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FEATURED RESEARCH

Automated Analysis of Phase-Contrast Magnetic Resonance Images in the Assessment of Endothelium-Dependent Flow-Mediated Dilation

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ABSTRACT

Measurement of flow-mediated arterial dilation (FMAD) provides information regarding the status of peripheral arterial endothelial function. Although phase-contrast magnetic resonance imaging (PC-MRI) can be used to measure FMAD, the manual analysis of one study (tracing regions of interest and processing data on 100 images) can require six or more hours. To enhance the clinical utility of the PC-MRI assessment of FMAD, we hypothesized that an automated technique (Multi-Stage Intensity Thresholding or MSIT) for determining femoral arterial area and flow before and after cuff inflation over the thigh could be used to evaluate FMAD in a rapid, accurate, and reproducible manner. Compared with manual analysis, automated analysis detected a similar percentage change in peak FMAD between healthy individuals (17.2% vs. 16.5%) and patients with congestive heart failure (4.0% vs. 5.1%). The correlation between percentage changes in arterial area after cuff release derived manually and automatically was very good ($r = 0.93$). Analysis time for 100 images averaged 10 minutes with MSIT vs. 6 hours for manual analysis. In conclusion, rapid, accurate assessments of femoral artery FMAD can be obtained using Multi-Stage Intensity Thresholding. This methodology may prove useful for the rapid MRI assessment of peripheral arterial endothelial function in a clinical setting when studying patients with cardiovascular disease.

Key Words: Endothelium; Magnetic resonance imaging; Peripheral vascular disease.

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INTRODUCTION

Assessment of peripheral arterial flow mediated arterial dilation (FMAD) provides insight into the status of peripheral arterial endothelial function (Anderson et al., 1995; Fan et al., 2000; Hayoz et al., 1993; Hundley et al., 1996; Hundley et al., 1999; Krug et al., 1995; Kubo et al., 1991; Uehata et al., 1997). To measure FMAD, sequential images of the vessel lumen are acquired in a near continuous fashion at rest, during a 3 to 5 minute cuff inflation, and for 5 minutes after cuff release (Fan et al., 2000; Playford and Watts, 1998; Uehata et al., 1997). Recently, phase-contrast magnetic resonance imaging (PC-MRI) has been used to measure FMAD (Alexander et al., 2001). Using this methodology, the arterial lumen of >100 images must be demarcated; if performed manually, the analysis can take several hours (Fan et al., 2000; Henriksen et al., 1989; Playford and Watts, 1998).

Multi-Stage Intensity Thresholding (MSIT) is a boundary detection algorithm that performs three stages of boundary detection with different searching criteria for each stage based on the average intensity of the pixels within the boundary. Although boundary detection algorithms have been used to measure cardiac cycle dependent changes in vessel area and flow (Chwailkowski et al., 1996), they have not been utilized to analyze dynamic changes in vessel area acquired from a series of images obtained before, during, and after an intervention. The purpose of this study was to determine the utility of the MSIT algorithm for assessing femoral arterial FMAD after thigh cuff inflation.

METHODS

Study Population

The study was approved by the Institutional Review Board of the Wake Forest University School of Medicine, Winston-Salem, NC, and participants provided written informed consent. The study population consisted of six healthy subjects (three women and three men) aged >60 years that took no medications, had no medical illness, a normal physical examination, a systolic and diastolic blood pressure below 140 and 90 mmHg, respectively, and a normal exercise echocardiogram; and six patients (three women and three men) aged >60 years with New York Heart Association class II or III heart failure and a left ventricular ejection fraction (EF) $<40\%$. The results of the manual analysis from three of these participants were reported as a portion of a previous study (Alexander et al., 2001). Participants ineligible for study included those with a contraindication to magnetic resonance imaging (MRI), such as an implantable pacemaker or defibrillator, intracranial metal, or claustrophobia, or those using medications or substances that may cause systemic vasoconstriction, such as over-the-counter decongestants, caffeine, or theophylline.

