Incremental Value of Parametric Quantitative Assessment of Myocardial Perfusion by Triggered Low-Power Myocardial Contrast Echocardiography

Eric H. C. Yu, MD, MED, FACC,* Danny M. Skyba, PhD,‡ Howard Leong-Poi, MD,† Cairrine Sloggett, RN, RDCS,* Michal Jamorski, RDCS,* Rohit Garg, MSEE,‡ R. Mark Iwanochko, MD, FACC,* Samuel C. Siu, MD, SM, FACC*

Toronto, Ontario, Canada; and Bothell, Washington

OBJECTIVES

The purpose of this study was to compare the assessment of myocardial perfusion by myocardial parametric quantification (MPQ) with technetium-99m sestamibi single-photon emission computed tomographic (SPECT) imaging in humans.

BACKGROUND

Accurate visual interpretation of myocardial contrast echocardiographic (MCE) images is qualitative and requires considerable experience. Current computer-assisted quantitative perfusion protocols are tedious and lack spatial resolution. Myocardial parametric quantification is a novel method that quantifies, color encodes, and displays perfusion data as a set of myocardial parametric images according to the relative degree of perfusion.

METHODS

Forty-six consecutive patients underwent prospective stress/rest technetium-99m sestamibi gated-SPECT imaging and MCE using intravenous Optison or Definity. Apical two- and four-chamber cine loops at rest and after dipyridamole (0.56 mg/kg) stress were acquired. For each patient, the following assessments of myocardial perfusion were performed: 1) visual cine-loop assessment (VIS); 2) MPQ assessment; and 3) combined VIS + MPQ assessment. The segmental rates of agreement for myocardial perfusion with SPECT were 83%, 89%, and

RESULTS

The segmental rates of agreement for myocardial perfusion with SPECT were 83%, 89%, and 92% (kappa = 0.46, 0.58, and 0.68) for VIS, MPQ, and VIS + MPQ, respectively. Similar trends were seen for the classification of the presence or absence of a moderate to severe perfusion defect, with the agreement for VIS, MPQ, and VIS + MPQ being 92%, 97%, and 97%, respectively.

CONCLUSIONS

Myocardial parametric quantification demonstrates good agreement with SPECT and incremental agreement with VIS. Analysis strategies that incorporate MPQ demonstrate better agreement with SPECT than visual analysis alone. (J Am Coll Cardiol 2004;43: 1807–13) © 2004 by the American College of Cardiology Foundation

The current clinical assessment of myocardial perfusion by myocardial contrast echocardiography (MCE) is by visual interpretation of perfusion images or quantitative off-line computer-assisted processing (1–3). Accurate visual interpretation remains subjective and is limited to experienced investigators, with mixed results (1,4). Although quantitative perfusion assessment may enhance the applicability of

See page 1814

MCE in the assessment of coronary artery disease (CAD) in patients, current quantitative protocols are tedious, with limited spatial resolution of quantitative perfusion data (5–9). Myocardial parametric quantification (MPQ) is a novel method of automated MCE quantitation, where dynamic perfusion information is quantified, color-encoded to the resolution of a single pixel, and displayed as a set of myocardial parametric images according to the relative degree of perfusion (10). The agreement of MCE using

MPQ to detect CAD in patients has not been compared with an independent measure of perfusion, such as single-photon emission computed tomographic (SPECT) imaging. In addition, there has not been a direct comparison between the qualitative (visual assessment of cine-loop data [VIS]) and quantitative (MPQ) approaches for the assessment of myocardial perfusion using MCE. The purposes of this study were to: 1) determine the agreement of MCE using MPQ with SPECT imaging in the assessment of myocardial perfusion in patients with suspected CAD; and 2) compare the incremental value of MCE using MPQ with visual assessment of myocardial perfusion by MCE in patients.

METHODS

Patient population. We prospectively studied 46 consecutive patients (28 men; mean age 60 years [range 34 to 79 years]) with known or suspected CAD. The patients' clinical characteristics included a history of unstable (n = 10) or stable angina (n = 6), previous non–ST-segment elevation myocardial infarction (n = 4), congestive heart failure (n = 3), and coronary artery bypass graft surgery (n = 3). All patients gave written, informed consent, and the study was approved by the Human Subjects Committee of the University Health Network.

