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Real-time perfusion adenosine stress echocardiography versus myocardial perfusion adenosine scintigraphy for the detection of myocardial ischemia in patients with stable coronary artery disease

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Short title: Myocardial perfusion in ischemia: echocardiography versus SPECT

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Abstract

Background Real-time perfusion (RTP) contrast echocardiography using low mechanical index power modulation technique allows for simultaneous myocardial perfusion and wall motion analysis. RTP-adenosine stress echocardiography (ASE) could be an alternative to dobutamine-atropine stress echocardiography; more tolerable for the patients and possibly similarly accurate. We aimed to evaluate RTP-ASE for the detection of myocardial ischemia, compared to 99mTc-sestamibi single-photon emission computed tomography (SPECT).

Methods Patients with suspected coronary artery disease, admitted to SPECT evaluation, were prospectively invited to participate. Patients underwent RTP imaging (SONOS 5500) using infusion of Sonovue® before and during ASE. Two separate readers performed off-line analysis of myocardial perfusion and wall motion by RTP-ASE. A perfusion defect was the principal marker of ischemia. Wall motion assessment was used to evaluate ischemia in segments with perfusion artefacts. Each segment was attributed to one of the three main coronary vessel areas of interest: the left anterior descending (LAD); the left circumflex (LCx); and the right posterior descending (RPD). Normal SPECT at stress was judged normal at rest.

Results In 33 patients, 99 coronary territories were analysed by SPECT and RTP-ASE. SPECT showed evidence of ischemia in 9 out of 33 patients. For the detection of ischemia, the overall level of agreement between RTP-ASE and SPECT was 92 % in all segments. The level of agreement was 88 % in LAD, 97 % in LCx and 91 % in RPD segments.

Conclusion RTP-ASE using power modulation could be an accurate and feasible tool for evaluation of ischemia in patients with suspected coronary artery disease. The results from this study need confirmation by a study of a larger patient sample.

Keywords: Myocardial Contrast Echocardiography (MCE), Power modulation, Bedside, SPECT, Coronary insufficiency.

Introduction

Low risk patients with suspected myocardial ischemia are often assessed using different types of exercise tests for ischemic evaluation due to current clinical guidelines (1997; Erhardt *et al.* 2002). Exercise ECG is commonly used because it is inexpensive and accessible. However, it shows low accuracy in patients with low pre-test probability. Single-photon emission computed tomography (SPECT) and dobutamine atropine stress echocardiography (DSE) are well established and more accurate methods in evaluating myocardial ischemia, although more expensive (Picano 2004; Schinkel *et al.* 2003; Sozzi *et al.* 2003; Underwood *et al.* 2004).

There is an increasing need for non-invasive, bedside risk stratification in patients with acute coronary syndrome (ACS) due to the increasing number of treatment options and strategies for these patients. The early invasive strategy with early referral to coronary angiogram and possible percutaneous coronary intervention (PCI) has recently been questioned due to the results of the ICTUS trial, where initial conservative treatment and later ischemic evaluation seemed to be a preferable strategy for patients with non ST elevation myocardial infarction (nonSTEMI)(Iavelov 2005). In patients with suspected ACS and nonSTEMI, clinical decision-making can be particularly difficult in smaller hospitals without invasive catheterisation laboratories (Boden 2003; Levinsky & Ohman 2002; McKay 2003). A selective invasive strategy in these patient groups creates a need for a (preferably) bedside, rapid and accurate method for evaluation and risk stratification.

Adenosine stress echocardiography (ASE) is a less expensive and more tolerable technique as compared to DSE and SPECT for the assessment of patients with suspected coronary artery disease. However, ASE is less accurate for the detection of myocardial ischemia as compared to DSE and SPECT. (Lafitte *et al.* 2001; Takeishi *et al.* 1994).

