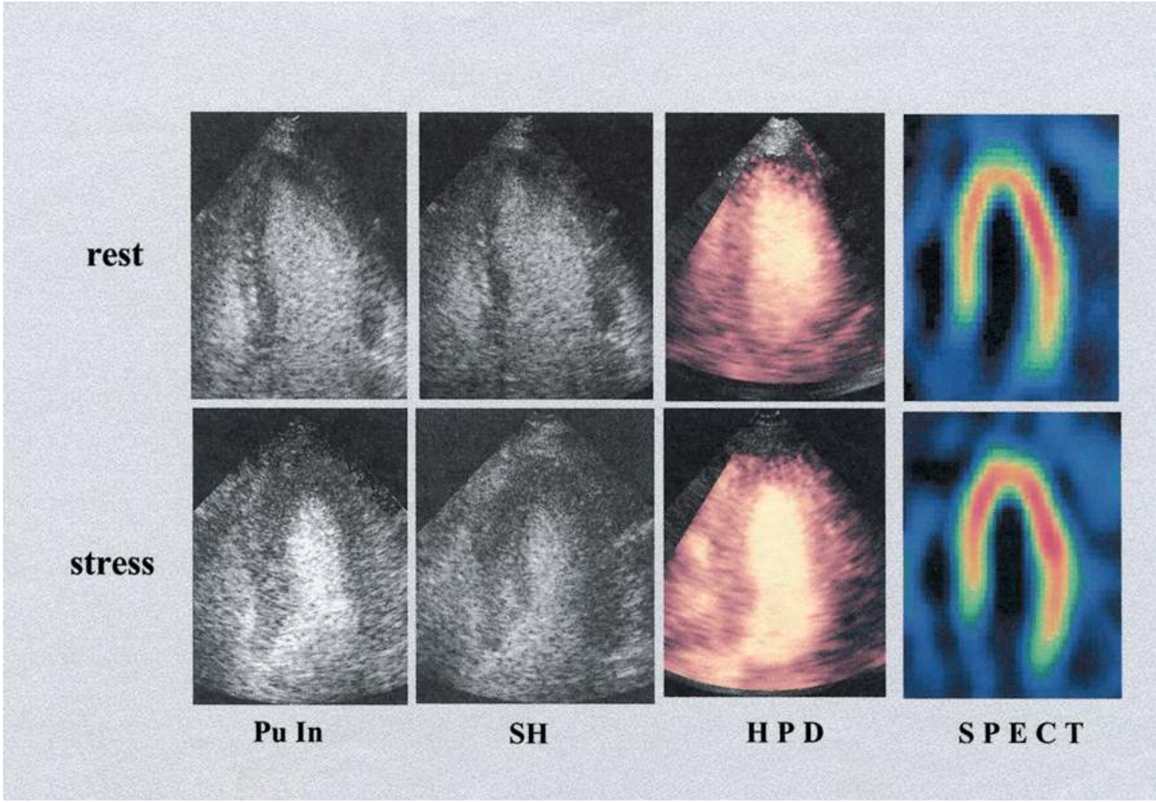

Figure 1. Imaging examples of a patient with normal myocardial perfusion at rest (top panels) and during stress (bottom panels) in pulse inversion technique (Pu In), second harmonic imaging (SH), harmonic power Doppler (HPD) and SPECT imaging. The uptake of contrast agent and tracer is homogenous during stress apart from some drop out in the lateral wall in harmonic power Doppler technique and is increased if compared to rest.

Significance level was established for two-tailed tests at $P<0{\cdot}05$. The intra- and inter-observer variability was calculated as the coefficient of variation. Kappa statistics[13] was used to determine concordance between scores, κ of <0·4, >0·4, >0·6 and >0·75 indicating a poor, fair, good and strong agreement. Agreement between ultrasound and SPECT results is demonstrated in contingency tables.

Results

SPECT

The quality of images was sufficient for analysis in all patients. Myocardial perfusion during stress and rest was considered normal in nine patients. The segments from these patients (n=36) were taken as a control group. Stress induced perfusion abnormalities were found in 14 patients. From each of these patients, the segment with the most abnormal perfusion pattern was selected for the pathologic group (n=14). Significant lesions were ascribed to the territory of the left anterior descending artery in six, to the right coronary artery in four and to the circumflex artery in six patients respectively. Tracer uptake at rest was slightly reduced in six of the patients but decreased even more during stress in all these cases. There were no severe perfusion defects at rest in the equivalent plane of the echocardiographic four-chamber view.