From the *Gordon Yu Hoi Chiu Echocardiographic Laboratory, The Toronto Western Hospital, Toronto; †St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; and ‡Philips Ultrasound, Bothell, Washington. Dr. Skyba and Mr. Garg are employees of Philips Ultrasound.

Manuscript received May 1, 2003; revised manuscript received July 28, 2003, accepted September 9, 2003.

Abbreviations and Acronyms

CAD = coronary artery disease

LAD = left anterior descending coronary artery MCE = myocardial contrast echocardiography

MI = mechanical index

MPQ = myocardial parametric quantification

ROI = regions of interest

SPECT = single-photon emission computed tomography

TRI = triggered replenishment imaging VIS = visual cine-loop assessment

Contrast and pharmacologic agent administration. The commercially available second-generation contrast agents Optison (Mallinckrodt, St. Louis, Missouri) and Definity (Bristol Myers Squibb Medical Imaging, N. Billerica, Massachusetts) were used. Intravenous contrast (1.5 ml Optison diluted in 8.5 ml saline administered at a rate of 2.0 ml/min or 1.3 ml Definity diluted in 50 ml saline administered at a rate of 3.0 ml/min) was administered as a continuous infusion at baseline and after dipyridamole (0.56 mg/kg) infusion. Infusion rates of the contrast agents were optimized for each patient to maintain optimal myocardial enhancement.

Myocardial contrast echocardiography. All patients underwent power-pulse inversion Doppler imaging using an HDI 5000cv echocardiograph with a P4-2 scan head (Philips Ultrasound, Bothell, Washington) (n = 28) or high-resolution gray-scale power-modulation imaging using a Sonos 5500 C.0 echocardiograph with an S-3 scan head (Philips Ultrasound, Andover, Massachusetts) (n = 18). The MCE images of the apical two- and four-chamber views were acquired at rest and after dipyridamole infusion. For each echocardiographic system, imaging was performed using a triggered replenishment imaging (TRI) mode, which acquired images at a low mechanical index (MI = 0.1to 0.2) and at a frame rate of one image per cardiac cycle using electrocardiographic (ECG) gating. Images were acquired near the end-systolic portion of the cardiac cycle (~300 ms after the R wave) and were optimized for each patient. At steady-state microbubble infusion, TRI at a triggering interval of 1:4 (1 image per 4 cardiac cycles) was used to evaluate and individually adjust the infusion rate. The settings on the echocardiograph were adjusted to optimize myocardial opacification and minimize attenuation artifacts. Once established, infusion and machine settings were held constant. The triggering interval was reduced to 1:1, and a manually delivered flash sequence of four "realtime" high-MI frames was used to destroy the microbubbles in the scan plane. On completion of the flash sequence, triggered imaging resumed at the previous 1:1 interval. Myocardial contrast replenishment was visualized, and digital image data were acquired for up to 15 cardiac cycles after the flash sequence.

SPECT imaging. All patients underwent stress/rest technetium-99m sestamibi gated-SPECT imaging within

one week of MCE. A stress SPECT study was obtained after dipyridamole (0.56 mg/kg) infusion over 4 min, and rest SPECT images were obtained 4 h later (11). For SPECT images, perfusion was independently quantified and scored using the identical segment model and scale used for MCE images by an experienced nuclear cardiologist (Dr. Iwanochko) blinded to clinical and MCE data. Composite reading included an assessment of wall motion (gated SPECT) and attenuation correction.

