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Comparison of the Detection of Subtle Changes in Myocardial Regional Systolic Function Using Qualitative and Semi-Quantitative Techniques

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ABSTRACT

Purpose: **To evaluate qualitative wall motion assessment vs. quantitative wall thickening for the assessment of subtle changes in myocardial systolic function using cine MRI.** ***Methods:*** **Cine MR images were obtained in 5 canines with a significant coronary artery stenosis and in 2 controls on a 1.5T scanner. Qualitative results were obtained using a numerical scoring system; quantitative analysis was performed using a semi-automatic segmentation program. The techniques were matched and compared using Spearman correlations.** ***Results:*** **All correlations in the experimental group revealed significant but weak to moderate relationships between the qualitative and quantitative results (e.g., at-risk tissue rho = 0.363, p < 0.0001; remote tissue rho = 0.275, p = 0.0002), with each identifying changes in regional function that ensued following creation of the stenosis. Intra-observer variability was reasonable in both methods when repeat analysis on a subset of the data was performed, with both techniques showing a significant correlation between the repeated measurements (quantitative − rho = 0.52, p < 0.0001; qualitative − rho = 0.54, p < 0.0001).** ***Conclusion:*** **Both methods were able to detect very limited wall motion abnormalities present in the canines with significant stenosis and either method gives comparable results.**

INTRODUCTION

Accurate assessment of regional myocardial systolic function is critical for proper diagnosis and management of patients

with cardiovascular disease. Magnetic resonance imaging (MRI) provides a non-invasive approach to evaluate the biomechanical dynamics of the heart, including morphological, functional, and metabolic information (1). By spatially registering tomographic images of the heart in different phases of the cardiac cycle, MRI can provide three-dimensional (3D) visualization of global cardiac function and regional function with accuracy and reproducibility (2–4). Furthermore, the advances in gradient technology and reconstruction techniques have increased magnetic resonance (MR) image acquisition speed and made real-time cine MRI possible (4). Thus, sampling of the myocardial wall thickness over the entire left ventricle is possible (5, 6), resulting in the improved assessment of myocardial systolic function (4, 7).

Most commonly, regional systolic function is analyzed qualitatively, although quantitative assessment by drawing myocardial contours to visualize movement of the inner wall of the heart is possible given the ability of MRI to define the endocardial and epicardial borders (3). Qualitative wall motion

assessment (regional endocardial surface motion) is a relatively quick and robust measurement but can be subject to bias and may be less accessible to researchers, whereas quantitative assessment of heart wall thickening (% change in wall thickness from end-diastole [ED] to end-systole [ES]) is more time-consuming (8) but less biased and most likely to yield reproducible results (9). It has been demonstrated previously that the use of quantitative analysis of cine MR images accurately determines degree and extent of regional LV dysfunction in the infarcted heart in vivo (10), where large regions of dysfunction are present. Such quantitative image analysis of the cardiac cycle requires identification of the endocardial and epicardial borders of the left ventricle. These borders are traditionally identified by manually tracing contours in the images (11–14). The examiner has a distinct influence on the accuracy of contours (2) and in the appropriate hands high reproducibility and reliability of manual contour tracings can be obtained (15). Alternatively, reliable automated or semi-automated image segmentation software has shown the ability to overcome the limitations associated with the manual processing of the images (9, 16). Thompson et al. (17) found that two different semi-automatic cardiac software analysis packages (MASS and ARGUS) provided similar results for regional percent wall thickening, with only 6.1% variability between the two packages. Therefore, using automatic segmentation software instead of manual tracing allows for a further examiner-independent process.

The study presented here was designed to compare qualitative wall motion measurements vs. quantitative wall thickening results using images obtained in a canine model of coronary heart disease in which only subtle changes in regional systolic function are anticipated and myocardial infarction is absent or minimal. It has been previously documented that this model induces small reversible reductions in regional wall motion (18). Hence, these two methods to evaluate perturbations in regional ventricular function are investigated in the setting of expected small, reversible changes. It was not the intent of this study to compare these two methods in the setting of severe wall motion abnormalities such as those resulting from moderate to large transmural infarction as this has already been demonstrated in the literature. Such major changes in regional function are usually easily detected with a number of methods including echocardiography, SPECT and PET, as well as MRI (19–22). Rather it was our goal to evaluate these methods based on MR images of subtle effects; effects that could signal early changes in regional function as an indicator of evolving myocardial hibernation.

