Estimation of vasodilator response by analysis of Doppler intensity kinetics with myocardial contrast echocardiography using an intravenous standardized bolus administration

A. Hagendorff\textsuperscript{a, *}, A. Werner\textsuperscript{a}, D. Pfeiffer\textsuperscript{a}, H. Becher\textsuperscript{b}

\textsuperscript{a}Department of Cardiology-Angiology, University of Leipzig, Johannisallee 32, 04103 Leipzig, Germany
\textsuperscript{b}Department of Cardiology, University of Oxford, Oxford, UK

Received 21 June 2003; received in revised form 6 October 2003; accepted 9 October 2003

Abstract

Myocardial perfusion can be analyzed by the first pass of Doppler intensity (DI) signals in the myocardium by myocardial contrast echocardiography with triggered power Doppler harmonic imaging (PDHI).

Methods and results

DI versus time plots during 1:1 triggering was acquired during a mechanically standardized intravenous bolus application of Levovist (400 mg ml\textsuperscript{-1}; 3 ml min\textsuperscript{-1}) at rest and during vasodilator stress with dipyridamole. Data were analyzed in 21 patients (pts) with normal coronary arteries and in 6 pts with left anterior descending artery (LAD) stenosis. Transthoracic distal LAD-flow velocities could be determined in 7 normal pts. At stress the DI wash-in rate and the DI plateau increased (3:14 \pm 0.3 versus 5.06 \pm 0.4 DI s\textsuperscript{-1}; 24.6 \pm 2.5 versus 30.8 \pm 1.8 DI, respectively). To analyze the effect of heart rate on the DI versus time plots investigations were performed in 7 additional controls at rest and during rapid pacing. Heart rates below 100 bpm did not disturb the DI kinetics at 1:1 triggering.

Conclusions

Myocardial perfusion can be assessed by the analysis of the first pass DI kinetics using Levovist. The estimation of vasodilator response by PDHI seems to be an alternative to the determination of coronary flow reserve.

ª 2003 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

Keywords

Myocardial contrast echocardiography; Power Doppler harmonic imaging; Dipyridamole stress; Coronary flow reserve.

Introduction

Recent clinical studies presented the capability of myocardial contrast echocardiography (MCE) with triggered power Doppler harmonic imaging (PDHI) to detect regional myocardial hypoperfusion in clinical practice.\textsuperscript{1–7} Two approaches were used: firstly, microbubbles are continuously...
infused and a replenishment curve with the equation Doppler intensity \( DI = A(1 - e^{-\beta t}) \) is calculated from the data acquired at different trigger intervals, where \( A \) is the DI plateau, \( \beta \) is the maximum DI upslope, and \( t \) is the trigger interval. Second-\( \text{y}, an intravenous (i.v.) contrast bolus is manually administrated followed by a rapid saline flush. Assessment or regional myocardial perfusion is possible by qualitative visual analysis or by a semiquantitative analysis according to the regional DI slopes especially during the wash-out period.\(^4,6,7\)

The feasibility of both approaches, however, is limited in clinical practice. Continuous infusion of microbubbles requires additional staff for shaking an infusion pump or the use of a rotating pump to secure a constant concentration of microbubbles during longer time durations. The i.v. bolus approach is methodologically criticized. The transit rate of the microbubbles cannot exactly be measured because the input function to the myocardium is wider than the transfer function through the myocardium.\(^8\) Thus, the DI upslope is generally too fast to enable perfusion analysis in clinical practice. This problem might be solved by the administration of Levovist using a prolonged exactly standardized bolus administrated via an injection pump. A high-dose Levovist bolus can be administrated within a time interval of 3–4 min because of its very low sedimentation rate. We hypothesized that a longer time interval with increasing DI values due to increasing microbubble concentration can improve the analysis of the first pass effect of the contrast agent. In addition, it was assumed that the DI wash-in has to be accelerated in patients (pts) with a normal vasodilator response and has to be decelerated in patients with regional hypoperfusion during stress tests. Thus, the aim of the present study was to test the feasibility of MCE with triggered PDHI by analysis of the DI first pass during a standardized i.v. contrast administration of Levovist. The results of the PDHI-data determined during dipyridamole stress were compared to the determination of coronary flow reserve (CFR) calculated from the increase of the maximum velocity of coronary flow measured in the distal parts of the left anterior descending artery (LAD) measured by transthoracic Doppler echocardiography (TTDE).