Study Design

All medications were withheld 12 hours before MRI, and all subjects fasted 4 hours prior to study. Marked physical activity such as heavy lifting, running, bicycling, or swimming was not performed 24 hours prior to testing. After lying quietly in a supine position for 30 minutes, each subject was positioned feet first on the MRI table with electrocardiographic monitoring leads, a brachial blood pressure cuff, a large thigh occlusion cuff, and a phased array surface coil over the thigh attached.

Participants were advanced into the MRI scanner (1.5 T Horizon LX, General Electric Medical Systems, Milwaukee, WI), and the left superficial femoral artery was visualized in coronal, sagittal, oblique, and axial planes. At a point 20 cm distal to the femoral head, perpendicular cross-sectional images of the superficial femoral artery were obtained along a straight vessel segment using a phase-contrast gradient echo technique. This provided a circular image of the vessel so that through-plane motion and partial volume effects would be minimal when subsequent images were collected for analysis. Image parameters included a 7 mm slice thickness, a 13 cm field of view (FOV), and a 256×256 matrix. The selected FOV and matrix yielded pixels that are 0.5 mm on a side; this resulted in approximately 16 pixels spanning a typical 8 mm diameter femoral artery. Other parameters included a 40° flip angle, an 18 ms repetition time (TR), a 6.7 msec echo time (TE), a velocity encoding of 150 cm/sec, and the incorporation of k-space segmentation so as to yield seven or more frames (temporal resolution of 90 to 105 ms) per cardiac cycle. After three measurements were made at rest (Fig. 1), the thigh cuff was inflated for 4 minutes to 100 mmHg above the systolic blood pressure measured with the brachial blood pressure cuff. During this time, two more phase-contrast MRI scans were performed to confirm the absence of flow in the vessel. The air pressure within the thigh cuff was then released, and MRI images of the vessel were taken at 30-second intervals for the next 5 minutes. Altogether, 12 to 17 scans were performed, with each scan containing seven or more frames, for a total of 84 to 153

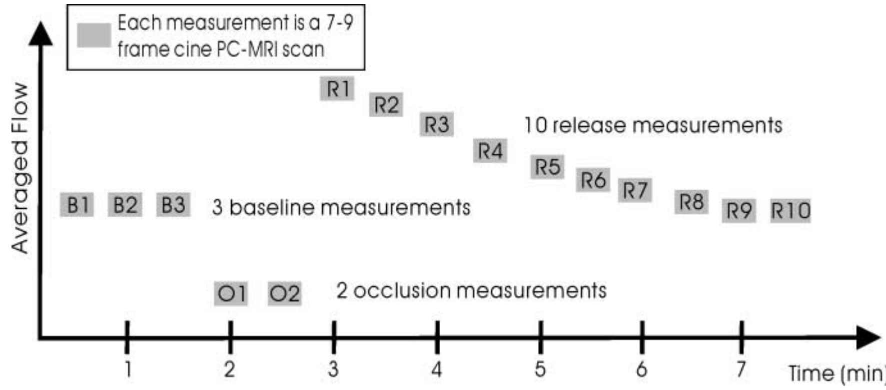

Figure 1. The time course for collection of a series (three at baseline, two during thigh cuff occlusion, and 10 after thigh cuff release) of 15 sequential scans is displayed. Each scan consists of seven frames.

images to be analyzed for each subject. Heart rate and systemic arterial blood pressure were monitored and recorded during scanning.

Image Analysis

Manual and automated techniques were used to analyze the MRI images. The manual method required the user to trace a ROI delineating the lumen of the femoral artery on the magnitude image of each frame. The interpolated image was magnified with interpolation by a factor of 8 (theoretically allowing the detection of a change in vessel area of $<1\%$ using the 0.5×0.5 mm spatial resolution specified above), and the lumen boundary was defined as the point at which the intensity of the blood dropped to 50% of the peak intensity within the lumen as judged visually. Information regarding the vessel boundary from the simultaneous display of the velocity maps was occasionally used to assist the analyst in defining the vessel lumen. The gamma value of the display and the room brightness were kept constant for all manual tracings to ensure consistency in boundary detection.