The use of second generation contrast agents in myocardial contrast echocardiography (MCE) enables assessment of myocardial perfusion during ECG triggered image acquisition echocardiography with high mechanical index, i.e. harmonic power Doppler. This technique is not only technically demanding, but also has limitations such as no wall motion evaluation and variable accuracy for the detection of myocardial ischemia. (Becher *et al.* 1997; Heinle *et al.* 2000; Kaul *et al.* 1997; Ronderos *et al.* 2002). Real-time myocardial perfusion echocardiography (RTP) has recently been developed using highly contrast specific, low mechanical index imaging techniques. RTP during intravenous infusion of a second generation contrast agent allows for simultaneous analysis of myocardial perfusion and wall motion. Early studies with RTP have shown promising results for the evaluation of myocardial perfusion (Main *et al.* 2003; Mor-Avi *et al.* 2001; Olszowska *et al.* 2003; Sieswerda *et al.* 2003). However, there is limited clinical data on the accuracy of RTP-ASE for the detection of myocardial ischemia in unselected patient groups.

Wall motion analysis using adenosine as stressor may be less sensitive in detecting ischemia. On the other hand, perfusion defects seem to be more visible with adenosine compared to dobutamine (Lafitte *et al.* 2001). Combining perfusion and wall motion assessment in RTP-ASE is therefore an appealing alternative. Furthermore adenosine gives less discomfort to patients than dobutamine and RTP-ASE is more accessible and

less time-consuming compared to SPECT. Since both wall motion and perfusion can be assessed from the same images, RTP-ASE has the potential of being as accurate as DSE and SPECT, and may be a swift, bedside-accessible, useful decision-making tool for risk assessment of patients with acute myocardial ischemia.

The aim of the present study was to investigate prospectively the ability of RTP-ASE to detect myocardial ischemia in comparison with 99mTc-sestamibi SPECT, in an unselected clinical patient population with suspected myocardial ischemia.

Methods

Patient population

We asked 35 consecutive patients with known or suspected coronary artery disease, admitted to SPECT evaluation, to participate in the study. One patient chose not to participate. The remaining 34 patients gave their informed consent. One of the 34 included patients had non-interpretable echocardiography images, both regarding wall motion and perfusion, and was therefore excluded from the comparison with SPECT.

Study protocol

The study protocol was approved by the local ethics committee. The echocardiographic equipment used was a Sonos 5500 (Philips, Andover Massachusetts) with S3 probe and RTP using power modulation (angio-mode). Patients were examined in a left lateral recumbent position. The second-generation contrast agent Sonovue® was infused in the left decubital vein using an infusion pump dedicated for this purpose (VueJect®, Bracco™), which automatically rotates the syringe to prevent sedimentation. For purposes of creating a simple protocol we chose a standardised infusion rate of

Sonovue, which was set to 1.3 ml/min (Becher & Burns 2000). Adenosine was infused in the same peripheral venous catheter as the echo contrast, using a separate infusion pump through a three-way tap. Adenosine was given at an infusion rate of 100 µg/kg/min during one minute, after which the infusion rate was increased to 140 µg/kg/min.

All 33 patients underwent RTP imaging (mechanical index=0.1) during infusion of echo contrast, at rest and during adenosine stress after a minimum of one minute of hyperaemia (at 140 µg/kg/min). Image acquisition was started after a minimum time of one minute of Sonovue infusion. RTP image loops containing 8-10 heartbeats were collected from the parasternal long- and short-axis and apical four- and two-chamber views, respectively. At the beginning of each loop a destruction impulse of 10 high mechanical index frames (mechanical index=1.5) were given to destroy all contrast micro bubbles in the myocardium (Bahlmann *et al.* 2002). The angio-mode gain was set between 60 and 70%, depending on what was suitable for the individual patient, from a visual on-line assessment. 2D greyscale gain was set at zero. Focus was set close to the base of the left ventricle. All images were stored digitally for later off-line analysis.