Methods

Characteristics of the patients

Twenty-seven patients (16 men, 11 women, mean age 59 ± 10) were investigated. All patients underwent coronary angiography because of non-specific chest pain. Thirteen patients had arterial hypertension with left ventricular hypertrophy, 8 pts had diabetes. No prior myocardial infarction was documented in any patient. All 27 pts underwent coronary angiography because of non-specific chest pain. Electrocardiogram showed no abnormalities at rest and during vasodilator stress. Exclusion criterion for MCE was poor image quality due to high acoustic impedance of the chest wall. Coronary arteries were documented by bpline recordings using a Poly Diagnostic C with an Optimus M2000 generator (Philips, Eindhoven, The Netherlands).

Myocardial contrast echocardiography and echo-contrast agent

MCE was performed at rest within 4 h after angiography using a high-concentration bolus of Levovist (Schering AG, Berlin, Germany) (400 mg ml\(^{-1}\), 3 ml min\(^{-1}\)). A high-concentration bolus of Levovist was used because the concentration of microbubbles is almost stable during the prolonged bolus due to its low sedimentation rate. Injection was performed with a Pulsar Ultrasound Injection System PMP Flex 810106 (Medrad, Volkach, Germany) via the cubital vein to reach sufficient opacification of the myocardium.

Study protocol

After information and written consent was obtained one vial of Levovist was infused with a rate of 3 ml min\(^{-1}\) at rest conditions. Images were acquired for 120–180 s. The microbubble wash-in phase (45–90 s) was acquired using trigger intervals of every heart beat. After reaching the DI plateau the trigger interval was increased to every third heart beat for a time period of 45 s to detect a possible DI increase due to a higher regional microbubble refilling. The wash-out period (30–45 s) was again acquired at 1:1 triggering. The ECG trigger was gated to end systole (133–233 ms after R-wave). According to the previously performed retrospective study,\(^6\) the apical 4-chamber view was chosen for perfusion analysis of the interventricular septum (LAD-territory) and the lateral wall. After the MCE measurement at rest, coronary flow of the distal parts of the LAD could be determined in only 7 of the 24 pts by conventional TTDE. MCE measurement with PDHI were repeated at two stress levels: 5–10 min after administration of 0.56 mg kg\(^{-1}\) body weight dipyridamole, and 5–10 min after injection of additional atropine (1 mg). TTDE was only performed at the dipyridamole stress
The scheme of the study protocol is given in Fig. 1. MCE with PDHI was performed in 7 additional pts at rest conditions with a heart rate of 60 bpm and at temporary pacing conditions with heart rates of 100 and 130 bpm to analyze the effect of heart rate on the regional DI signal. These investigations were performed after exclusion of coronary artery disease (CAD) by angiography.

Imaging modalities

The PDHI investigations were performed with a System Five Performance Ultrasound System (GE Vingmed Ultrasound AS, Horten, Norway). Imaging was acquired in continuous second harmonic (octave) mode for conventional diagnostics, in the intermittent coded harmonic angio mode for perfusion imaging with a standard phased array transducer which transmits ultrasound at a mean frequency of 1.5 MHz and receives it at 3.0 MHz. Ultrasound pulses were gated to end systole once every or every third cardiac cycle. The transmission power was set at maximum power. Mechanical index was 1.4. The transmit focus was set between 6 and 10 cm. A maximum dynamic range of 60 dB was used. Pulse repetition frequency was 3000 Hz. TTDE for acquisition of the LAD velocity profile was performed with a standard phased array transducer, which transmits ultrasound at a mean frequency of 10 MHz. The data were digitally stored as cineloops and transferred after completion of the investigation to a standard Macintosh personal computer.