Automated analysis was performed using the MSIT technique (implemented in Interactive Data Language, Research Systems Inc., Boulder, CO). The technique required the user to place an elliptical spline with eight evenly spaced control points inside the lumen of the femoral artery on the first frame of each scan. The program calculated the mean intensity level of the pixels inside the spline and this mean value was used as the initial threshold reference for sequentially selecting the control points of the boundary of the ROI. The algorithm determined the lumen boundary in three stages (Fig. 2). After the lumen boundary was determined for the first frame, the initially drawn ROI was propagated to the next frame where its center was derived from center of the final ROI of the previous frame. The three stages were then executed to identify the lumen boundary for the subsequent frames in the scan.

For manually and automatically analyzed images, the lumen area was calculated for each frame by counting all pixels within the ROI and multiplying by the pixel dimensions (Table 1). Peak FMAD was defined as the percentage increase (compared to the mean area of the three baseline acquisitions) in the largest lumen area occurring 60 to 90 seconds after cuff release.

Data Analysis

The peak systolic area for each scan was defined as the average of the areas of frames 2 through 4 of the imaging sequence. All data were expressed as mean $+1$ standard deviation. Paired groups were compared using Student's t-test; a p-value <0.05 was considered significant. The correlation and limits of agreement among results generated automatically and manually were compared using linear regression and the technique described by Bland and Altman, (1986). Two observers processed the same data set by manual and automatic methods twice for the determination of intra- and inter-observer variability.

RESULTS

Using manual analysis, FMAD was $17.1\% \pm 4.9\%$ (range 11.7% to 23.5%) in normals, and $4.1\% \pm 1.3\%$