MATERIALS AND METHODS
Animal preparation and surgery

These studies in female canines were performed in accordance with the University of Western Ontario Council on Animal Care guidelines. Anesthesia for surgery and all follow-up imaging sessions was induced with Propofol 1% (Astra Zeneca, Mississauga, Canada) intravenously and then maintained using 2–2.5% isoflurane after endotracheal intubation. The animal

model methodology has been described previously (18). A significant coronary artery stenosis (average stenosis $76 \pm 4.8\%$; SEM) was created in the left anterior descending coronary artery and confirmed using quantitative digital coronary angiography. Six radioactively-labeled microspheres were available for analysis of regional myocardial blood flow (BF): ^{141}Ce, ^{85}Sr, ^{46}Sc, ^{95}Nb, ^{51}Cr, and ^{103}Ru (Perkin-Elmer, Boston, MA, USA). Blood flow was measured six times in the following order: 1) during a complete transient occlusion to measure the region at risk (RAR; 45 sec); 2) at rest following stenosis formation; 3) during coronary hyperemia at the time of surgery; and 4–6) weekly thereafter. Coronary hyperemia was induced using dobutamine (30 μg/kg/min). Following the third microsphere blood flow measurement the chest was closed and the dog recovered. Subsequent blood flow measurements were acquired by infusing the microspheres through a pig-tail catheter placed in the left ventricular cavity.

After the completion of the experiment at 3 weeks post-surgery, potassium chloride was injected to sacrifice the animal, and the heart quickly excised. The heart was sliced into five to seven slices and sectioned into pieces. These tissue samples were counted for radioactivity to determine myocardial blood flow by microspheres and the at-risk region was determined from these blood flow results (see *Myocardial Blood Flow Analysis* below).

Imaging protocol

MR cine images were obtained prior to baseline (B) and at 1 week (W1), 2 weeks (W2), and 3 weeks (W3) following the surgical intervention. All imaging was performed on a Siemens Vision 1.5T clinical system (Siemens, Erlangen, Germany), and the same imaging protocol was used for all imaging sessions.

Animals were placed prone in a head coil and the heart centered within the coil. A 0.2 mmol/kg/min bolus of gadolinium diethylenetriaminepetaacetic acid (Gd-DTPA) was injected at a rate of 46 mL/min, followed by a constant infusion of 0.004 mmol/kg/min to investigate myocardial viability. Short axis cine images (TR/TE 10/4.8 ms, 8 mm slice thickness, 30° flip, FOV 254–300 mm, 128×128 matrix) were obtained at rest and during dobutamine-induced stress for assessment of contractile function using qualitative and quantitative analysis. On average, 10 phases were acquired, resulting in an average of 19 frames per cardiac cycle per slice by making use of echo sharing (Siemens, Erlangen, Germany). Each slice position was acquired during a breath-hold by suspending ventilation and took approximately 30 seconds to acquire. Total short-axis cine imaging throughout the left ventricle took about 10 minutes to complete.

Image and data analysis
Qualitative analysis

Qualitative wall motion analysis was performed on all cine MR images throughout the left ventricle at every slice position and time-point in each animal. Qualitative analysis of images was based on the assessment of regional endocardial systolic wall motion determined in six regions (inferoseptal, septal,

anteroseptal, anterolateral, lateral, and inferolateral) using a seven-point scoring system, with 1 to 7 representing dyskinetic, akinetic, severely hypokinetic, moderately hypokinetic, mildly hypokinetic, normal, and hyperkinetic wall motion, respectively. This analysis was performed by an experienced cardiologist (GW), who was kept blinded to the dog number and time-point of each study. The assessment of regional wall motion depends on the quality of the images (23). Therefore, subjective ranking of cine image quality was performed. Two slices out of 80 were deemed of poor quality and were removed and not included in the subsequent analysis, for both the qualitative and quantitative results. In one animal, wall motion analysis was repeated for all time-points to measure intra-observer variability including potential drift in scoring with time. The second analysis was performed several weeks after the first analysis and was kept blinded from the observer.

Quantitative analysis

Quantitative analysis was performed using a semi-automatic segmentation program (ARGUS; Siemens, Erlangen Germany). Contours were drawn around the endocardium and epicardium of the ED and ES frames for each slice position (Fig. 1). A reference sector was placed at the inferior border where the right ventricle meets the left ventricle in both the ED and ES images to compensate for cardiac twist (2, 9). The percent wall thickening between these contours in twelve different sectors was calculated and averaged to obtain wall-thickening values for six regions corresponding to the six regions used in the qualitative analysis. Global function, expressed as ejection fraction, was also calculated. Repeat analysis of wall thickening was performed in the same animal as in the qualitative analysis, and the two sets of results were investigated for intra-observer variability.

Comparisons between the qualitative and quantitative measurements were made for all RAR and remote values obtained from all animals. These comparisons included evaluating whether correlations were stronger in certain regions of the heart (RAR vs. remote), in different slices (apex [A], mid-apex [MA], mid-base [MB], base [B]) or at certain times after stenosis formation. A total of 494 pairs were available for the various comparisons.

Both the qualitative and quantitative measurements were repeated using the same data acquired from one animal to determine reliability of the measurements. The ejection fraction measurements were repeated by another user to obtain the inter-examiner variability of the endocardial contour placement using the semi-automatic segmentation program.

