Assessment of Myocardial Perfusion by Harmonic Power Doppler Imaging at Rest and During Adenosine Stress
Comparison With $^{99m}$Tc-Sestamibi SPECT Imaging

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Background—Harmonic power Doppler imaging (HPDI) is a novel technique for assessing myocardial perfusion by contrast echocardiography in humans. The purpose of this study was to compare myocardial perfusion by HPDI with that obtained by $^{99m}$Tc-sestamibi single photon emission computed tomography (SPECT) during rest and pharmacological stress.

Methods and Results—HPDI was performed on 123 patients who were referred for SPECT imaging for known or suspected coronary artery disease. Images were obtained at baseline and during adenosine infusion ($0.14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \times 6 \text{ minutes}$) in 3 apical views. Myocardial perfusion by HPDI was graded for each coronary territory as absent, patchy, or full. The persistence of absent or patchy myocardial perfusion by HPDI between rest and adenosine was interpreted as a fixed defect, whereas any decrease in perfusion grade was interpreted as a reversible defect. Overall concordance between HPDI and SPECT was 83 (81%) of 103 for normal versus abnormal perfusion. Agreement between the 2 methods for each of the 3 coronary territories was 81% ($\kappa=0.57$) for the left anterior descending artery, 76% ($\kappa=0.52$) for the right coronary artery, and 72% ($\kappa=0.40$) for the left circumflex artery. Discrepancies between the 2 techniques were most notable in the circumflex territory, where fixed defects were observed in 33% by HPDI but in only 14% by SPECT ($\chi^2=15.8, P=0.0001$).

Conclusions—This study demonstrates that HPDI can reliably detect myocardial perfusion during pharmacological stress, although there was a significantly higher number of falsely abnormal results in the circumflex territory. (Circulation. 2000;102:55-60.)

Key Words: contrast media ■ echocardiography ■ perfusion ■ stress ■ tomography ■ adenosine

Recently, harmonic power Doppler imaging (HPDI) has emerged as a promising tool to detect myocardial perfusion after intravenous injection of second-generation contrast agents. Initial studies of HPDI have indicated that it can accurately detect resting perfusion abnormalities in patients with a previous myocardial infarction. However, it is well known that resting perfusion may be normal even in the presence of a severe coronary stenosis, a fact that serves as the basis for both exercise and pharmacological stress imaging. Therefore, this study was undertaken to assess the ability of HPDI to identify perfusion abnormalities at rest and during pharmacological stress imaging with adenosine. Results were compared with $^{99m}$Tc-sestamibi single photon emission computed tomography (SPECT) imaging, which has emerged as the clinical reference standard for perfusion imaging.

Methods

Patient Population
The protocol was approved by the Human Studies Subcommittee, and all patients gave written informed consent. A total of 123 patients with suspected or known coronary artery disease who were scheduled for adenosine stress $^{99m}$Tc-sestamibi SPECT were included in this study if they were >18 years of age and had adequate visualization of the myocardium in the apical views on echocardiography. Exclusion criteria included myocardial infarction within 1 week, unstable angina, second- or third-degree atrioventricular block, wheezing, systolic blood pressure <90 mm Hg, ingestion of caffeine within 24 hours or methylxanthine derivatives within 48 hours, pregnancy, or lactation. Myocardial contrast echocardiography (MCE) and $^{99m}$Tc-sestamibi data were acquired at baseline and after intravenous adenosine at $0.14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ over a period of 6 minutes.

Myocardial Contrast Echocardiography
Optison (Molecular Biosystems, Inc) is a second-generation contrast agent consisting of perfluoropropane-filled albumin microspheres (mean diameter 3.9 $\mu$m, concentration 5 to $8 \times 10^{10}$/mL). The safety of Optison and its lack of adverse effects on hemodynamics, left ventricular function, and pulmonary gas exchange have been demonstrated. An intravenous infusion of Optison was given by injecting 3 mL into an extension tubing through a stopcock placed just proximal to an 18- or 20-gauge intravenous catheter. Since Optison floats to the surface, the extension tubing was directed...
upward from the floor toward the patient’s arm. The plug of Optison in the tubing was pushed into the intravenous infusion by 0.9% saline at a rate of 50 mL/h at baseline imaging and 2 minutes into the adenosine infusion for stress imaging. The rate was adjusted upward or downward as needed to eliminate attenuation artifacts and to maximize the left ventricular cavity signal without creating a “blooming” artifact (ie, avoidance of white as opposed to yellow signal in the left ventricular cavity). The benefits of an intravenous infusion of microbubbles include the avoidance of far-field attenuation and blooming artifacts seen with bolus injections.13,14