SPECT

The rest and stress studies were performed using a 2-day protocol, with 800 MBq 99mTc-tetrofosmin at rest and 600 MBq at stress. Stress was simultaneous with the RTP-ASE. A five minute adenosine infusion protocol was used. Starting the infusion with 100 µg/ml/min of adenosine for 1 minute, the dose was then increased to 140 µg/ml/min for two minutes before injecting 99mTc-tetrofosmin. Infusion of adenosine was continued for 2 min after the injection of 99mTc-tetrofosmin. The scintigraphic data were acquired one hour after the end of the stress test, using continuous SPECT

over 180 degree elliptical rotation from the 45 degree right anterior oblique position, with a dual-head gamma camera (Siemens ECAM, Siemens Medical Systems, USA). Low energy high-resolution collimator and a zoom factor of 1.0 were used. We obtained 64 projections in a 128x128 matrix, with an acquisition time of 20 s per projection. Tomographic reconstruction and calculation of short axis slice images were performed using Siemens software. A two-dimensional Butterworth pre-reconstruction filter was used with critical frequency of 0.35, order 5. For each patient, the same sets of short axis slices were then processed with an automatic software package (4D-MSPECT). The software package defined apex and base and generated polar maps. Both rest and stress studies were presented in polar maps, with the schematic map of the territories of the coronary arteries for scoring. Radiotracer uptake of the vascular segments were scored visually and stress images were compared with rest images regarding ischemia or no ischemia. The specialist in nuclear medicine who performed the scoring was blinded to the results of the RTP analysis. Normal SPECT at stress was considered normal and not followed by a rest study.

RTP-ASE image interpretation

Two separate readers performed off-line analysis of myocardial perfusion and wall motion by RTP-ASE, using the EnConcert Image Diagnosis Application (Philips, Andover, Massachusetts). The left ventricular myocardium was divided into three segments. Each segment was attributed to one of the three main coronary vessel areas of interest; the left anterior descending (LAD); the left circumflex (LCx); and the right posterior descending (RPD). Myocardial ischemia was visually evaluated comparing rest and stress images, using both perfusion and wall motion analysis in a complementary manner. A visually detected perfusion defect during stress was used as

the principal marker of ischemia. Thus, a myocardial segment was considered ischemic if perfusion was impaired in the stress images, compared to the rest images (Lafitte *et al.* 2001). Perfusion defects were analysed at the earliest four beats following the destruction impulse at rest and two beats at peak stress. An example of a perfusion defect at RTP-ASE and the corresponding SPECT image is shown in Figure 1.