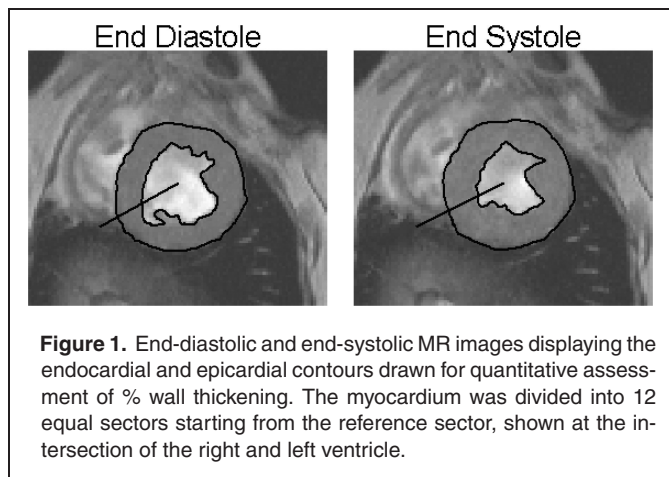## Myocardial blood flow analysis

Regional myocardial blood flow (BF, mL/min/g) was determined using standard microsphere blood flow measurement techniques and has been explained previously (18). The RAR tissue was determined by identifying the tissue with blood flow ≤ 0.3 mL/min/g during a 45s transient occlusion of the LAD as measured with microspheres. Regions with blood flow > 0.3 mL/min/g were defined as remote tissue. This segmentation was performed in all animals, including the control animals even though no stenosis was created for comparison between heart regions. Perfusion reserve (PR; BF_{stress}/BF_{rest}) and perfusion reserve ratio (PR_{RAR}/PR_{remote}) were calculated in the RAR and remote tissue and correlated to regional wall motion. These correlations were a further measurement of the sensitivity of the two wall motion analysis techniques.
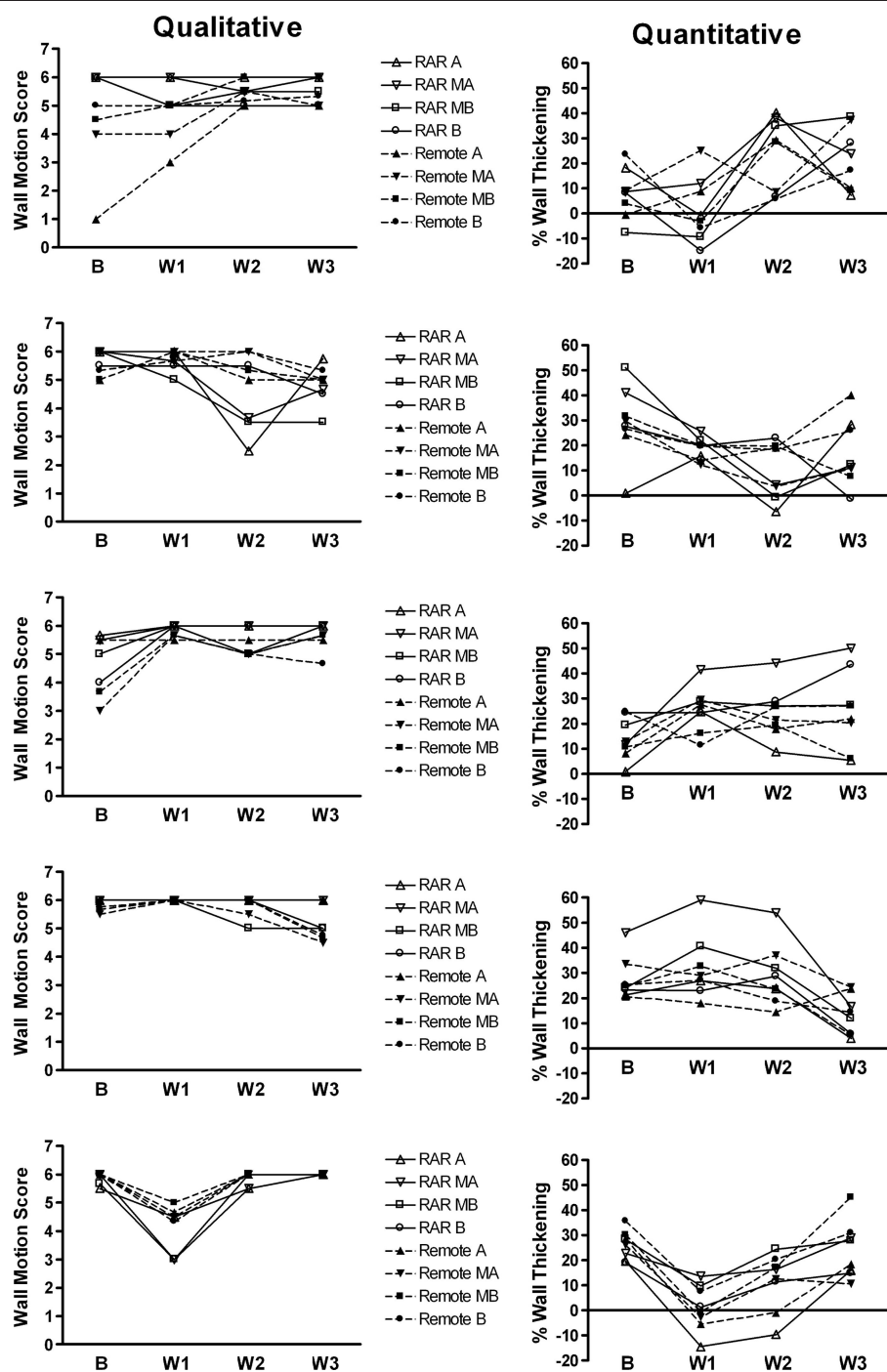
Statistical analysis