HPDI was performed with a broad-band harmonic transducer (Hewlett-Packard Sonos 5500) transmitting and receiving at a mean frequency of 1.8 MHz and 3.6 MHz, respectively. The dynamic range of this system is 40 dB. The mechanical index was set as high as possible to increase microbubble destruction. A dual-trigger flash mode was used in which the first ultrasound trigger results in microbubble destruction followed by an imaging trigger gated to the T wave of the ECG every fourth cardiac cycle. End-systolic triggering was used because the myocardial wall segments are thicker and the left ventricular cavity size smaller, resulting in less contrast attenuation. In addition, end-systolic dual triggers were carefully adjusted to avoid cardiac motion between the first and second triggers. Extending the ultrasound pulse interval over several cardiac cycles had the advantage of increased time for microbubble replenishment in the myocardium, thus resulting in improved detection of myocardial perfusion.15,16 In our experience with this technique in a pilot study of 20 subjects, triggering intervals of <4 beats often failed to show myocardial perfusion. Ultrasound system gains were optimized at the beginning of the study and held constant for subsequent image acquisitions. Gain settings were maintained at <70% to avoid a myocardial “blooming” artifact that could be falsely interpreted as “perfusion.” HPDI images were displayed on a split screen simultaneously with a destruction phase image to minimize the misinterpretation of artifacts (Figure 1). Images were acquired at rest and during adenosine. Since peak hyperemia begins 3 minutes into the adenosine infusion and lasts up to 30 seconds afterward,17 image acquisition was initiated 3 minutes after the start of the infusion. Since only 3.5 minutes of maximal hyperemia was available for imaging, HPDI was performed only in the apical views by obtaining 3 to 5 beats gated to every fourth cardiac cycle. If a myocardial defect was noted, the triggering interval was increased to every sixth or eighth beat, and the focus was adjusted to the level of the perfusion defect.

**Single Photon Emission Tomography**

All patients received an adenosine infusion at a rate of 0.14 mg·kg⁻¹·min⁻¹ for a total of 6 minutes. At 3 minutes of infusion, 8 to 10 mCi of ⁹⁹mTc-sestamibi was injected intravenously, and adenosine stress images were acquired 1 hour later. After a 3- to 4-hour interval, patients received 21 to 28 mCi of ⁹⁹mTc-sestamibi intravenously, and delayed rest images were acquired 1 hour after the second (rest) injection. Patients weighing >250 lb were imaged by means of a 2-day protocol with a ⁹⁹mTc-sestamibi dose of 30 mCi for each image. SPECT images were obtained with the use of a triple-head camera (Toshiba 9300). Data were acquired over 360°, by means of a 64×64 matrix with 60 projections. The acquisition time per projection was 30 seconds for the low-dose image and 20 to 25 seconds for the high-dose image. The data were reconstructed with the use of a Ramp prefilter with a cutoff frequency of 0.20. A Butterworth filter was applied during back-projection. The reconstructed slices were displayed into vertical, horizontal, and short-axis planes. All ⁹⁹mTc-sestamibi images were interpreted by independent observers blinded to the HPDI results.

**Image Interpretation**

HPDI was evaluated in blinded fashion by 2 observers (S.H. and P.G.). Each apical view was divided into 5 segments, and myocardial perfusion was graded as absent, patchy, or full. During adenosine-induced hyperemia, persistence of absent or patchy myocardial opacification was interpreted as a fixed defect (Figure 2), whereas any decrease in perfusion grade was interpreted as a reversible defect (Figure 3). HPDI observers were blinded to the clinical history and SPECT data. HPDI was interpreted independently for interobserver and intraobserver variability in 59 subjects. Horizontal and vertical long-axis views by SPECT imaging were interpreted by 2 observers to evaluate the myocardial segments that corresponded most closely to the echocardiographic segments.

**Statistical Analysis**

Concordance between MCE and ⁹⁹mTc-sestamibi was determined by κ statistics with κ values >0.2=fair, >0.4=moderate, >0.6=substantial, and >0.8=almost perfect.18 McNemar’s test19 was used to...
evaluate differences between HPDI and SPECT for normal versus abnormal perfusion. A value of $P < 0.05$ was considered to be significant.

**Results**

**Patient Characteristics**

The clinical characteristics of the patients are listed in Table 1. SPECT imaging was scheduled to evaluate atypical chest pain in 42% of patients, and 27% were studied for preoperative risk assessment. Left ventricular dysfunction (ejection fraction $<40\%$) was present in 15 (12%) patients. HPDI and SPECT studies were available for comparison in 103 patients. HPDI was not completed in 18 patients because of poor image quality ($n=12$), inadequate contrast opacification ($n=3$), or artifacts present in $>1$ view ($n=3$). In addition, SPECT images were not completed in 3 patients, 1 of whom also did not complete the HPDI study.