The angiographic results from the eight patients who had a coronary angiogram were completely concordant with the SPECT data both for the interpretation of normal (n=1) vs pathologic vascular status (n=7) and the site of abnormality.

When assessed for normal vs pathologic perfusion pattern, intra-observer and inter-observer agreement occurred in 72/80 left ventricular segments (κ=0·79). With respect to the individual three grades of perfusion abnormalities, intra-observer agreement occurred in 90% of segments (κ0·79). There was $\leq$1 grade difference in the remaining eight segments. Inter-observer agreement occurred in 82% of segments (κ=0·62). Differences in the remaining 11/80 segments did not exceed one grade.

Dipyridamole Stress Test

During the pharmacologic stress test, heart rate increased from 65 ± 11 to 90 ± 14 bpm. Systolic blood pressure decreased from 151 ± 26 to 142 ± 19 mmHg

Table 1. Normal values of myocardial opacification (a.u.) and contrast effect (%).

		Septal wall basal	Septal wall apical	Lateral wall basal	Lateral wall apical	LV
Pulse inv ΔSI (a.u) stress	Mean	8·0	5·8	5·9	4·4	17·8
	SD	3·5	2·1	3·4	1·9	6·4
CE (%)	Mean	47·2	33·9	32·1	27·2	
	SD	17·7	11·5	14·5	12·9	
ΔSI (a.u.) rest	Mean	6·3	5·2	5·6	3·6	21·1
	SD	2·8	2·4	4·1	1·5	9·0
CE (%)	Mean	30·6	26·1	25·9	18·7	
	SD	14·2	12·7	13·0	8·7	
Sec. harm ΔSI (a.u.) stress	Mean	6·9	5·5	5·6	4·7	16·3
	SD	3·6	1·9	2·0	2·1	6·2
CE (%)	Mean	47·6	36·8	38·0	32·3	
	SD	23·5	15·9	18·6	17·5	
ΔSI (a.u.) rest	Mean	5·2	4·3	4·7	3·5	19·0
	SD	1·9	2·5	2·5	1·7	4·4
CE (%)	Mean	28·0	22·5	25·1	18·0	
	SD	9·3	11·3	13·5	8·6	
H.P. Doppler ΔSI (a.u.) stress	Mean	8·6	10·1	5·3	7·8	18·3
	SD	3·7	2·3	3·2	3·2	4·3
CE (%)	Mean	46·0	55·6	28·0	42·9	
	SD	16·1	9·5	13·2	15·9	
ΔSI (a.u.) rest	Mean	6·2	6·1	4·7	4·2	19·3
	SD	3·6	3·0	2·9	1·8	4·7
CE (%)	Mean	30·7	30·9	22·6	22·1	
	SD	16·9	16·1	13·1	8·8	

Pulse inv=pulse inversion technique, ΔSI=myocardial opacification, CE=contrast effect, Sec. harm=second harmonic imaging, H.P. Doppler=harmonic power Doppler imaging, lv=left ventricular cavity.

Table 2. Comparison of contrast effect (%) in the group of normal vs pathologic perfusion.

	Pulse inversion (%)		Second harmonic (%)		Harm power D (%)	
	Stress	Rest	Stress	Rest	Stress	Rest
Normal						
Mean	35·1	25·4	38·7	23·4	43·1	26·6
SD	15·6	12·5	19·1	11·0	16·7	14·1
P (stress vs rest) <	0·003		0·0001		0·0001	
P (normal vs path) <	0·0001		0·0001		0·0006	
Pathologic						
Mean	11·3	23·7	14·1	14·6	24·3	25·9
SD	10·8	18·8	8·6	7·6	14·0	14·5
P (stress vs rest) <	0·003		ns		ns	

Harm power D=harmonic power Doppler imaging, vs=versus, ns=not significant.

and diastolic blood pressure from 81 ± 10 to 72 ± 11 mmHg (P<0·01). These haemodynamic data were similar in the two subgroups with normal or pathologic myocardial perfusion. The infusion of dipyridamole was stopped at 0·56 mg/kg in one patient who developed angina and wall motion abnormalities. Four patients experienced angina after the full dose of dipyridamole and two of them developed wall motion abnormalities. There were no significant adverse reactions like severe arrhythmia or myocardial infarction.