Spearman correlation coefficients were calculated for the resting left ventricular function data to determine how well the qualitative and quantitative results were related. Intraclass correlation (ICC; two-way mixed model) was used to determine reliability of the quantitative ejection fraction measurements and the repeated quantitative wall motion results. An ICC value of > 0.8 suggested good reliability. Non-parametric (Wilcoxon) and parametric paired t-tests were used to determine the systematic changes when repeating qualitative and quantitative measurements, respectively. $p < 0.05$ was considered significant for all tests other than the intraclass correlation. Correlations were considered strong if $1.0 > rho > 0.7$, moderate if $0.7 > rho > 0.4$; weak if $0.4 > rho > 0.1$. GraphPad Prism (San Diego, CA, USA) was used for all Spearman correlations and t-tests and SPSS 10 (Chicago, IL, USA) was used for the ICC analysis. Average wall motion and wall thickening results are displayed as mean $\pm$ SD.

RESULTS

Figure 2 shows the average qualitative (left figures) and average quantitative (right figures) results from each animal in the RAR and Remote tissue regions for all 4 slices analyzed in the stenosis and control animals, respectively. Viability was maintained in all but one animal (2nd panel in Fig. 2), where a limited subendocardial infarction was noted at the final imaging session as evidenced by contrast-enhanced imaging. Average qualitative and quantitative results from each time-point in the RAR tissue identified W1 as the nadir of left ventricular function (quantitative: B = $20.5 \pm 14.7\%$, W1 = $17.7 \pm 19.0\%$, W2 = $22.1 \pm 17.3\%$, W3 = $20.0 \pm 14.0\%$, qualitative: B = 5.74 ± 0.49, W1 = 5.25 ± 1.10, W2 = 5.32 ± 1.01, W3 = 5.52 ± 0.72). Visual

Figure 1. End-diastolic and end-systolic MR images displaying the endocardial and epicardial contours drawn for quantitative assessment of % wall thickening. The myocardium was divided into 12 equal sectors starting from the reference sector, shown at the intersection of the right and left ventricle.
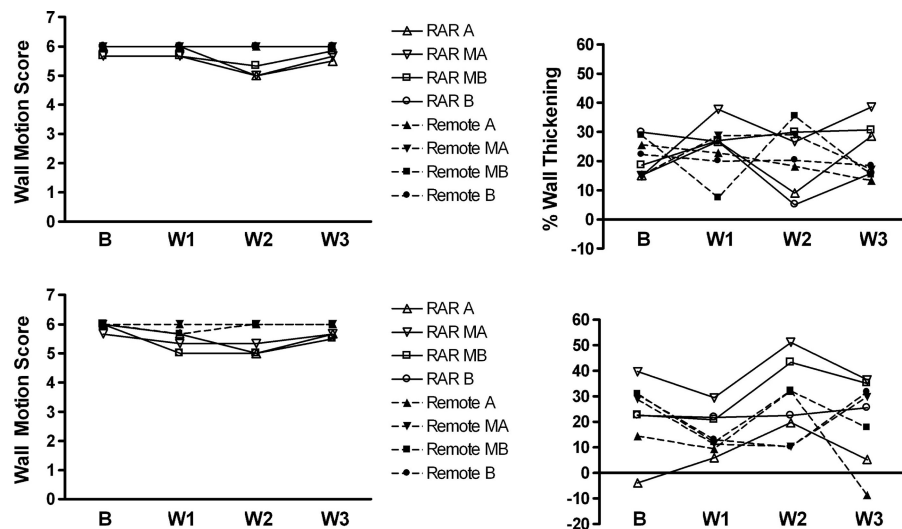
Figure 2. Average qualitative and quantitative results from the five experimental animals over the course of the experiment. B = Baseline, W1, W2, W3 = Weeks 1, 2, and 3 following surgery. Similar trends are apparent in most of the animals, with obviously more variability in the quantitative measurement. A—Apex; MA—Mid-Apex; MB—Mid-Base; B—Base.

assessment of the qualitative and quantitative results (Figs. 2 and 3) suggests reasonable agreement, but further investigation into the relationship between the values was performed using correlation analysis.