**Comparison of HPDI and SPECT by Patient**

In the 103 patients who underwent successful myocardial perfusion studies by both HPDI and SPECT, there was concordance for normal versus abnormal perfusion in 83 (81%) of 103 cases ($\kappa = 0.6$). As shown in Table 2, the concordance was better when the SPECT images were normal or consistent with multivessel disease. When SPECT suggested single-vessel involvement, HPDI was only concordant in 28 (68%) of 41 cases, compared with 28 (93%) of 30 when SPECT showed evidence of multivessel disease and 27 (84%) of 32 when SPECT was normal.

**Comparison of HPDI and SPECT by Coronary Territory**

Both HPDI and SPECT studies were analyzable in 304 coronary territories. The contingency tables comparing HPDI and SPECT for the left anterior descending (LAD), right coronary artery (RCA), and left circumflex (LCx) territories are shown in Figure 4. Concordance between the 2 techniques for normal versus abnormal myocardial perfusion was 81% ($\kappa = 0.57$) in the LAD territory, 76% in the RCA territory ($\kappa = 0.52$), and 72% in the LCx territory ($\kappa = 0.40$). Overall agreement was present in 232 (76%) of 304 territories. When HPDI and SPECT were compared for agreement between normal perfusion versus reversible defects versus fixed defects, concordance was 74% for the LAD, 64% for the RCA, and 64% for the LCx. There were no significant differences between HPDI and SPECT for the LAD and RCA territories, respectively. In contrast, fixed defects were present in the LCx territory in 33% of patients by HPDI compared with only 14% by SPECT ($x^2=15.8$, $P=0.0001$).

**Comparison by Myocardial Segments**

Of 1329 myocardial segments, 1125 (85%) were adequately visualized by HPDI, with concordance in 786 (70%) ($\kappa = 0.32$). The highest concordance (82%) was obtained in the mid-anteroseptal segment, with the lowest concordance in the basal lateral (51%) and basal posterolateral (59%) segments. It is the lack of concordance in the lateral segments that accounted for the difference described between HPDI and SPECT in the LCx territory.

**Interobserver and Intraobserver Variability**

The interobserver agreement was 97% ($\kappa = 0.93$) for identifying normal versus abnormal perfusion and 77% ($\kappa = 0.57$).
for reversible versus fixed defects. The intraobserver variability was 93% and 89% for the 2 observers. The time period between interobserver and intraobserver interpretations ranged from 1 to 6 months.

**Correlation to Coronary Angiography**

Coronary angiography done within 3 months of the HPDI study and without intervening revascularization was only available in 15 patients. With regard to the presence of single-vessel versus multivessel versus normal, both SPECT and HPDI were concordant to angiography in 9 (60%) of 15 and to each other in 13 (87%) of 15 cases (Table 3). Angiographic comparisons were not available in the majority of patients in whom HPDI and SPECT were discordant.

**Discussion**

This study demonstrates that HPDI with the use of an intravenous contrast agent can detect myocardial perfusion at rest and during pharmacological stress. HPDI and SPECT were not significantly different for the LAD and RCA territories; however, fixed defects in the LCx were commonly seen by HPDI despite normal perfusion by SPECT. The major strength of this study is its large size, prospective data collection, and simultaneous acquisition of SPECT and MCE images during a single adenosine infusion.

**Mechanism of Perfusion Detection by HPDI**

HPDI, like conventional Doppler velocity imaging, transmits a packet of ultrasound pulses along each scan line, with the use of an autocorrelator to compare differences in the received signals. Conventional Doppler displays the frequency shift of the received signals (a marker of velocity); HPDI displays the amplitude of the received signals, which reflects the number of scatterers. The use of a packet of ultrasound pulses offers 2 major advantages over B-mode imaging. First, it increases the sensitivity of HPDI and allows for removal of the tissue harmonic signal with a wall filter, albeit at a cost of a lower frame rate. Second, a packet of ultrasound pulses increases microbubble destruction, paradoxically enabling HPDI to detect perfusion. Because flow velocity in the myocardial capillaries is extremely low (<1 mm/s), Doppler velocity mapping is not capable of detecting perfusion. However, the destruction of microbubbles from one packet to the next is detected by the HPDI autocorrelator. Thus, the signal displayed by HPDI reflects myocardial perfusion in that microbubbles must be present in the myocardial capillary bed and must undergo destruction between pulses to be detected.

Two mechanisms have been proposed for the detection of myocardial perfusion by HPDI. One has been termed “stimulated acoustic emissions” and postulates that microbubble destruction produces an acoustic energy that results in an HPDI signal. A second, more likely explanation is that microbubble destruction results in a decrease in backscattered intensity and a change in phase between pulses; the autocorrelator interprets this as motion and therefore displays a signal. In either case, microbubble destruction is necessary for HPDI to detect myocardial perfusion.