Myocardial Contrast Echocardiography, Quantitative Analysis

Myocardial contrast echocardiography could be performed in the three imaging modalities in all patients at

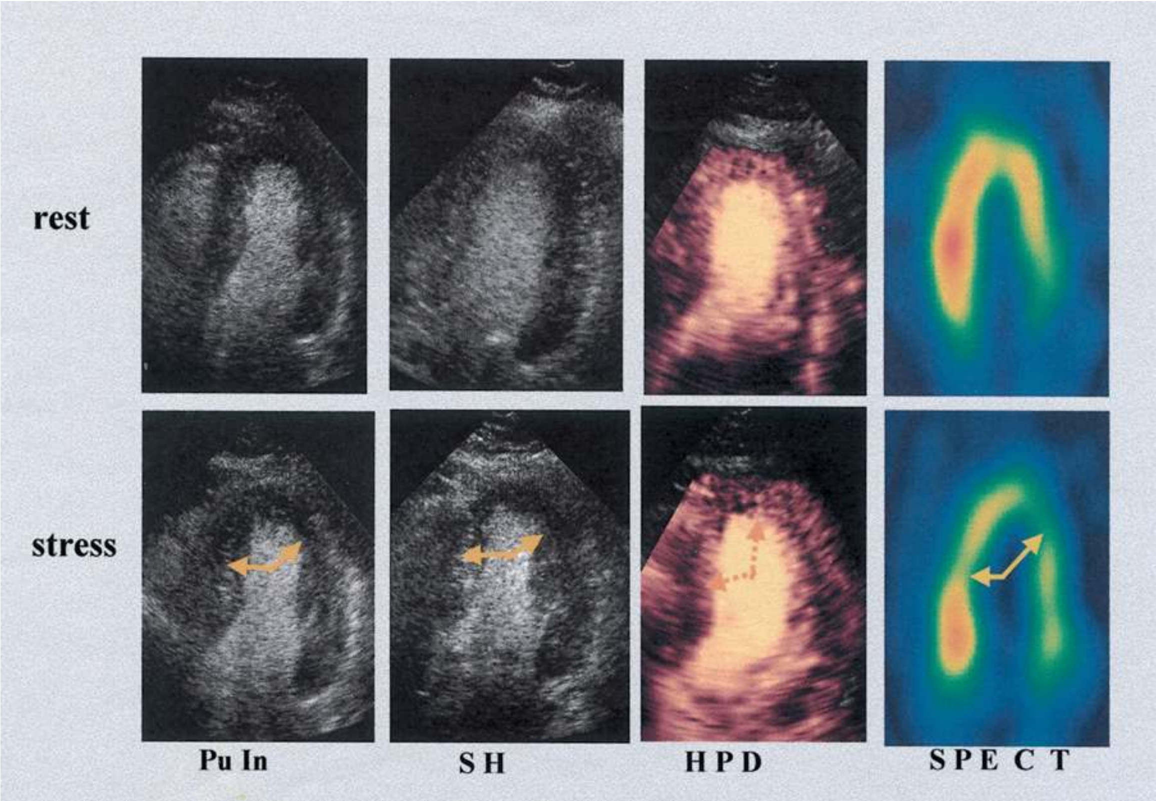

Figure 2. Same setting as in Fig. 1 for a patient with a 90% stenosis of the left anterior descendent coronary artery. There is a stress induced contrast defect in pulse inversion and second harmonic imaging (arrows) corresponding well with the stress induced perfusion defect in SPECT imaging (arrows). In harmonic power technique, contrast uptake is scanty at rest and during stress, so that assessment of a perfusion defect during stress is limited (half transparent arrows) being based mainly on the comparison to rest.

rest and during stress. The quality of the recorded images was insufficient for analysis of myocardial signal intensity in 11 (12%) of the left ventricular segments at rest and four (4%) at stress. These unanalysable contrast images occurred due to myocardial attenuation artefacts/signal drop out in harmonic power Doppler (nine segments) or second harmonic imaging (two segments) and due to an error in setting the ultrasound system before recording in pulse inversion technique (four segments at rest). The intra-observer variability was 0·7 a.u. (6·7%) in pulse inversion technique 1·1 a.u. (9%) in second harmonic imaging and 1·3 a.u. (10·4%) in harmonic power Doppler. The inter-observer variability was 1·0 a.u. (9%), 1·2 (10·6%) and 1·5 a.u. (11·6%) respectively.