Figure 4 illustrates some of the correlation analyses performed with the remainder of the correlation results reported in Table 1. These results showed weak but significant correlations when all the data (stenosis and control animals) were assessed (rho = 0.237) as well as when the RAR (rho = 0.363) and remote (rho = 0.275) results from the stenosis animals were analysed separately. Analysis of the control data alone revealed that the qualitative and quantitative data were not significantly

Figure 3. Average qualitative and quantitative results from the two control animals over the course of the experiment. Similarly to the results in Fig. 2, the qualitative and quantitative results show comparable trends with increased variability in the quantitative results.
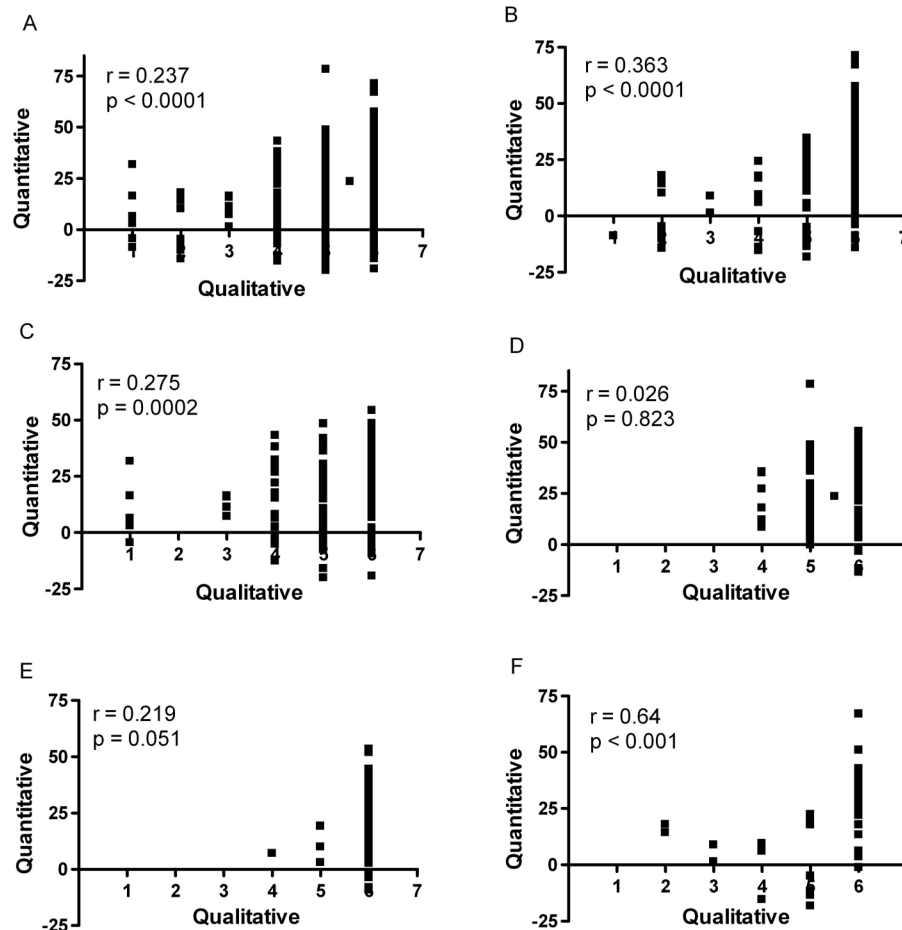
Figure 4. Selected graphs from the correlation analyses performed. A—all values from both the control and experimental animals (n = 494); B—values from the experimental animals in the RAR tissue (n = 160); C—values from the experimental animals in the remote tissue (n = 178); D—values from the control animals in the RAR tissue (n = 76); E—values from the control animals in the remote tissue (n = 80); F—values from the experimental animals in the RAR tissue at W1 (n = 40), where the strongest correlation was noted.

Table 1. Spearman rho correlations assessing the associations between qualitative and quantitative values calculated in the experimental animals in the RAR and remote tissue over time

| | Spearman rho Values | | | |
	RAR	**Remote**	**All Values by Slice**	
B	−0.122 (NS)	0.426[‡]	**Apex**	0.325[†]
W1	0.640[†]	0.442[‡]	**Mid-Apex**	0.284[‡]
W2	0.489[‡]	−0.055 (NS)	**Mid-Base**	0.282[‡]
W3	0.294 (NS)	0.212 (NS)	**Base**	0.464[†]

(B = Baseline; W1 = Week 1; W2 = Week 2; W3 = Week 3). Correlations were also evaluated for all tissue regions and time-points combined in the 4 slice positions acquired (Apex, Mid-Apex, Mid-Base, Base).
[†] $p < 0.001$.
[‡] $p < 0.01$.