Quantitative analysis

Quantitative analysis was performed by two independent investigators using the EchoPac 6.2b.134 software (GE Vingmed Ultrasound AS, Horten, Norway). After storage of the cineloops myocardial regions of interest (ROI) with a size of $3 \times 3 - 7 \times 7$ pixels were defined. To illustrate the DI kinetics, the traces of each ROI were shown in a logarithmic scale with DI of the acoustic power in dB on the y-axis and time in s on the x-axis. Colored M-modes crossing the apical regions of the left ventricle also show the alterations of the myocardial opacification during the continuous infusion without initial intravenous bolus application. The following parameters were numerically evaluated: heart rate (HR), the time between the first appearance of the DI signals in the myocardium and the left ventricular cavum ($T_{FALV}$), the DI wash-in rate in the apical septal and apical lateral myocardium ($WIR_s, WIR_l$), maximum DI-plateau determined in the apical septal and apical lateral myocardium ($DI_{1s}, DI_{3s}, DI_{1l}, DI_{3l}$) during triggering

---

**Figure 1** Scheme of the study protocol. The arrows mark the beginning of stress levels and the recovery period.
on every cardiac cycle (1) as well as on every third cardiac cycle (3), the DI wash-out rate in the apical septal and apical lateral myocardium (WOR, WOR), and the peak velocity of coronary flow measured in the distal parts of the LAD by TTDE (V_LAD). For illustration, the DI versus time plots are smoothed in the figures by calculation of mean values of three consecutive DI values for each measurement. Analysis of the DI kinetics was time consuming because of the positioning of the respective ROIs for each single frame (more than 10 min for each measurement). The illustration of myocardial opacification by colored M-mode for semiquantitative analysis is easy and fast (within 10–30 s).

Calculation of coronary flow reserve (CFR) and CFR-like parameters

CFR was computed as the ratio of hyperemic to basal average peak velocity: \( V_{LAD, Stress}/V_{LAD, rest} \). The following CFR-like parameters were calculated for estimation of the vasodilator response from the PDHI data: \( WIR_{stress}/WIR_{rest} \); \( DI_3\text{-stress}/DI_3\text{-rest} \); \( WIR_{stress}/WIR_{rest} \); \( DI_3\text{-stress}/DI_3\text{-rest} \); \( WIR_{stress} \times DI_3\text{-stress}/WIR_{rest} \times DI_3\text{-rest} \); \( WIR_{stress} \times DI_3\text{-stress}/WIR_{rest} \times DI_3\text{-rest} \).

Statistical analysis

Numerical data are presented as mean values ± standard deviation. Differences between rest and stress conditions were evaluated for all parameters using the Wilcoxon-W-test and Mann–Whitney-U-test for dependent samples. Differences were considered significant at P-levels (*) < 0.05.

Results

CAD was excluded in 21 pts. In 6 patients significant LAD stenosis (>70%) was found. Mean values ± SD of the relevant parameters determined by PDHI with MCE after prolonged bolus application of Levovist are given in Table 1.

The heart rate at rest determined in the cohort of the patients was 72 ± 10 bpm. Dipyridamole stress increased heart rate up to 89 ± 14 bpm. Additional atropine caused a further significant increase to 110 ± 19 bpm. Blood pressure did not change between rest and stress conditions. The parameter \( TFA_{LV,-M} \) decreased from control values of 8.5 ± 2 s at rest to values of 4.5 ± 1 s at stress. The regional WIR increases from values of 3.3 ± 0.3 dB s\(^{-1}\) at rest to the range between 4.2 ± 0.5 and 5.1 ± 0.6 dB s\(^{-1}\) at stress. The DI plateau values significantly increased by changing of trigger on every heart beat to the trigger on every third heart beat at rest and during stress. The maximum DI plateau increased from a range of 22.5 ± 1.0 dB–25.0 ± 1.5 dB at rest to 29.5 ± 1.5 dB–32.0 ± 1.5 dB at stress. No significant changes in WOR were found. The schemes of the typical changes of the DI versus time plots between rest and vasodilator stress conditions are shown in Fig. 2.