Data analysis. The MCE data were transferred to an off-line computer workstation (1.0-GHz Pentium III, Compaq, Dallas, Texas) for analysis using QLAB (version 1.0, Philips Ultrasound) and a proprietary MPQ algorithm. The TRI cine loops were evaluated according to the following criteria: 1) complete microbubble destruction in the image immediately after the flash frames; 2) good myocardial replenishment in at least two segments; and 3) good image alignment with minimal artifacts due to patient respiration, sonographer motion, or shadowing. Cine loops that satisfied all of these conditions were selected for visual analysis of myocardial perfusion. Identical copies of the cine loops were used by an independent observer (Dr. Skyba) blinded to the clinical and nuclear data, in order to construct the corresponding MPQ images. To generate these images, an assisted border detection algorithm was employed to segment the myocardium from the rest of the image. An exponential curve-fitting function of the form—I(t) = $A(1 - \exp^{-\beta t})$ —was then fitted to the intensity vector from each pixel position in the segmented cine loop, where I(t) represents the intensity of a pixel as a function of time; A represents the intensity of full myocardial replenishment; and β represents the rate constant of intensity change (8). Parameters of A and β were automatically tabulated according to pixel position and scaled, and a color map was applied to generate parametric images of blood volume (A), blood velocity (β) , and myocardial blood flow $(A \times \beta)$ for each pixel in the myocardium (Fig. 1). A median filter was applied to the final parametric images to reduce noise caused by poor curve fits to noisy intensity vectors. A relative scale was used to render the parametric images, where the mean parameter within the myocardial border was calculated, and the parameter values from each pixel were color-encoded relative to the mean value. Gradations of color were linearly applied based on fractions of the mean value, with fixed breakpoints at the mean (green), two-thirds of the mean (yellow), and one-third of the mean (red), corresponding to a normal, mild, and moderate to severe reduction in myocardial perfusion, respectively. A complete image set for each patient consisted of the resting and peak stress apical two-chamber and apical four-chamber cine loops and the corresponding MPQ images. For each patient, three independent assessments of myocardial perfusion were performed: 1) visual cine-loop assessment (VIS); 2) MPQ image assessment; and 3) combined VIS + MPQ assessment. For VIS + MPQ, if only one modality had analyzable images, then that modality was used for analysis. For

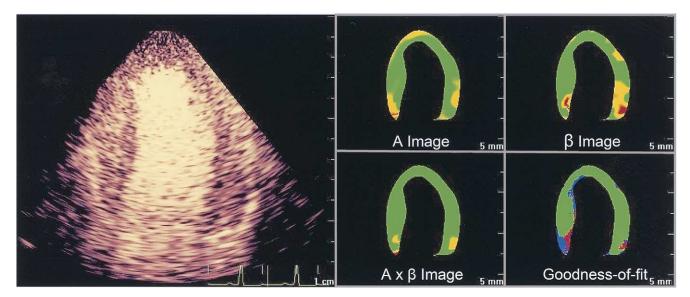


Figure 1. An assisted border detection algorithm was employed to segment the myocardium from the rest of the ultrasound image. An exponential curve-fitting function of the form— $I(t) = A(1 - \exp^{-\beta t})$ —was fit to the intensity vector from each pixel position in the segmented cine loop, where I(t) represents the intensity of a pixel as a function of time; A represents the intensity of full myocardial replenishment; and β represents the rate constant of intensity change. The parameters of A and β were automatically tabulated according to the pixel position and scaled, and a color map was applied to generate parametric images (four panels on the right) of blood volume (A image), blood velocity (β image), and myocardial blood flow (A × β image) of each pixel in the myocardium. A goodness-of-fit map for the data was also generated by the algorithm.

discordant results, the modality with the best analyzable images was used for analysis. For each perfusion assessment (VIS, MPQ, VIS + MPQ), 12 myocardial segments (6 from each of the apical 2- and 4-chamber views) were scored for myocardial perfusion, using the following scale: 3 = normal; 2 = mild reduction; and 1 = moderate to severe reduction (12). All images were independently analyzed by an experienced observer (Dr. Yu) blinded to both the clinical and nuclear data. The MCE data for all patients were randomly analyzed; thus, image sets from individual patient studies were not analyzed together.