Table 2. LV ejection fraction values determined by two different users (KSL and MF) in the five experimental dogs using the semi-quantitative software employed for the % wall thickening analysis

| | Examiner 1(MF) | | | | | Examiner 2(MF) | | | |
DOG	**B**	**W1**	**W2**	**W3**	**DOG**	**B**	**W1**	**W2**	**W3**
1	29.8	23.9	46.1	37.3	1	31.8	27.7	42.6	39.3
2	40.7	44.5	31.7	34.7	2	38.3	42.4	31.3	33.6
3	28.7	45.0	37.0	41.0	3	24.2	40.9	35.8	38.1
4	46.7	53.7	50.9	26.7	4	45.9	52.2	49.4	28.3
5	38.0	21.0	36.2	35.1	5	33.9	18.3	34.2	33.7
AVG	36.4	37.6	49.4	35.0	**Avg**	31.2	37.0	36.3	37.0

The ejection fraction results were not significantly different between the two users, suggesting that placement of the endocardial contours was relatively reproducible.
Imaging Sessions: B—Baseline; WI—Week 1; W2—Week 2; W3—Week 3.

correlated in the RAR tissue or in the remote tissue. Most (70%) of the correlations reported were significant but only weak to modest. At one week after stenosis formation, when regional wall motion was most abnormal, the correlation between the two techniques in the RAR tissue was strongest, with rho = 0.64 and $p < 0.0001$.

Correlation analysis between the qualitative and quantitative techniques during dobutamine stimulation was often not possible since only one score was available using the wall motion scoring technique. In 77.4% of tissue regions, wall thickening was increased by more than one standard deviation over the corresponding resting wall thickening values, and 75.5% of the wall motion scores were considered hypercontractile during low-, mid-, and high-dose dobutamine infusions.

To investigate the intra-user variability, both the qualitative and quantitative analyses were repeated in one animal. For the quantitative data, the percent difference, intraclass correlation

(ICC), significant difference (paired t-test) and spearman correlation were computed. Only the spearman correlation and non-parametric t-test (Wilcoxon) were performed on the qualitative data since these data are subjective and on an ordinal scale. Figure 5 shows the averaged original and repeat qualitative and quantitative results. The quantitative technique measurements were not statistically different from one another, the average percent difference was 8.4% over all the regions, and the ICC result was 0.56. The repeated qualitative measurements were found to be significantly different from one another. Spearman correlation analysis revealed moderate and significant correlations in both the quantitative (rho = 0.52, $p < 0.0001$) and qualitative (rho = 0.54, $p < 0.0001$) techniques.

Table 2 illustrates the ejection fraction results calculated by two different users (MF and KSL), which allowed for a comparison of inter-examiner variability of EFs and, indirectly, the
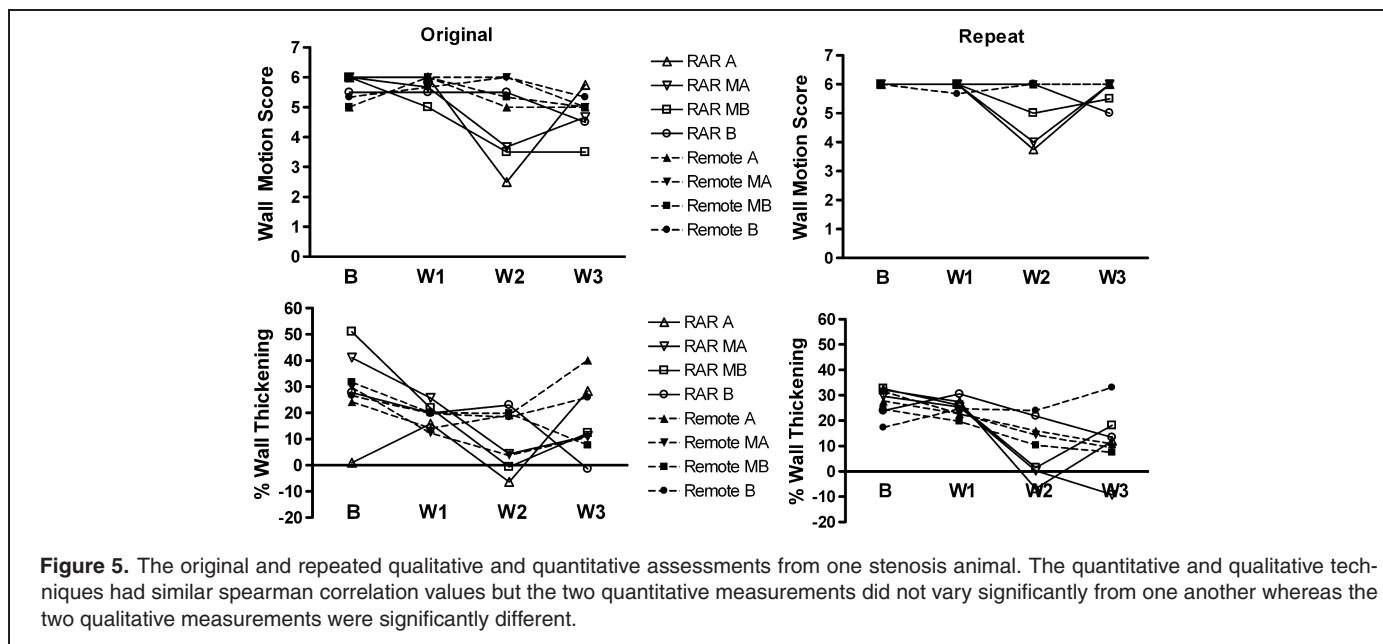
Figure 5. The original and repeated qualitative and quantitative assessments from one stenosis animal. The quantitative and qualitative techniques had similar spearman correlation values but the two quantitative measurements did not vary significantly from one another whereas the two qualitative measurements were significantly different.