The mean maximum velocity of coronary flow determined in the distal parts of the LAD at rest was 0.18 ± 0.03 m s\(^{-1}\). The mean value increased, at vasodilator stress conditions, to 0.39 ± 0.07 m s\(^{-1}\). The mean values ± SD of the PDHI data determined in the subgroup of the 7 pts with LAD-flow measurements do not significantly differ in comparison with the respective values determined in the cohort of all 21 pts. The ratio of hyperemic to basal average peak velocity determined in the distal parts of the left anterior descending artery was 2.2 ± 0.1 in patients without CAD representing the CFR. The WIR ratios were between 1.27 ± 0.21 and 1.56 ± 0.12, the ratios of DI plateau were between 1.29 ± 0.06 and 1.31 ± 0.08, and the ratios of the product, WIR × DI plateau, were between 1.89 ± 0.19 and 2.01 ± 0.17. The ratios of the parameters calculated from the PDHI data are lower than the CFR determined by peak velocity changes during TTDE. The stress–rest-ratios calculated from the PDHI data of the vasodilator stress series are given in Table 2.

A typical example of the DI kinetics at rest and during dipyridamole stress during prolonged Levovist bolus without initial bolus application is given in Fig. 3. The parameter \( TFA_{LV,-M} \) significantly increased and the parameters WIR and DI plateau significantly decreased in 6 patients with significant LAD stenosis (see Table 1). Thus, the calculated stress–rest-ratios decreased below values of 1 (see Table 2). A typical example of the DI kinetics at rest and during dipyridamole stress during a prolonged Levovist bolus in a patient with severe LAD stenosis is given in Fig. 4. The DI wash-in rate and the DI plateau is markedly reduced at stress in comparison to rest conditions in this case. Because the stress–rest-ratios calculated from the PDHI-parameter in this patient are lower than 1, it is obvious that the numerical value of the stress–rest-ratios cannot be synonymously compared to CFR-data.