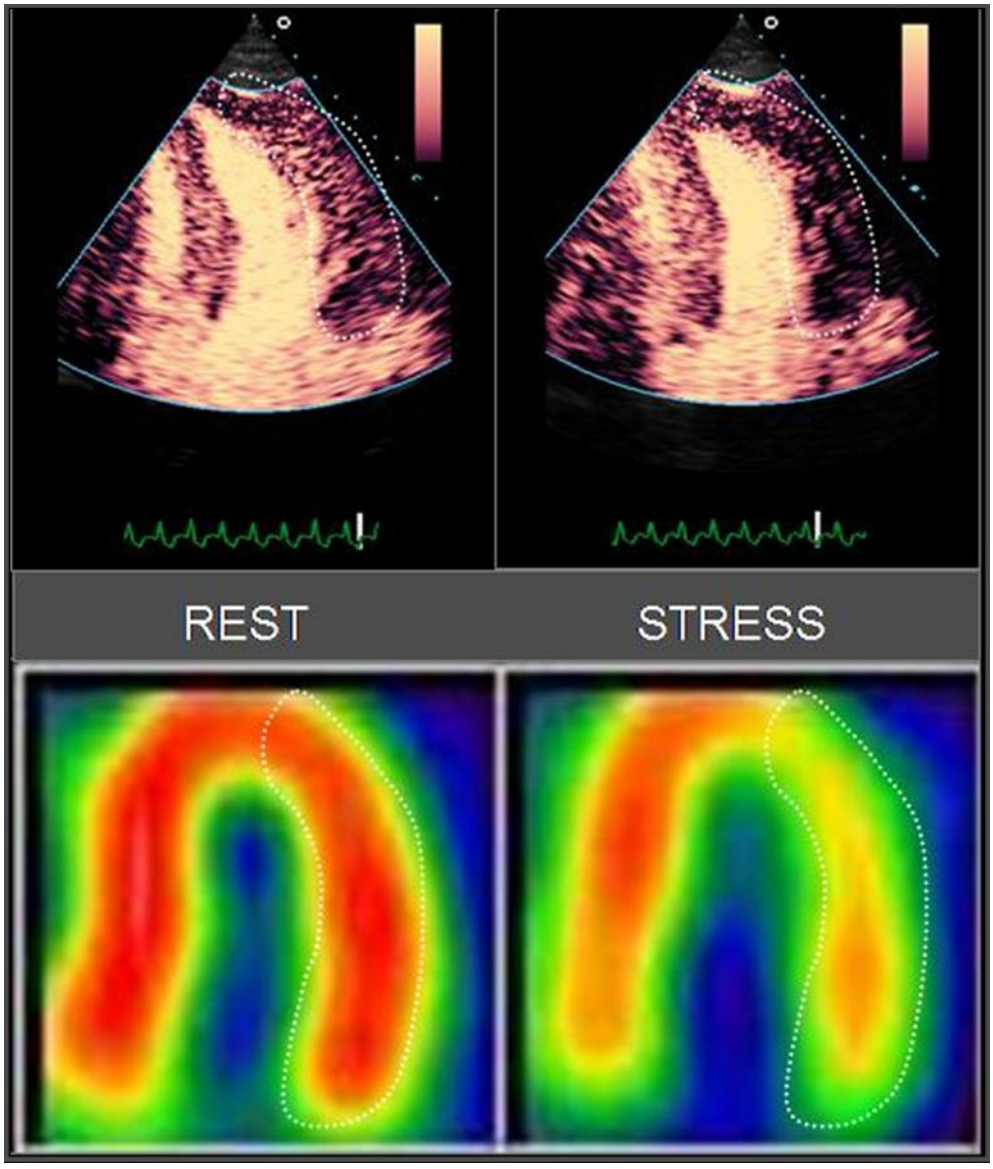

Figure 1. Anterior ischemia seen as a perfusion defect during adenosine stress in RTP (top) and SPECT (bottom).

Wall motion was used in addition to reveal perfusion defect artefacts at rest and to evaluate segments with suspected perfusion artefacts at stress. Since wall motion should not be normal if a segment has a true perfusion defect at rest, a perfusion defect at rest was considered to be an artefact when wall motion was normal in the segment. A perfusion defect at stress was considered to be an artefact if there was a suspicion of a perfusion artefact, such as lateral or anterior shadowing from ribs or lungs or basal segments shadowed by contrast. In such segments, the ischemic evaluation was based on wall motion analysis alone. If wall motion decreased at stress compared to rest images, the segment was considered ischemic.

Since perfusion can be decreased without a decrease in wall motion in ASE, the use of wall motion analysis in segments with perfusion artefacts might decrease the sensitivity with regard to ischemia. However, this complementary use of wall motion analysis increases the number of interpretable segments without negatively affecting specificity. (Winter et al. 2005)

If there was disagreement between readers with regard to one segment, this particular segment was re-assessed in a joint reading to reach consensus.

Statistical analysis

Power calculation was based on a sensitivity and specificity between 80 and 90 % of the methods used. We assumed a sensitivity and specificity of 85% in the study. With 30 patients we would have a 95% confidence interval of ± 13 % around sensitivity and specificity.

The SPSS® statistical program was used for the statistical analysis. We calculated sensitivity and specificity, positive and negative predictive values (PPV, NPV), as well as accuracy and Kappa values in the three predefined distribution areas of the three

main coronary vessels. Gold standard for the ischemia evaluation in the study was the presence or absence of reversible ischemia in the SPECT study as scored by the specialist in nuclear medicine. Results are expressed as mean ± SD and as percent. $P<0.05$ denoted significance.