Control Group

The echocardiographic images of a typical patient with normal SPECT (Fig. 1) demonstrate homogenous myocardial opacification in the pulse inversion and second harmonic techniques and an attenuation artefact in the basal lateral wall in harmonic power Doppler. Table 1 displays the quantitative ultrasound data of the individual myocardial segments. There was significant myocardial opacification after injection of the contrast agent in all segments measurable by all imaging modalities during rest and stress. Comparing stress with rest, there was an increased myocardial contrast effect during stress ($P \leq 0{\cdot}003$) in all three imaging modalities (Table 2).

Pathologic Group

Figures 2 and 3 display ultrasound and SPECT images of patients with a stenosis of the left anterior descending artery and the circumflex coronary artery respectively. Size and site of the perfusion defects correspond for pulse inversion and second harmonic imaging. Interpretation of the power Doppler perfusion images is more ambiguous due to the scanty display of myocardial opacification. In the pathologic group, myocardial opacification and contrast effect were significantly reduced if compared to the control group ($P \leq 0{\cdot}002$) with the smallest overlap of data in the pulse inversion technique [Fig. 4(a),(b)]. For the pathologic group, a stress induced reduction of the contrast effect was

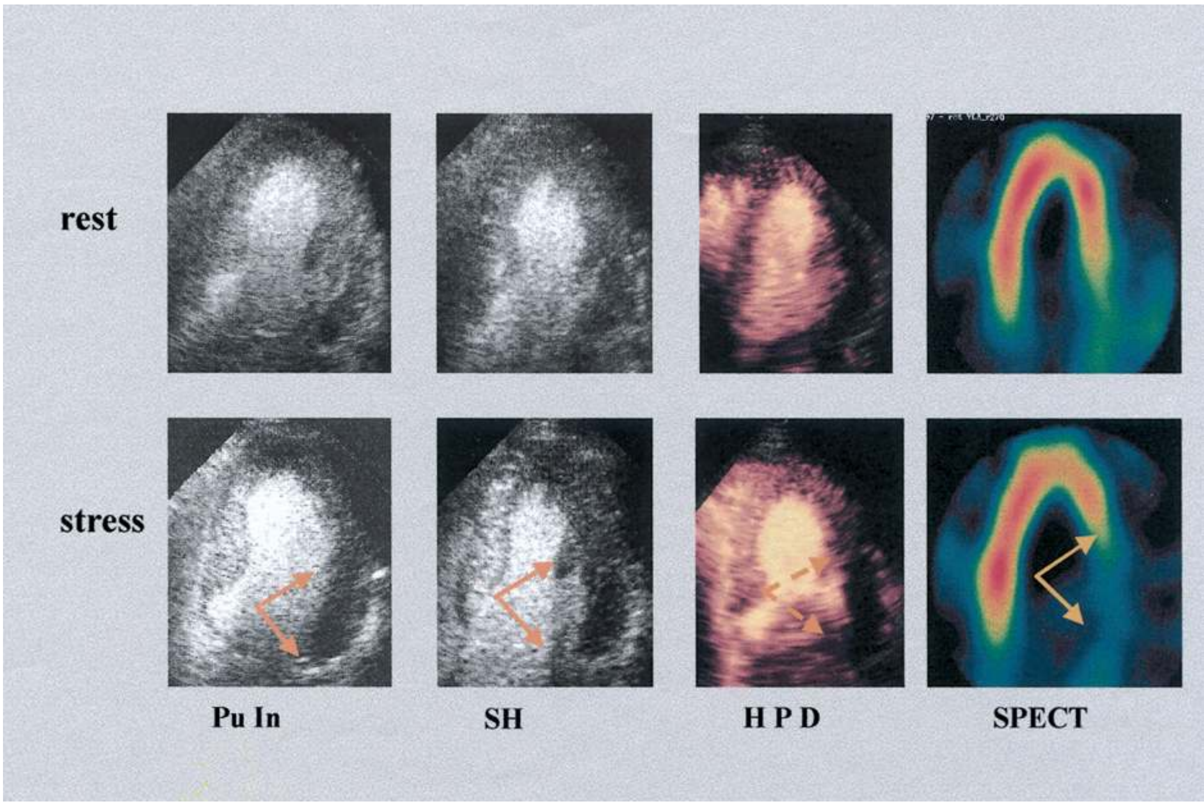

Figure 3. Same setting as in Fig. 1 for this patient with a distinct stress induced perfusion defect in SPECT in the mid to basal lateral wall (arrows) demonstrating a significant increase of the mild perfusion defect present in the very basal lateral wall at rest in both gray scale ultrasound techniques (arrows). In harmonic power technique, contrast uptake is not seen in the lateral wall at rest so that assessment of a perfusion defect during stress is limited (half transparent arrows).