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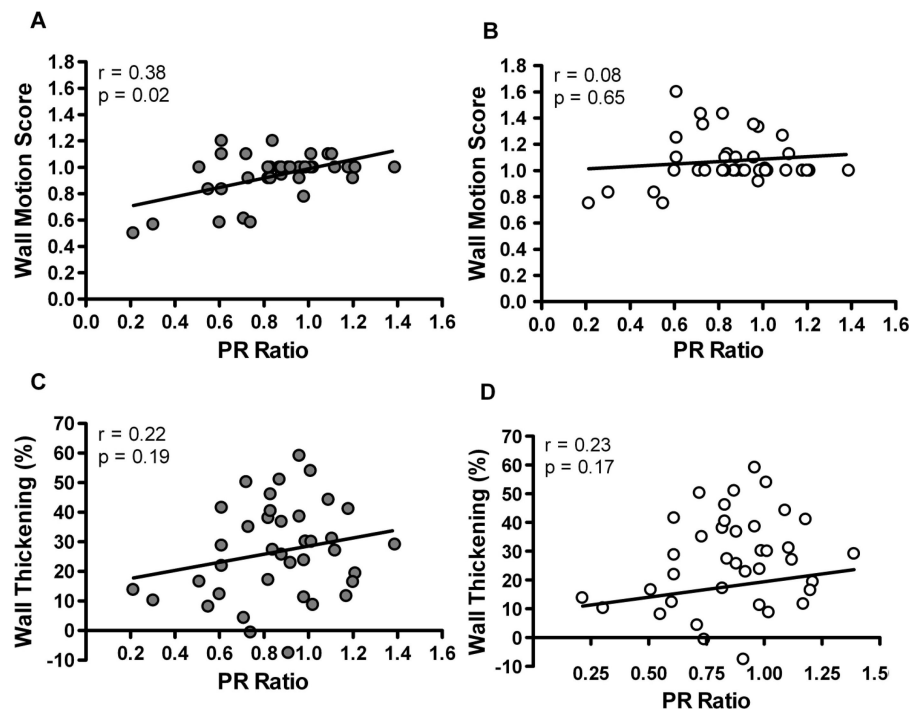
Figure 6. Spearman correlations between wall motion scores (A and B) or wall thickening values (C and D) and perfusion reserve (PR) ratio values in the RAR (A and C) and remote (B and D) tissue. A significant correlation was found between wall motion scores and PR ratio in the RAR tissue but no such relationship was found either in the remote tissue or in the RAR tissue between the wall thickening values and PR ratio, suggesting that the qualitative technique is more sensitive for small changes in left ventricular function.

reproducibility of the placement of the endocardial contours during wall thickening analysis. The results are similar to one another, with the average intraclass correlation between the ejection fraction results were 0.95 for baseline, 0.98 for week 1, 0.97 for week 2, 0.94 for week 3, and 0.96 overall, and were found to not be statistically different from each other.

Correlations between the perfusion reserve ratio values measured using microspheres and the quantitative and qualitative wall thickening and wall motion results are shown in Fig. 6. A significant correlation was found in the RAR tissue between PR ratio and wall motion score but not between PR ratio and wall thickening. In the remote tissue, no relationship was present between wall motion or wall thickening and PR ratio.

DISCUSSION

This study compared regional contractility results obtained using semi-quantitative (wall thickening) and qualitative (wall motion) techniques in the setting of subtle, reversible myocardial dysfunction. The results indicate that, while not strong, many of the correlations were significant and similar trends were seen with the two techniques. Further, both techniques have comparable reproducibility in the one animal in which repeat analysis was performed, with modest repeatability and significant correlation found with either technique. Correlation results suggest that matching of the qualitative and quantitative wall function analysis is better when function is reduced, where the strongest

correlation was seen in the RAR tissue at one week post-stenosis. Our group has previously shown that function is significantly lower at 1 to 2 weeks post-surgery in this canine model (18). The correlation results between perfusion reserve ratio and wall motion or wall thickening may suggest that the qualitative technique is a more sensitive measure of these subtle changes in regional function caused by a transient decrease in regional perfusion reserve. Therefore, qualitative analysis may have increased sensitivity in the setting of evolving myocardial hibernation secondary to repetitive stunning in the setting of coronary artery disease (24).