Results

Baseline characteristics are shown in Table 1. Mean age of the 33 patients was 66 years, two thirds were women and mean left ventricular ejection fraction was close to normal. A history of previous myocardial infarction was found in less than half of the patients, around one third had undergone previous coronary intervention, a majority had no previous coronary hospitalisation or intervention, and around one fifth of the patients had no cardiac medication. At SPECT, 9 (27%) of the patients were ischemic in which 12 segments were ischemic.

Of 102 coronary territories assessed, 99 (97%) were considered interpretable. These 99 territories were analysed both using SPECT and RTP. The overall level of agreement between RTP-ASE and SPECT in detecting ischemia was 92% in all segments with a Kappa value of 0.67. The level of agreement was 97 % in LCx, 91 % in RPD and 88 % in LAD segments. Accuracy, sensitivity, specificity, predictive values and Kappa values for the detection of myocardial ischemia of RTP-ASE compared to SPECT are shown in Table 2. Inter- and intra-observer agreements for the interpretation of ischemia according to the RTP-ASE examinations are presented in Table 3.

Perfusion artefacts were present in 35 (35%) segments at rest and in 24 (24%) segments at peak. Of the 59 segments with artefacts, 34 (58%) were located in basal parts of the

left ventricle in apical views, and 23 (68%) of these 34 basal segments had artefacts at rest.

Wall motion was non-decisive with regard to ischemia evaluation in a segment with a perfusion artefact at rest if the perfusion at stress was normal, since normal perfusion at stress is not consistent with ischemia.

Results regarding perfusion artefacts are summarised in Table 4. In 26 (44%) of the segments with perfusion artefacts, wall motion was decisive for the ischemic evaluation; two at rest and 24 at peak. Wall motion was decisive in two segments at rest, since perfusion defects in these two segments were observed both at rest and during hyperaemia. The perfusion defect at rest was considered to be an artefact due to normal wall motion at rest, since wall motion should not be normal if a segment has a true perfusion defect at rest. Hence, when perfusion and/or wall motion was impaired during stress the segment was judged ischemic despite unchanged impaired perfusion. The ischemic evaluation was in accordance with SPECT in 25 (96%) of these 26 segments. In 23 (88%) of the 26 segments, wall motion correctly acquitted segments from ischemia.

On a patient basis (n=33), the ischemic evaluation with RTP-ASE showed an accuracy of 91% with sensitivity, specificity, positive and negative predictive values of 78%, 96%, 88% and 92%, respectively.

Discussion

The main finding of this study is that regional myocardial ischemia can be reliably diagnosed in patients with known or suspected coronary artery disease, using visual analysis of RTP-ASE, with SPECT as the method of reference. Earlier studies have

shown promising but variable results for the detection of myocardial ischemia with RTP-ASE compared to SPECT, and also varying fractions of interpretable segments in the study population (Main *et al.* 2003; Mor-Avi *et al.* 2001; Olszowska *et al.* 2003; Sieswerda *et al.* 2003). This may be due to the fact that RTP is a quite new technique and that echocardiographers still are learning how to use the technique properly. In the present study wall motion analysis replaced perfusion analysis at rest and at stress if there were suspected perfusion artefacts. The use of wall motion assessment to evaluate ischemia in segments with artefacts allowed us to avoid a large number of non-interpretable segments, without losing more than marginal accuracy. Nevertheless, the RTP technique was still not adequately accurate for myocardial perfusion evaluation in certain regions. This is especially evident for basal antero-lateral and posterior segments.

Myocardial areas judged ischemic by RTP-ASE but not by SPECT, could be small, perhaps sub-endocardial areas that are truly ischemic. These might not be detected by SPECT due to the lower spatial resolution of this method (Main *et al.* 2003; Mor-Avi *et al.* 2001; Olszowska *et al.* 2003; Sieswerda *et al.* 2003). Thus, although it cannot be concluded from the results of the present study that RTP-ASE is more sensitive in detecting ischemia compared to SPECT, the possibility should be considered. Indeed, there are cases and studies suggesting this might be true (Hagendorff *et al.* 2003; Senior *et al.* 2004; Tiemann *et al.* 2001). Nevertheless, prognosis has been proven favourable when myocardial ischemia has been excluded by SPECT (Underwood *et al.* 2004), which suggests that ischemia detected with RTP-ASE but not with SPECT probably will not affect prognosis substantially. Perfusion defects by RTP-ASE but not by SPECT, may also be caused by apical perfusion artefacts. This phenomenon is due to