The effect of heart rate on DI versus time plots during a prolonged Levovist bolus was tested by
PDHI measurement at temporary pacing conditions with heart rates of 100 and 130 bpm. Whereas the parameters TFA_{LV-M} and the DI plateau did not significantly differ between rest and pacing conditions, the DI wash-in rate was significantly increased at pacing rates of 100 min^{-1} (4.2 ± 0.7 s^{-1} versus 3.4 ± 0.5 s^{-1}; P<0.05). However, this increase was minor in comparison to vasodilator stress. In contrast to vasodilator stress, myocardial blood volume (MBV) is almost unchanged at pacing conditions documented by the stable DI plateau values. Thus, the increase of the product DI wash-in rate × DI plateau was less than during vasodilator stress (see Tables 2 and 4). Mean values ± SD of the relevant parameters determined by PDHI with MCE during prolonged bolus administration of Levovist are given in Table 3. The stress—rest-ratios calculated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control conditions at rest (non-CAD pts)</th>
<th>Stress condition dipyridamole (0.56 mg kg^{-1}) (non-CAD pts)</th>
<th>Control conditions at rest (CAD pts)</th>
<th>Stress condition dipyridamole + atropin (1 mg) (CAD pts)</th>
<th>Stress condition dipyridamole (0.56 mg kg^{-1}) + atropin (1 mg) (CAD pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (min^{-1})</td>
<td>72 ± 10</td>
<td>89 ± 14*</td>
<td>69 ± 4</td>
<td>88 ± 13</td>
<td>109 ± 10</td>
</tr>
<tr>
<td>TFA_{LV-M} (s)</td>
<td>8.5 ± 2.0</td>
<td>4.5 ± 1.0*</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>WIR_s (dB s^{-1})</td>
<td>3.3 ± 0.3</td>
<td>5.1 ± 0.4*</td>
<td>4.2 ± 0.6*</td>
<td>3.5 ± 0.5</td>
<td>3.5 ± 3.0†</td>
</tr>
<tr>
<td>WIR_l (dB)</td>
<td>23 ± 2</td>
<td>62 ± 2*</td>
<td></td>
<td>21 ± 2</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>DI_{1s} (dB)</td>
<td>25 ± 1</td>
<td>32 ± 2*</td>
<td>29 ± 2*</td>
<td>26 ± 3</td>
<td>23 ± 2</td>
</tr>
<tr>
<td>DI_{1l} (dB)</td>
<td>22 ± 1</td>
<td>29 ± 1*</td>
<td>26 ± 2*</td>
<td>21 ± 2</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>DI_{3s} (dB)</td>
<td>25 ± 1</td>
<td>31 ± 2*</td>
<td>28 ± 2*</td>
<td>23 ± 4</td>
<td>24 ± 5</td>
</tr>
<tr>
<td>DI_{3l} (dB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOR_s (dB s^{-1})</td>
<td>0.3 ± 0.1</td>
<td>0.9 ± 0.1*</td>
<td>0.6 ± 0.2</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1†</td>
</tr>
<tr>
<td>WOR_l (dB s^{-1})</td>
<td>0.2 ± 0.1</td>
<td>0.8 ± 0.2*</td>
<td>0.7 ± 0.3*</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1†</td>
</tr>
<tr>
<td>V_{LAD} (m s^{-1})</td>
<td>0.18 ± 0.03</td>
<td>0.39 ± 0.07*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The abbreviations of the parameters are explained in the Section Quantitative analysis (Wilcoxon-test, Mann–Whitney-U-test).

* P<0.05 versus control.
† P<0.05 versus respective condition in non-CAD pts.

Figure 2  Scheme of the typical changes of the DI versus time plots between rest and vasodilator stress. The arrows mark the beginning of the DI wash-in, the DI plateau during triggering on every or every third heart beat and the DI wash-out.
from the PDHI data of the pacing stress series are given in Table 4. A scheme of the typical changes of the DI versus time plots between rest and pacing induced stress conditions is given in Fig. 5. A typical example of the DI kinetics at rest and during pacing induced stress during a prolonged Levovist bolus is given in Fig. 6.

The PDHI data at temporary pacing, obviously document that increase of heart rate to levels of 100 bpm will not significantly influence the level of the DI plateau. Thus, the shortening of the trigger interval due to increasing heart rate up to levels of 100 bpm seems to have no influence on myocardial opacification using PDHI with MCE using prolonged high-dose Levovist.

### Discussion

The main finding of the present study is that an empiric approach using MCE with PDHI for estimation of vasodilator response seems to be suitable for detection of myocardial hypoperfusion in clinical practice. The described approach of contrast administration and the acquisition of DI versus time plots during 1:1 triggering mainly resulted from considerations due to practical and feasible aspects.

Dipyridamole stress echocardiography is an established pharmacological stress test in clinical practice, which is very feasible, safe and easy to interpret.11–13 The analysis of inducible regional wall motion abnormalities after dipyridamole administration can be extended by the determination of regional perfusion, which is possible by several clinical methods.14–17 CFR can be determined by invasive as well as non-invasive Doppler analysis, which showed good correlations in the literature.14,18–23 Vasodilator stress, however, produces different CFR changes due to the used agent.1,12,13,19–23 After administration of nitroglycerine only small alterations in regional myocardial blood flow were detected. Mean values of CFR after low- and high-dose dipyridamole administration are reported between 2.2 and 2.8. The highest CFR ranges between 2.7 and 3.8 were observed using adenosine infusion. The CFR value of 2.20 ± 0.10 determined in the present study by TTDE corresponds to the inferior border of the CFR range determined at low dose of dipyridamole.