The segmental agreement between VIS, MPQ, VIS + MPQ, and SPECT myocardial perfusion scores were calculated as the percentage of agreement and kappa score. Concordance between each analysis strategy (VIS, MPQ, or VIS + MPQ) and SPECT perfusion scores in the entire data set was also calculated using tests of marginal homogeneity (McNemar's test when mildly reduced and normal perfusion scores were combined into a single category, and the Stuart-Maxwell test when the three levels of perfusion were used in the analysis) (13). When the perfusion scores were coded into three levels (normal, mild reduction, and moderate to severe reduction), McNemar's test was also used to assess for bias (tendency of each analysis strategy to rate perfusion to be higher or lower than SPECT). The results of tests of marginal homogeneity were expressed as chi-square statistics. The larger the chi-square statistic, the poorer the agreement between each analysis strategy and SPECT. These chi-square statistics were used to rank the methods from best to worst. Ranking of the level of significance associated with these tests of agreement should also be interpreted in the same manner, rather than using a

cutoff value of 0.05 to decide whether agreement is present or absent. The agreement between coronary artery distribution, the presence or absence of multivessel CAD, and the presence or absence of fixed or reversible perfusion defects were also determined. The myocardial segments and their corresponding anatomic coronary artery supply were classified using published guidelines (12). A second experienced observer (Dr. Leong-Poi) independently analyzed MCE data from all patients. The degree of agreement in perfusion assessment between the two observers was also determined for each modality. Ten randomly chosen studies (240 segments) were re-analyzed for intra-observer variability.

RESULTS

A total of 1,104 myocardial segments (from 46 patients) were imaged by MCE and SPECT. A total of 1,101 SPECT images (99%) were analyzable. For MCE, 1,049 segments (95%) were analyzable using VIS, 975 segments (88%) using MPQ, and 1,060 segments (96%) using VIS + MPQ. Of the 1,060 segments analyzed using VIS + MPQ, 81 (8%) were analyzable only by VIS and 24 (2%) only by MPQ. Segments classified as nonanalyzable using VIS were due to attenuation, artifact, or nonvisualization. For MPQ, segments were coded as nonanalyzable when the goodness-of-fit was poor. The predominant distribution of nonanalyzable segments by MCE comprised the basal segments (75%), and this was noted regardless of the method of perfusion assessment.

Figure 2 illustrates the agreement between MCE and SPECT for analyzable segments. When the perfusion score was in the form of normal, mildly reduced, and moderate to

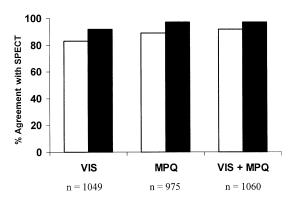


Figure 2. This graph demonstrates the percentage of agreement between myocardial contrast echocardiography and single-photon emission computed tomography (SPECT) perfusion scores, where segmental perfusion scores are available for both modalities. Rates of agreement for visual cine loop assessment (VIS), myocardial parametric quantification image assessment (MPQ), and VIS + MPQ were 83%, 89%, and 92%, and kappa values were 0.46, 0.58, and 0.68, respectively (white bars). Rates of agreement for the classification of a moderate to severe perfusion defect for VIS, MPQ, and VIS + MPQ were 92%, 97%, and 97%, and kappa values were 0.53, 0.76, and 0.81, respectively (black bars).

severely reduced, the tests of marginal homogeneity resulted in chi-square statistics of 47, 8, and 15 (associated p values of <0.001, 0.015, and 0.007, respectively) corresponding to VIS versus SPECT, MPQ versus SPECT, and VIS + MPQ versus SPECT, respectively, demonstrating best overall agreement with SPECT using MPQ analysis. The amount of bias (the tendency for each analysis strategy to rate perfusion as more or less severe than SPECT) was lowest with the use of MPQ (chi-square statistics of 36, 8, and 14, respectively, with associated p values of <0.001, 0.019, and 0.0007, respectively) for VIS versus SPECT, MPQ versus SPECT, and VIS + MPQ versus SPECT, respectively. When normal and mild reductions in perfusion were combined into a single category, the marginal homogeneity chi-square statistics were 38, 0.1, and 7, respectively, (associated p values of <0.001, 0.72, and 0.0082, respectively) for VIS versus SPECT, MPQ versus SPECT, and

Table 1. Comparison Between Myocardial Contrast Echocardiography and Single-Photon Emission Computed Tomography Perfusion Scores

MCE Strategy	SPECT			
	Perfusion Score	1	2	3
VIS	1	59	9	63
	2	8	21	47
	3	7	27	808
MPQ	1	56	7	10
	2	10	21	52
	3	5	20	794
VIS + MPQ	1	66	1	20
	2	3	35	36
	3	4	19	876

MPQ = myocardial parametric quantification image assessment; SPECT = single-photon emission computed tomography; VIS = visual cine-loop assessment; VIS + MPQ = combined VIS and MPQ image assessment. Perfusion scores: 1 = normal perfusion; 2 = mild reduction; 3 = moderate to severe reduction.