apical overlapping of ultrasound beams when the focal zone is placed close to the base of the ventricle in the apical projections. This increases the local mechanical index in the apex and, therefore, increases bursting of contrast micro-bubbles compared to the mid- and basal parts (Becher & Burns 2000). This particular problem can be overcome by placing the focal zone near the apex in cases of suspected apical perfusion defects. Another possible solution to this problem is to collect triggered RTP images (Yu *et al.* 2004), thus avoiding continuous ultrasound exposure, which would result in fewer apical perfusion artefacts. However, then the advantage of combining assessment of perfusion and wall motion would of course be lost.

At present, tools for quantification of myocardial perfusion by MCE are under development. These tools have been tested in animal models (Agati *et al.* 2004; Lafitte *et al.* 2002) and are currently undergoing testing in healthy subjects as well as in patients (Bekeredjian *et al.* 2003; Korosoglou *et al.* 2004; Peltier *et al.* 2004). Preliminary results indicate that quantitative MCE may be ready for clinical use in selected patients. However, there is still a need for larger multi-centre studies.

Our conclusions are that RTP-ASE using power modulation could be an accurate and feasible tool for the evaluation of myocardial ischemia in patients with suspected coronary artery disease. The combination of perfusion and wall motion evaluation increases the number of interpretable segments and, hence, the feasibility, when using adenosine as stressor.

The results from this study need confirmation by a study of a larger patient sample.

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Table 1. Patient characteristics.

Age	66 (±11)
Male	33 %
LVEF at rest	52 (±12) %
Previous AMI	42 %
Previous PCI	18 %
Previous CABG	15 %
Heart failure	21 %
Hypertension	36 %
Valvular surgery	0 %
Beta-blocker	54 %
ACE inhibitor	33 %
ARB	9 %
Nitro-glycerine (short acting)	54 %
Nitrates (long acting)	27 %
Diuretics	21 %
Calcium blocker	6 %
Sinus rhythm	94 %
Dilated left ventricle	21 %
Dilated left atrium (n=22)	41 %
Significant valvular disease (n=21)	19 %
Regional WMA/PD at rest	52 %

LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention, CABG, coronary artery bypass grafting; ACE,

angiotensin converting enzyme; ARB, angiotensin-receptor blocker, WMA, wall motion abnormality; PD, perfusion defect.

Table 2. Accuracy, positive (PPV) and negative (NPV) predictive values, sensitivity, specificity and Kappa values of RTP-ASE using SPECT as “gold standard”.

	Any territory (n=99)	LAD (n=33)	LCx (n=33)	RPD (n=33)
Accuracy (%)	92	88	97	91
PPV (%)	63	63	83	0
NPV (%)	98	96	100	97
Sensitivity (%)	83	83	100	0
Specificity (%)	93	89	96	94
Kappa	0.67***	0.64***	0.89***	-0.042 ns

LAD, left anterior descending coronary artery; LCx, left circumflex artery; RPD, right posterior descending coronary artery, ***=$p<0.001$, ns=not significant.

Table 3. Agreement of MCE ischemia interpretation (n=33).

	Total	LAD	LCx	RPD
Inter-observer agreement (%)	91	88	97	88
Kappa	0.72***	0.73***	0.90***	0.28 ns
Intra-observer agreement (%)	94	94	91	97
Kappa	0.76***	0.84***	0.62***	0.78***

LAD=Left anterior descending coronary artery, LCx=Left Circumflex artery,

RPD=Right posterior descending coronary artery, ***=p<0.001, ns=not significant.

Table 4. Perfusion artefacts characteristics.

	Rest	Stress	Total
Basal	23	11	34
Over all	35	24	59
WMA decisive	2	24	26
Accurate	2	23	25

WMA, wall motion analysis.