CFR determinations by TTDE are not always possible due to poor ultrasound windows. Thus, alternatives for the CFR determinations using MCE were proposed.4,6,7 The present protocol is proposed as an additional alternative approach for the detection of the vasodilator response in the myocardium. The advantage of the proposed Levovist administration and data acquisition is the possibility to standardize the bolus and to spread the DI wash-in interval. In addition, transducer positioning is easier with triggering on every heart beat than with higher trigger intervals. Whereas the DI kinetics are still influenced by ventilation artefacts or transducer movement, the variations of the DI upslopes seem to be smaller than those of a replenishment curve because many frames are acquired during the up slopes and single frames with bad image quality can be eliminated by
Figure 3  A typical example of the DI kinetics and the velocity profile of the coronary flow measured in the distal parts of the LAD by TTDE at rest and during dipyridamole stress during prolonged Levovist bolus. (a–e) Illustrate the data determined at rest. (a) Shows the color coded 2D-image with labeled regions of interest put into the left ventricular cavum, the apical septum, and the apical lateral wall. In (b) the corresponding DI kinetics are illustrated. (c) Shows the color coded 2D-image with the axis of a color-M-mode given in (d). (e) Shows the velocity profile of the coronary flow in the LAD. (f–k) Illustrate the corresponding results determined during stress.
Figure 4  A typical example of the DI kinetics at rest and during dipyridamole stress during prolonged Levovist bolus in a patient with significant LAD stenosis. (a–d) Illustrate the data determined at rest. (a) Shows the color coded 2D-image with labeled regions of interest put into the left ventricular cavum, the apical septum, and the apical lateral wall. In (b) the corresponding DI kinetics are illustrated. (c) Shows the color coded 2D-image with the axis of a color-M-mode given in (d). (e–h) illustrate the corresponding results determined during stress.
Table 3  Mean values ± SD of the relevant parameters determined by PDHI with MCE at temporary pacing conditions during prolonged Levovist bolus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control conditions at rest</th>
<th>Stress condition pacing (80–110 min⁻¹)</th>
<th>Stress condition pacing (120–140 min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (min⁻¹)</td>
<td>65 ± 15</td>
<td>100 ± 10</td>
<td>130 ± 5</td>
</tr>
<tr>
<td>TFALV-M (s)</td>
<td>8.5 ± 3.0</td>
<td>8.0 ± 2.0</td>
<td>9.0 ± 3.0</td>
</tr>
<tr>
<td>WIR₁ (dB s⁻¹)</td>
<td>3.4 ± 0.5</td>
<td>4.2 ± 0.7*</td>
<td>3.6 ± 0.9</td>
</tr>
<tr>
<td>WIR₂ (dB s⁻¹)</td>
<td>3.5 ± 0.6</td>
<td>4.2 ± 0.6*</td>
<td>3.7 ± 0.8</td>
</tr>
<tr>
<td>DI₁ (dB)</td>
<td>24 ± 1</td>
<td>24 ± 3</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>DI₂ (dB)</td>
<td>26 ± 2</td>
<td>27 ± 3</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>DI₃ (dB)</td>
<td>22 ± 2</td>
<td>23 ± 3</td>
<td>23 ± 2</td>
</tr>
<tr>
<td>WOR₁ (dB s⁻¹)</td>
<td>–0.4 ± 0.1</td>
<td>–0.5 ± 0.1</td>
<td>–0.5 ± 0.1</td>
</tr>
<tr>
<td>WOR₂ (dB s⁻¹)</td>
<td>–0.4 ± 0.1</td>
<td>–0.6 ± 0.1</td>
<td>–0.5 ± 0.1</td>
</tr>
</tbody>
</table>

The abbreviations of the parameters are explained in the Quantitative analysis, section (Wilcoxon-test, Mann–Whitney-U-test). * P < 0.05 versus control.