Table 2. Agreement With Single-Photon Emission Computed Tomography for a Moderate to Severe Perfusion Defect

Modality	Analyzable Segments (% of Total)	Agreement (%)	Kappa Value
Apical 2C			
VIS	523 (95)	91	0.60
MPQ	492 (89)	96	0.76
VIS + MPQ	529 (96)	97	0.85
Apical 4C			
VIS	526 (95)	91	0.38
MPQ	483 (88)	98	0.70
VIS + MPQ	531 (96)	98	0.76
Rest MCE images			
VIS	525 (95)	92	0.41
MPQ	493 (89)	97	0.71
VIS + MPQ	536 (97)	98	0.75
Stress MCE images			
VIS	524 (95)	92	0.59
MPQ	482 (87)	96	0.76
VIS + MPQ	524 (95)	98	0.86
SONOS 5500			
VIS	422 (97)	89	0.56
MPQ	404 (93)	95	0.62
VIS + MPQ	427 (99)	98	0.84
HDI 5000			
VIS	630 (94)	89	0.45
MPQ	571 (85)	94	0.72
VIS + MPQ	633 (94)	97	0.79

2C and 4C = two- and four-chamber view, respectively; MCE = myocardial contrast echocardiography; other abbreviations as in Table 1.

VIS + MPQ versus SPECT, respectively. Again, the smallest chi-square statistic and the largest p value were observed for SPECT using MPQ analysis, demonstrating the best agreement for this analysis strategy.

Table 1 demonstrates the concordance of segmental perfusion scores between MCE and SPECT. The incremental agreement of MPQ compared with VIS for the classification of a moderate to severe perfusion defect was also observed when the data were stratified by: 1) the echocardiographic view (apical two-chamber vs. apical four-chamber); 2) the protocol stage (rest or stress); and 3) the echocardiographic system used (Table 2). Concordance for normal versus abnormal perfusion

Table 3. Concordance Between Myocardial Contrast Echocardiography and Single-Photon Emission Computed Tomography (SPECT) According to SPECT Results

Modality	Patients (n/N)	Agreement (%)	Kappa Value
Normal/abnormal			
VIS	34/46	74	0.49
MPQ	44/46	96	0.91
VIS + MPQ	43/46	93	0.87
LAD disease			
VIS	15/17	88	0.75
MPQ	18/18	100	1.00
VIS + MPQ	18/18	100	1.00
Multivessel disease			
VIS	13/17	76	0.51
MPQ	18/18	100	1.00
VIS + MPQ	18/18	100	1.00
	· ·	· ·	

LAD = left anterior descending coronary artery; other abbreviations as in Table 1.

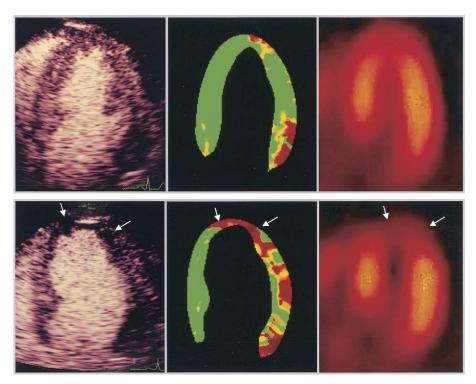


Figure 3. The **upper panels** demonstrate a contrast-enhanced apical four-chamber echocardiographic image at rest **(left)** alongside its corresponding parametric **(middle)**, and single-photon emission computed tomography (SPECT) image **(right)**. The **bottom panels** demonstrate a contrast-enhanced apical four-chamber echocardiographic image at peak stress **(left)** alongside its corresponding parametric **(middle)**, and SPECT image **(right)**. The parametric image has been color-coded: **red** indicates a moderate to severe perfusion deficit; **yellow** indicates a mild deficit; and **green** indicates normal perfusion. A stress-induced perfusion defect has developed in the apical segments **(arrows)**, with apical thinning. The basal lateral segment on the parametric image was classified as nonanalyzable, using the goodness-of-fit image.