observed only in pulse inversion technique ($P<0{\cdot}01$; Table 2, Figure 5).

Comparison of the Three Imaging Modalities with SPECT

Quantitative Assessment

In stress perfusion scintigraphy, 19/92 segments were classified as reduced and 73 as having a normal tracer uptake. With reference to individual patients, pathologic stress tests were diagnosed as displayed in the top contingency tables (Table 3) resulting in agreement with SPECT data of 87% ($\kappa=0{\cdot}73$) for the pulse inversion technique, 83% ($\kappa=0{\cdot}62$) for second harmonic imaging and 78% ($\kappa=0{\cdot}51$) for harmonic power Doppler. The regional agreement for the four possible sites of a perfusion abnormality was 83% (76/92) with the pulse inversion technique, 79% (73/92) with second harmonic imaging and 67% (62/92) with harmonic power Doppler.

Visual Assessment

During visual inspection, analysis was of limited confidence (score 1) in 10 patients with harmonic power Doppler, in three patients with second harmonic imaging and in two patients with pulse inversion technique. Harmonic power Doppler images were very sensitive to attenuation artefacts, resulting in scanty and non-homogenous display of myocardial opacification. Pulse inversion images demonstrated the best resolution and, thus, definition of the myocardium. The agreement for patient based diagnosis of stress induced perfusion defects with perfusion scintigraphy is plotted in the bottom contingency tables of Table 3. It was 78% ($\kappa=0{\cdot}51$) for the pulse inversion technique, 70% ($\kappa=0{\cdot}37$) for second harmonic imaging and 65% ($\kappa=0{\cdot}35$) for harmonic power Doppler. The regional agreement to the site of a perfusion abnormality was 76% (70/92), 68% (63/92) and 71% (65/92) respectively.

Discussion

The present study demonstrates the feasibility of quantifying ultrasound myocardial perfusion studies during dipyridamole stress using analysis of digital data. This approach allowed an objective comparison of the three