Table 4  Mean values ± SD of the CFR parameters calculated from the PDHI data of the temporary pacing stress series during prolonged Levovist bolus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio stress condition temporary pacing (100 min⁻¹) versus rest</th>
<th>Ratio stress condition temporary pacing (130 min⁻¹) versus rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIR₃stress/WIR₃rest</td>
<td>1.24 ± 0.24</td>
<td>1.05 ± 0.16</td>
</tr>
<tr>
<td>DI₃stress/DI₃rest</td>
<td>1.34 ± 0.09</td>
<td>0.97 ± 0.08</td>
</tr>
<tr>
<td>WIR₃stress × DI₃stress/ WIR₃rest × DI₃rest</td>
<td>1.66 ± 0.32</td>
<td>1.07 ± 0.22</td>
</tr>
<tr>
<td>WIR₃stress/WIR₃rest</td>
<td>1.23 ± 0.24</td>
<td>1.06 ± 0.15</td>
</tr>
<tr>
<td>DI₃stress/DI₃rest</td>
<td>1.09 ± 0.12</td>
<td>0.93 ± 0.11</td>
</tr>
<tr>
<td>WIR₃stress × DI₃stress/ WIR₃rest × DI₃rest</td>
<td>1.34 ± 0.33</td>
<td>1.03 ± 0.22</td>
</tr>
</tbody>
</table>

The abbreviations of the parameters are explained in the section calculation of coronary flow reserve (CFR) and CFR-like parameters (Wilcoxon-test, Mann–Whitney-U-test; * P < 0.05).
the increase of perfusion due to rapid pacing. The unchanged DI plateau, however, might point to unchanged MBV during pacing. Heart rates above 130 bpm, however, reduce WIR and the DI plateau because of methodological and physiological factors. Stress induced vasoconstriction during pacing can contribute to the DI reduction.

Limitations

PDHI with MCE in the present study was only performed by scanning the 4-chamber view. Myocardial opacification during PDHI, however, is often limited in basal regions of the left ventricle. Therefore, the applicability of the present empiric pragmatic approach was proven only for regions with good acoustic window. The PDHI investigations are certainly limited in the basal left ventricular regions especially analyzing the 2- and 3-chamber view. Future studies using the present protocol have to demonstrate the feasibility of detecting hypoperfusion during stress in other myocardial regions.

The aim of the present communication was to introduce the feasibility of a new method for detection of hypoperfusion. Thus, the proposed protocol was not studied with different contrast agents. Special contrast differences of the wash-in after starting of a continuous infusion, e.g. of Optison or Sonovue in comparison to Levovist, were not evaluated. It has to be expected that the MCE results, which will be obtained with other contrast agents using PDHI, depend on the different properties of the contrast agents. In addition, the present approach was not planned and approved for comparison with other current MCE methods like power modulation due to methodological, practical and ethical reasons.

Conclusions

Myocardial perfusion can be assessed by the analysis of the first pass DI kinetics using the proposed protocol with Levovist, if heart rates are below 100 bpm during vasodilator stress. The estimation of vasodilator response by PDHI seems to be an alternative to the determination of coronary flow reserve.

Acknowledgements

The authors are grateful for the technical assistance to A. Golding, S. Herrmann, B. Müller, A. Nägler, and A. Ruschel.
References


Figure 6  A typical example of the DI kinetics at rest and during pacing induced stress during prolonged Levovist bolus. (a–d) Illustrate the data determined at rest. (a) Shows the color coded 2D-image with labeled regions of interest put into the left ventricular cavum, the apical septum, and the apical lateral wall. In (b) the corresponding DI kinetics are illustrated. (c) Shows the color coded 2D-image with the axis of a color-M-mode given in (d). (e–h) Illustrate the corresponding results determined at stress during pacing at a rate of 100 bpm, (i–m) illustrate the corresponding results determined at stress during pacing at a rate of 130 bpm.