(for a moderate to severe perfusion defect) for each individual patient is illustrated in Table 3. There was good concordance between normal versus abnormal perfusion using VIS, with incremental agreement with VIS demonstrated by MPQ. Concordance for left anterior descending coronary artery (LAD) disease and multivessel CAD was greater with MPQ and VIS + MPQ compared with VIS. Rates of concordance for VIS, MPQ, and VIS + MPQ for the determination of a reversible LAD perfusion defect in 14 patients were 86%, 100%, and 93%, respectively, and for the determination of a reversible non-LAD distribution perfusion defect in 15 patients, the rates were 80%, 93%, and 93%, respectively. Concordance for VIS, MPQ, and VIS + MPQ for the determination of a fixed non-LAD distribution perfusion defect in two patients was 100% for all modalities. There were no fixed LAD perfusion defects. For each method of MCE assessment (VIS, MPQ, VIS + MPQ), a high degree of interobserver agreement (97%, 99%, and 99%; kappa = 0.86, 0.96, and 0.95, respectively) and intraobserver agreement (97%, 99%, and 99%; kappa = 0.86, 0.98, and 0.97, respectively) was observed. Figure 3 illustrates the echocardiographic, MPQ, and SPECT images from a patient with a stress-induced apical perfusion defect.

DISCUSSION

This study demonstrates that parametric quantification of images obtained by triggered low-power MCE is feasible

and can be utilized in a busy clinical laboratory with the use of commercially available software, contrast agents, and echocardiographs. We observed an excellent agreement between parametric quantification of MCE data and myocardial perfusion assessment by SPECT imaging. Although our results for the agreement of visual assessment of MCE for myocardial perfusion with SPECT imaging are consistent with those previously reported (1,3,6,14), we observed that analysis strategies that incorporated parametric quantification of myocardial images provided incremental agreement over visual assessment.

Currently, the assessment of MCE perfusion in patients is performed mainly by qualitative visual analysis. The accuracy of such analysis is dependent on investigator expertise and has been previously challenged (4). Techniques of MCE have been developed that allow for the quantitative assessment of myocardial perfusion, and although these methods have been validated in the experimental setting, protocols are laborious and generally not widely applicable in the clinical setting (15–17). Parametric imaging of quantitative MCE perfusion has previously been validated in an experimental dog model and has allowed for the spatial assessment of myocardial ischemia. Parametric images of blood volume (A), velocity (β), and flow (A $\times \beta$) have been shown to correlate with images depicting regional radiolabeled microsphere-derived blood flow (the gold standard) (10). The present study extended the results of **Parametric Quantitative Myocardial Perfusion by MCE**

1812

previous animal models by demonstrating that parametric imaging in patients with suspected CAD showed excellent agreement with SPECT assessment, a well-accepted clinical standard for the assessment of myocardial perfusion (1).

This study also compared parametric imaging with visual assessment of myocardial perfusion. Parametric analysis automatically quantitated dynamic perfusion information to the resolution of a single pixel and displayed them in a color-encoded format relative to the degree of perfusion. The advantages of this method over traditional methods of MCE quantification include: 1) avoidance of the tedium and potential errors associated with manually drawing and positioning of regions of interest (ROI); 2) simplification of perfusion analysis by curve fitting and generation of perfusion parameters for each pixel within the myocardium; and 3) improved spatial assessment of the perfusion data, as the resolution is equal to the number of pixels within the image, typically thousands of values, compared with the resolution of the quantitative perfusion information obtained using ROI analysis, which is dependent on the number of ROIs