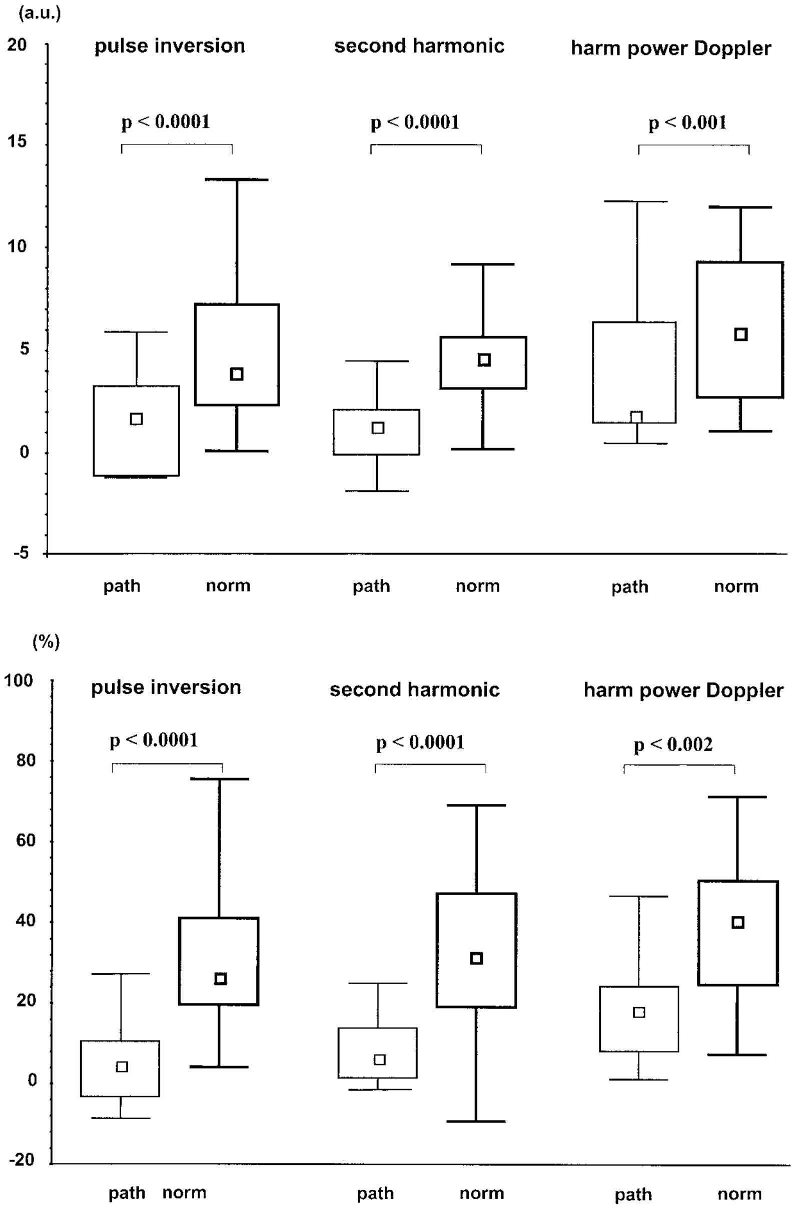

Figure 4. (a) Box plot of myocardial opacification (a.u.) during stress in the three ultrasound imaging techniques, pulse inversion technique, second harmonic imaging and harmonic power Doppler (harm power Doppler). The open columns represent results in left ventricular segments with normal perfusion as defined by SPECT and the gray columns data in segments with pathologic perfusion. The box plots display the 50th median (□), 25th–75th percentiles (▯), 24th to minimal (⊥) and 76th to maximal percentiles of the variable (⊤). The difference between left ventricular segments with normal vs reduced perfusion is significant in all ultrasound modalities albeit a specific amount of overlap. (b) Box plots of the same setting for the normalized contrast effect CE (%) during stress demonstrating less overlap between the normal and the pathologic perfusion groups. Harmonic power Doppler, again, shows the greatest overlap between the normal and the pathologic group.

bubble specific imaging modalities, pulse inversion technique, second harmonic imaging and harmonic power Doppler, in man with SPECT as reference method. Quantitative analysis resulted in superior diagnostic accuracy compared with traditional visual assessment. It also demonstrated the best diagnostic accuracy for the pulse inversion technique, followed by second harmonic imaging.

Table 3. Diagnostic accuracy of myocardial contrast echocardiographic stress test for the assessment of coronary artery stenosis — patient based contingency tables.

	Pulse inversion		Second harmonic		Harm power D	
	+	−	+	−	+	−
Quantitative assessment						
SPECT						
+	12	2	13	1	13	2
−	1	8	3	6	3	5
Agreement	20 (87%)		19 (83%)		18 (78%)	
Kappa	0·73		0·62		0·51	
Visual assessment						
SPECT						
+	12	2	10	3	13	6
−	3	6	4	6	2	2
Agreement	18 (78%)		16 (70%)		15 (65%)	
Kappa	0·51		0·37		0·35	

Harm power D=harmonic power Doppler imaging.