Since microbubble destruction is dependent on multiple variables, it is crucial that these be optimized during HPDI. Microbubbles have different sensitivity to ultrasonic destruction, depending on the thickness and composition of their shells. We used Optison, which is sensitive to microbubble destruction at diagnostic ultrasound frequencies. Microbubble destruction is directly related to acoustic power and inversely related to transducer frequency. Therefore, we always used maximal acoustic power, and the mechanical index was >1.0 in every patient, well above the threshold for maximal microbubble destruction by HPDI. Importantly,
mechanical index varies with focus, sector width, and depth and is not uniform throughout the ultrasound field. This nonuniformity means that microbubble destruction will be greater in some parts of the sector ( apex) than in others (lateral wall), a fact that may explain why the lateral segments had a higher false-positive rate in this study. We have found that by adjusting the transducer position laterally to move the lateral wall toward the center of the sector helps eliminate this artifact. However, this is not possible in all patients. Newer advances in transducer design, including lower frequencies and smaller apertures, are being developed to help overcome the problem of false-positive defects in the lateral wall.

Previous studies of HPDI used a low pulse repetition frequency. 5,6 This increases the time between pulses in a packet and therefore improves sensitivity by increasing the time for changes in the bubbles ( ie, dissolution) to occur. However, it also increases the likelihood that cardiac motion will produce an artifactual color signal. We avoided this problem by using a high pulse repetition frequency and a dual screen that displayed 2 sequential frames side by side. 23 This allowed us to verify that no significant cardiac motion occurred between frames and that microbubble destruction was near complete. It also enabled us to increase the gain settings to the highest level possible without introducing an HPDI color signal on the destruction image (second frame). This is critical because high gain settings can introduce artifact and low gain settings may create a false-positive perfusion defect.

The focus setting also plays a major role in HPDI because it affects bubble destruction. For example, we commonly encountered perfusion “defects” in the apex that resolved when the focus was moved from base to apex. Had we not done this systematically, we might have had a high rate of false-positive defects in the apex. Lengthening the triggering interval, as done in this study, is also helpful in avoiding false-positive perfusion defects.

Study Limitations
There is no perfect reference standard for regional myocardial perfusion because radiolabeled microspheres are not suitable for human studies. Coronary angiography does not evaluate myocardial perfusion and therefore is a poor reference standard for HPDI. For example, myocardial perfusion as the result of collaterals may be present despite coronary artery occlusion, 24 and there may be absence of perfusion despite a widely patent coronary artery (no reflow phenomenon). 25 Therefore, we chose to compare HPDI with SPECT imaging, which is the most widely used clinical test for assessing myocardial perfusion.

We used qualitative analysis of the HPDI and SPECT images as is used in routine clinical practice to distinguish normal, reversible, and fixed defects. Digital acquisition of HPDI should lend itself to quantitative analysis, which may be more accurate in distinguishing normal perfusion from mild defects. Moreover, quantitative analysis offers the potential to actually measure flow reserve ratio noninvasively. Unfortunately, quantification of the digital HPDI signal is not readily available on the instrument used in this study. We did not use off-line quantification of videotape because it is not readily applied to clinical practice because of time constraints, and it has potential for loss of data quality and errors in extrapolating signal intensity from the color bar to the myocardial regions.

These data demonstrate that HPDI can identify normal versus abnormal perfusion with the use of current technology. However, distinguishing normal from a fixed or reversible defect by HPDI shows only a modest correlation with SPECT imaging and greater interobserver variability. This finding may be explained in part by differences in the 2 techniques. SPECT requires both perfusion and cellular viability for radionuclide uptake, whereas HPDI is strictly dependent on microvascular integrity. HPDI has an axial resolution superior to that of SPECT (1 mm versus 1 cm). Furthermore, the classification of defects as fixed or reversible is not an all-or-none phenomenon. Often, defects may be predominantly fixed with some reversibility at the edges. This can result in a classification difference between SPECT and HPDI. The evolution of quantitative techniques may allow more precise classification of fixed versus reversible defects.

Finally, the short duration of action of adenosine may have limited our technique. A longer infusion or the use of high-dose dipyridamole may have enabled us to use off-axis views and to systematically vary the triggering intervals, which in turn may have led to even better concordance with SPECT imaging. In addition, adenosine caused side effects in 99 (80%) of 123 patients, including dyspnea, flushing, chest pain, headache, and lightheadedness.

Conclusions
HPDI is a promising new technique for contrast echocardiographic assessment of myocardial perfusion at rest and during pharmacological stress. False-positive perfusion abnormalities are common in the lateral wall with the use of current HPDI technology. Future advances in instrumentation and quantitative analysis should further improve the accuracy of this method for the noninvasive clinical assessment of myocardial perfusion.

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