When a cine loop is used to analyze myocardial perfusion, it is difficult to visually track each pixel within the image. Within a myocardial segment, a relative intensity change that appears visually significant may not be considered significant by the MPQ algorithm, as it compares the intensity parameter to the normal value for the entire myocardium. Because the algorithm performs comparisons and curve fits on a pixel-by-pixel basis, this should result in a more accurate assessment than with visual assessment, which is consistent with our findings. Successful parametric quantification analysis requires the majority of the data set to be of sufficient quality, as noisy or attenuated data will result in analysis failure. Despite careful image acquisition, invariably there are segments, particularly basal segments, with noisy data, resulting in analysis failure. However, visual analysis of these segments may still be possible, as the presence of a few frames during the microbubble replenishment period may be sufficient to render an assessment and explains why more segments were analyzable using VIS versus MPQ. Furthermore, the observation that the greatest number of myocardial segments were analyzable using VIS + MPQ suggests that these techniques are not mutually exclusive but are, in fact, complementary, in that one modality may allow for the analysis of segments which the other modality may be unable to evaluate, and vice versa. Although this strategy allows for the greatest number of analyzable segments, it is also associated with a mild reduction in agreement with SPECT compared with MPQ. It has not yet been determined if this reduction is clinically significant. The incremental agreement and ease of use of MPQ may be of particular importance to novice interpreters. Study limitations. One of the limitations of contrast imaging lies with accurate resolution of basal myocardial segments. Segments are nonanalyzable by both visual and parametric techniques as a consequence of: 1) contrast

attenuation; 2) insufficient or a failure to detect contrast signal; and 3) shadowing. The frequency and distribution of nonanalyzable segments that we reported are similar to those of previous studies (4,14,18). In our opinion, most cases of insufficient basal resolution were due to the inability of the ultrasound beam to penetrate these segments. As the power of the ultrasound beam decreases in proportion to the cosine of the angle from the center scan line in a typical 90° phased-array profile, imaging of lateral segments is a particularly challenging problem when using low-MI imaging techniques. Attenuation of ultrasound energy will also result in nonhomogeneity of quantitative parameters of A and β within different myocardial segments. However, as MPQ utilizes a relative scale to render the parametric images, this likely improves on the nonhomogeneity of quantitative perfusion parameters. Although in the majority of our patients with normal rest and stress SPECT studies, the MPQ images were fairly homogeneous between myocardial segments (Fig. 1), issues of nonhomogeneity will need to be assessed in future studies. A potential limitation to the use of relative scaling is that MPQ may potentially misinterpret perfusion abnormalities, particularly in situations of diffuse or balanced ischemia. Although this may be minimized by the concomitant visual analysis of MCE perfusion data, this patient population requires further study. In addition, there will need to be age- and gender-specific normal ranges established, similar to SPECT techniques, before widespread clinical adoption of this quantitative method. As the primary goal was to compare measures of perfusion, wall motion was not assessed. Although this may have improved the results for the rest stages, its utility is greater at higher doses than those used in this study (19). Although SPECT and MCE images were not acquired simultaneously, no cardiac events occurred between SPECT and MCE studies. Although this was not a comparative study, equivalent quantitative results with different combinations of imaging platforms and contrast agents increase the generalizability of our study results by demonstrating that the quantitation can be utilized with different combinations of imaging platforms and contrast agents.

Conclusions. This study demonstrates that MCE using MPQ is feasible and accurate, can be incorporated into standard qualitative MCE techniques, and has excellent agreement with SPECT imaging. Analysis strategies that incorporate MPQ demonstrate better agreement than VIS alone. The automated analysis algorithms of MPQ may potentially allow real-time, quantitative perfusion analyses, bringing us closer to the goal of real-time quantitation of myocardial perfusion in diagnostic and prognostic studies in the clinical setting.

Acknowledgments

The authors thank Drs. Jeff Powers and Patrick G. Rafter for their contributions and support of this study.

Reprint requests and correspondence: Dr. Eric H. C. Yu, Toronto Western Hospital, 399 Bathurst Street, East Wing 5-559, Toronto, Ontario, Canada M5T 2S8. E-mail: eric. yu@uhn.on.ca.