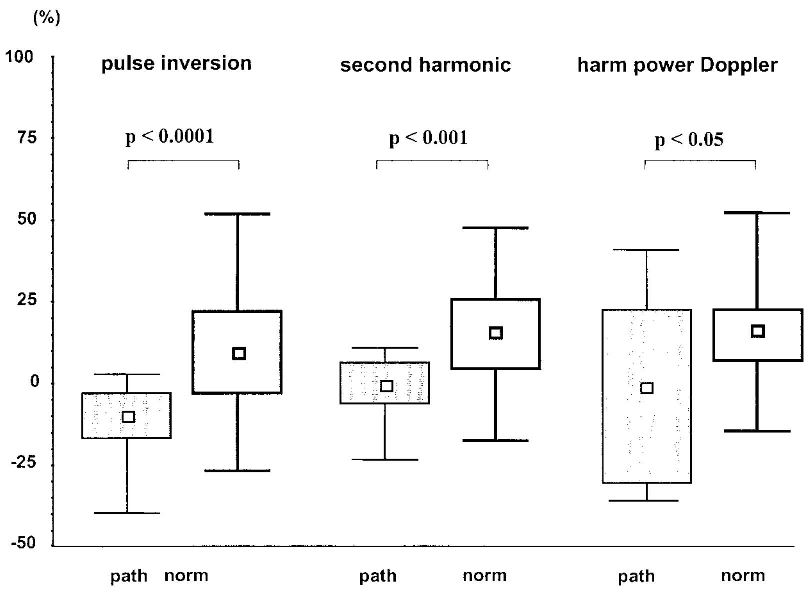

Figure 5. Box plots of the stress induced changes in normalized contrast effect CE (%) using the same setting as in Fig. 4. Normally perfused segments increase perfusion during dipyridamole stress, whereas segments depending on a stenosed coronary artery cannot. This distinction is clearest by pulse inversion technique followed by second harmonic imaging. Harmonic power Doppler just reaches significance.

Imaging Modalities for Myocardial Contrast Echocardiography

In the present era of interventional and pharmacological strategies aimed at the restoration of blood flow to hibernating myocardium, it has become increasingly important to establish a method for the repetitive bed-side assessment of regional myocardial perfusion[14]. The potential for myocardial contrast echocardiography to perform this task has recently been realized due to the production of suitable contrast agents and the almost explosive development of several bubble specific imaging modalities. The present comparative study was designed to support the cardiologist on the point of using myocardial contrast echocardiography in the selection of the adequate technique. The following details should clarify the possible benefits and limitations of the three imaging modalities. Power Doppler technique requires the destruction of bubbles for their display (loss of correlation imaging). As this technique works like an on-line subtraction — tissue does not produce loss of correlation effects — it appears easy to interpret by simple inspection. The destruction of bubbles, however, requires high levels of acoustic energy which may not have been available locally due to technical factors or tissue attenuation, particularly in the basal segments of the heart[15]. This often results in lack of opacification which may be misinterpreted as a perfusion defect[10,11]. Grey scale methods like second harmonic imaging and pulse inversion require background subtraction. Accordingly, these techniques are time consuming in analysis. They are, however, not based on bubble destruction and are, therefore, only moderately limited by tissue attenuation. Both methods result in displaying signals in the second harmonic frequency range. Second harmonic imaging achieves this by the use of filters which may lead to considerable overlap and ambiguity particularly in the range of low intensity signals[16]. Pulse inversion technique uses pairs of pulses, which allow mathematical differentiation between signals reflected by bubbles vs those, reflected from tissue. These sophisticated processes result in excellent image resolution, high sensitivity of bubble detection and improved performance at low levels of acoustic energy or increased tissue attenuation[7]. From a theoretical perspective, pulse inversion technique offers the most robust approach to bubble specific imaging, which is confirmed by the present results (Table 3; Figs 3 and 5).

Quantification vs Visual Assessment Using Digital Data

Our data demonstrate the superiority of all quantitatively achieved diagnostic accuracy over visual assessment (Table 3). It is noteworthy, that Porter[17] reported only 42% concordance for visual assessment of the second harmonic images of myocardial contrast echocardiography compared to 92% for quantitative evaluation of video signals. Conversely, Kaul and coworkers achieved a concordance of 82% with SPECT imaging by visual scoring after applying sophisticated, colour coded post-processing methods[18]. However, the persisting problem of this post-processing method is the use of video signals which are well known to contain only a minute amount of the information available in digital data or RF data[19–21]. Consequently, the limited dynamic range of video signals (20–30 dB vs $\geq$50 dB available in digital data) often masks contrast effects in the lowest and highest range of signal intensities (figure 8 in reference[21]). This limited dynamic range does not even cover the range of attenuation induced changes within cardiac tissues, which may be up to 40 dB in individual patients[15]. These substantial limitations may be the main reason why subjective scoring has been used for analysis in clinical studies based on video signals in spite of the elaborate post processing method[10,18,22].