However, our results are at variance with other studies, which have demonstrated increased sensitivity for wall thickening measurements in comparison to wall motion, both with echocardiography and MRI in canine models of myocardial infarction (25, 26). It should be noted that the measurement of wall motion and wall thickening are similar but slightly different parameters. The qualitative assessment of wall motion, i.e., the endocardial movement, is influenced by, but not precisely the same as, the degree of thickening between endocardial and epicardial edges during systole. Regional endocardial motion may be influenced by the contraction of adjacent myocardial segments, and, therefore, has the potential to be less sensitive, as a truly dysfunctional segment may be assessed as normal. However, there may be factors within a two-dimensional slice, (translational and rotational motion) which may affect the accuracy of any quantitative wall thickening measurement, particularly with

a fixed centroid method (25); a non-fixed centroid method was used in this study.

The inter-examiner variability between the left ventricular EF values suggests very minimal variability between users exists for determining EF from the ARGUS software program and, hence, indicate that the reproducibility of EF values with the quantitative approach are independent of examiner. However, the determination of inter-examiner variability or correlation for wall thickening (or wall motion) cannot be inferred from this EF correlation, since the procedures for defining contours around the epicardial border and placing the reference sector were not undertaken when determining EF. The result does suggest, however, that the differences noted between the repeated wall thickening analysis were due to the placement of the epicardial contour and not the endocardial contour. Given the enhanced contrast between the blood pool and the endocardial border compared to the epicardial border and surrounding tissues (27), this result is not surprising. Other research has shown the inter-examiner variability of qualitative and quantitative LV contractility analysis by cine MRI to be comparable (2). The quantitative technique has been shown to offer substantial advantages in MRI studies performed for the detection of coronary artery disease and LV function (11) and Hundley et al. (28) stated that a limitation to their study was using a qualitative rather than quantitative assessment of endocardial thickening with MRI.

The qualitative and quantitative techniques were difficult to compare due to the difference in scales and measurement for wall motion and wall thickening scores. This was apparent for the control and dobutamine LV contractility results. Since contractility was not significantly affected in the control animals, the qualitative results generally reported normal wall motion in both the RAR and remote tissue. Similarly, due to only a single "score" available for hypercontractile tissue when assessed qualitatively, most of the tissue regions were assigned a score of 7, resulting in restricted data range and the inability to perform correlation analysis.

The qualitative technique, which, because of convenience, is primarily used today, required a portion of the analysis time compared to the quantitative technique. A particular strength of the qualitative analysis is that it allows subjective examination of the changes that occur throughout the cardiac cycle and in each region of interest. For example, assessment of delay in systolic contraction and diastolic relaxation were parameters also taken into account when assigning the qualitative score in addition to the degree of systolic movement. However, the qualitative method relies heavily on image quality and has a limited range of numerical wall motion scores in the seven point scoring system, especially in our canine model of subtle changes in contractility. Even more restrictive scaling is occasionally used in the clinical setting, with sometimes a 3 or 4 point scoring system for fewer regions of the heart (29–31). However, in comparison to the quantitative technique, reproducibility of results is an issue for the qualitative assessment of heart wall motion in the setting of detection of small reversible changes in cardiac function.

Limitations existed in the ARGUS segmentation algorithm that was used, preventing fully automatic processing causing lengthy manual editing of all ED and ES image contours. In addition to contour editing, the identification of the epicardial border was difficult to visualize because of partial volume effects and alterations to the location of the reference sector resulted in slight deviations of percent wall thickening values. Foreseeable improvements in currently available segmentation algorithms should make the quantitative analysis technique faster and less reliant on examiner oversight (32, 33). Improvement in image quality and thinner slices should also improve wall thickening results. Williams et al. (9) suggested that, as with any automation strategy, much of the value of improved image processing software comes not from novel capabilities but rather from increased utility. Therefore, continuous use of the ARGUS semi-automatic segmentation program would aid the user's image processing ability. The quantitative technique would most likely be useful in assessment of regional myocardial thickening when analysis time is not a factor and is a step towards examiner-independent assessment of cardiac function.

CONCLUSIONS

The qualitative and quantitative techniques were significantly correlated in regions of subtle changes in regional systolic function, and both techniques had comparable reproducibility. Therefore, the quantitative technique is anticipated to be as useful in cardiac function assessment as the qualitative technique, although the qualitative technique may be superior in the detection of small changes in myocardial wall motion secondary to reduced perfusion reserve. The quantitative method increases accessibility to researchers, as opposed to having an experienced observer (cardiologist or radiologist) analyze the images and may also be used clinically if a cardiologist/radiologist was not readily available. Future intra- and inter-examiner variability of both methods would also be an asset to conclusively determine which technique is more reproducible and sensitive to the detection of small changes in regional systolic function.

ACKNOWLEDGMENTS

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