REFERENCES

- Kaul S, Senior R, Dittrich H, Raval U, Khattar R, Lahiri A. Detection of coronary artery disease with myocardial contrast echocardiography: comparison with ^{99m}Tc-sestamibi single-photon emission computed tomography. Circulation 1997;96:785–92.
- Porter TR, Xie F, Kilzer K, Deligonul U. Detection of myocardial perfusion abnormalities during dobutamine and adenosine stress echocardiography with transient myocardial contrast imaging after minute quantities of intravenous perfluorocarbon-exposed sonicated dextrose albumin. J Am Soc Echocardiogr 1996;9:779–86.
- 3. Heinle SK, Noblin J, Goree-Best P, et al. Assessment of myocardial perfusion by harmonic power Doppler imaging at rest and during adenosine stress: comparison with (99m)Tc-sestamibi SPECT imaging. Circulation 2000;102:55–60.
- Marwick TH, Brunken R, Meland N, et al., the Nycomed NC100100 Investigators. Accuracy and feasibility of contrast echocardiography for detection of perfusion defects in routine practice: comparison with wall motion and technetium-99m sestamibi single-photon emission computed tomography. J Am Coll Cardiol 1998;32:1260-9.
- Porter T, Li S, Kilzer K, Deligonul U. Correlation between quantitative angiographic lesion severity and myocardial contrast intensity during a continuous infusion of perfluorocarbon-containing microbubbles. J Am Soc Echocardiogr 1998;11:702–10.
- Porter TR, Li S, Kricsfeld D, Armbruster RW. Detection of myocardial perfusion in multiple echocardiographic windows with one intravenous injection of microbubbles using transient response second harmonic imaging. J Am Coll Cardiol 1997;29:791–9.
- 7. Becher H, Burns PN. Handbook of Contrast Echocardiography. Berlin/Heidelberg/New York: Springer-Verlag, 2000.
- 8. Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation 1998;97:473–83.
- 9. Ohmori K, Cotter B, Kwan OL, Mizushige K, DeMaria AN. Relation of contrast echo intensity and flow velocity to the amplification of

- contrast opacification produced by intermittent ultrasound transmission. Am Heart J 1997;134:1066–74.
- Linka AZ, Sklenar J, Wei K, Jayaweera AR, Skyba DM, Kaul S. Assessment of transmural distribution of myocardial perfusion with contrast echocardiography. Circulation 1998;98:1912–20.
- Emmett L, Iwanochko RM, Freeman MR, Barolet A, Lee DS, Husain M. Reversible regional wall motion abnormalities on exercise technetium-99m-gated cardiac single photon emission computed tomography predict high-grade angiographic stenoses. J Am Coll Cardiol 2002;39:991–8.
- Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67.
- Everitt B. The Analysis of Contingency Tables. London: Chapman & Hall, 1977.
- 14. Shimoni S, Zoghbi WA, Xie F, et al. Real-time assessment of myocardial perfusion and wall motion during bicycle and treadmill exercise echocardiography: comparison with single photon emission computed tomography. J Am Coll Cardiol 2001;37:741–7.
- Lindner JR, Villanueva FS, Dent JM, Wei K, Sklenar J, Kaul S. Assessment of resting perfusion with myocardial contrast echocardiography: theoretical and practical considerations. Am Heart J 2000; 139:231–40.
- Leistad E, Ohmori K, Peterson TA, Christensen G, DeMaria AN. Quantitative assessment of myocardial perfusion during graded coronary artery stenoses by intravenous myocardial contrast echocardiography. J Am Coll Cardiol 2001;37:624–31.
- Masugata H, Peters B, Lafitte S, Strachan GM, Ohmori K, DeMaria AN. Quantitative assessment of myocardial perfusion during graded coronary stenosis by real-time myocardial contrast echo refilling curves. J Am Coll Cardiol 2001;37:262–9.
- Haluska B, Case C, Short L, Anderson J, Marwick TH. Effect of power Doppler and digital subtraction techniques on the comparison of myocardial contrast echocardiography with SPECT. Heart 2001; 85:549-55.
- Imran MB, Palinkas A, Picano E. Head-to-head comparison of dipyridamole echocardiography and stress perfusion scintigraphy for the detection of coronary artery disease: a meta-analysis. Comparison between stress echo and scintigraphy. Int J Cardiovasc Imaging 2003;19:23–8.