The present study clearly demonstrates the feasibility of using the more complete information contained in digital signals for quantitative analysis, which results not only in improved diagnostic accuracy compared to visual scoring (κ=0·73 vs κ=0·51), but also in objective results. Due to the severe limitations cited above, it is our opinion, that the use of video signals for diagnostic myocardial perfusion studies should be avoided.

Scintigraphic Tracers and Microbubbles in Perfusion Imaging

Microbubbles remain strictly intra-vascular unlike scintigraphic tracers which dissolve quickly into the extravascular space and are extracted by myocytes. Sestamibi uptake in the presence of coronary stenosis depends on distal capillary derecruitment during hyperaemia which is associated with a decreased capillary surface area and, thus, reduced extraction of the isotope[23]. In myocardial contrast echo, signal intensity during short replenishment time has been shown to depend on flow rate which is more sensitive for the detection of coronary stenosis than peak contrast effects during long replenishment times[24]. For the present study, therefore, a trigger interval (two cardiac cycles) just shorter than replenishment time at maximal vasodilatation in man ($\geq$3 cardiac cycles) was selected so that the rate of refilling determines the actual peak contrast effect.

Scintigraphic perfusion assessment uses normalization with respect to the myocardial region with the highest tracer uptake and, therefore, lacks information about absolute regional flow values. Myocardial contrast echocardiography allows regional assessment of myocardial opacification. If normalization is needed it should be calculated using the microbubble signal intensity within the LV bloodpool, so that regional data retain their absolute specificity for serial comparison. The usefulness of this approach has been shown in the present study [Figs 4(a),(b), 5]. The inter- and intra-observer variability data (7–12%) confirm, that the difference in contrast effects between normal segments and pathologic segments (45–60%) is meaningful.

Limitations

The evaluation of myocardial perfusion data recorded with SPECT was assessed from a diagonal, thin sector of the polar map rather than a single tomographic plane with the same orientation as the ultrasound image due to the difficulty in defining the exact ultrasound plane in three-dimensional orientation. The orientation of this sector, invariably, excluded the display of a severe permanent perfusion defect in the three patients with a history of inferior myocardial infarction. The use of only one imaging plane may limit diagnostic accuracy. This restriction was imposed by the necessity for three bolus injections of the contrast agent in order to create the same condition for each imaging modality. As the comparative analysis of SPECT data was restricted to the same tomographic plane, the conditions for comparing methods have been met. Although the reference method, SPECT, was used in a semiquantitative way, the total concordance with the angiographic results in the subgroup of eight patients and the documented intra- and inter-observer variability demonstrate its validity as reference technique. The control group may not represent a group of normals. As they represent the same pre-test selection bias as the patients with acute ischaemia, the observed differences of myocardial perfusion are, however, realistic and meaningful for clinical investigations in individual patients. The number of patients included in this study was rather small, but still sufficient to define the most accurate imaging technique. Prospective studies in large patients cohorts using at least two apical imaging planes and systematic variation of the trigger intervals are now required to determine diagnostic accuracy.

Conclusions

It is feasible and advisable to perform ultrasound myocardial perfusion studies based on the analysis of digital data, so that the severe limitations of video signals do not hamper evaluation of perfusion in the clinical setting. The pulse inversion technique has shown superior diagnostic accuracy as compared to second harmonic imaging and the harmonic power Doppler technique. Quantitative analysis is required for optimal diagnostic accuracy, with the additional advantage of yielding objective data sets for sequential studies. At present, however, its time consuming nature limits clinical use. It can be expected that facilitating software[25] and semi-automatic analysis tools will be integrated into the ultrasound systems. This in combination with real time imaging should help this method to achieve acceptance as a clinical tool for the non-invasive, non-ionizing bedside assessment of myocardial perfusion at low cost.

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