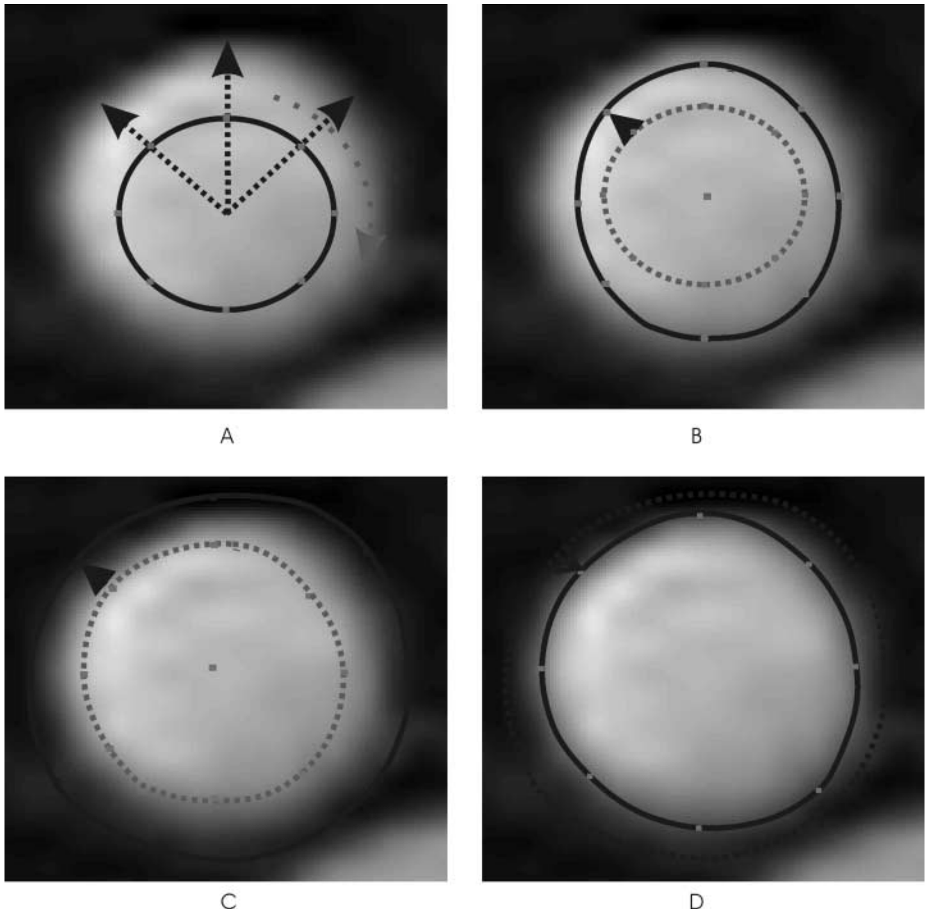

Figure 2. Operational diagram for the MSIT algorithm. In Panel A, a spline (normally eight control points) is placed within the ROI. After calculating the mean gray level within the spline area, the program searches outward sequentially from the control points using 60% of the mean gray level as the threshold and 15 pixels as the grow limit. The resultant spline is identified by the solid black circle in Panel B. In the second phase, the algorithm repeats the outward search by decreasing the threshold to 50% of the mean gray level within the new spline, and reducing the outward grow limit to 5 pixels. As shown in Panel C, the boundary identified on the second search may extend beyond the true lumen. On the last search in Panel D, the final spline (circle with solid black line) may be defined by expanding or reducing the final boundary using a threshold of 40% of the mean gray level and a grow limit of three pixels.

(range 2.5% to 6.3%) in congestive heart failure (CHF) patients. With the MSIT algorithm, arterial area increased 16.3% ± 4.5% (range 12.1% to 22.2%) in normals, and 5.1% ± 1.7% (range 2.9% to 7.1%) in the CHF patients. Figure 3 displays the percentage change in arterial area using the manual and MSIT techniques in a normal (Fig. 3A) and a CHF patient (Fig. 3B) for a single femoral cuff-release experiment. The correlation (Fig. 4) among results generated manually and with the MSIT algorithm in 12 patients was very good ($r = 0.93$). As shown in Fig. 5, the mean percentage change for the manual and MSIT methods was 0, and the 2 standard deviation difference between the methods was 1.17%. The time to analyze (organize, trace, and report) a complete data set (all scans) from one patient was 10 ± 1 minutes and 240 ± 30 minutes for the MSIT and manual techniques, respectively.

They were no significant differences ($p = 0.15$ to 0.68) in the intra- and inter-observer variability for both observers using the MSIT algorithm (Table 2).

DISCUSSION

Assessment of FMAD in peripheral arteries provides insight into peripheral arterial endothelial function. Although MRI data for assessing arterial dilation may be acquired relative rapidly, its manual analysis is time

Table 1. Area values measured by MSIT and manual methods.

	Manual			MSIT		
Normal	baseline	release	% change	baseline	release	% change
Subject-1	32	36.40	***13.75***	30.25	34.15	***12.92***
Subject-2	24.9	27.82	***11.73***	26.13	29.29	***12.07***
Subject-3	21.21	24.57	***15.84***	21.92	25.60	***16.80***
Subject-4	22.57	27.78	***23.08***	24.60	29.79	***21.10***
Subject-5	23.5	26.95	***14.68***	26.09	29.37	***12.56***
Subject-6	31.63	39.05	***23.46***	35.45	43.31	***22.18***
CHF						
Subject-1	24.48	25.10	***2.53***	24.32	25.03	***2.94***
Subject-2	21.36	22.35	***4.63***	23.32	24.26	***4.02***
Subject-3	16.63	17.67	***6.25***	17.82	18.95	***6.32***
Subject-4	21.69	22.74	***4.84***	22.70	23.99	***5.67***
Subject-5	25.24	26.08	***3.33***	31.54	32.95	***4.46***
Subject-6	31.44	32.51	***3.40***	32.52	34.83	***7.09***

consuming (Fan et al., 2000; Furber et al., 1998; Liang et al., 1998; Playford and Watts, 1998). For this reason, the utility of MRI FMAD assessments has been confined primarily to research studies. In the current study, we demonstrate the accuracy of an automated algorithm (MSIT) for measuring dynamic changes in arterial area over time. We accomplish this by showing near equivalence of the peak FMAD results generated with the MSIT algorithm to those generated manually in healthy individuals and those with CHF. In addition, with MSIT algorithm, the clinical utility of MRI FMAD measurements may be realized due to the reduction in analysis time from 6 hours to 10 minutes.

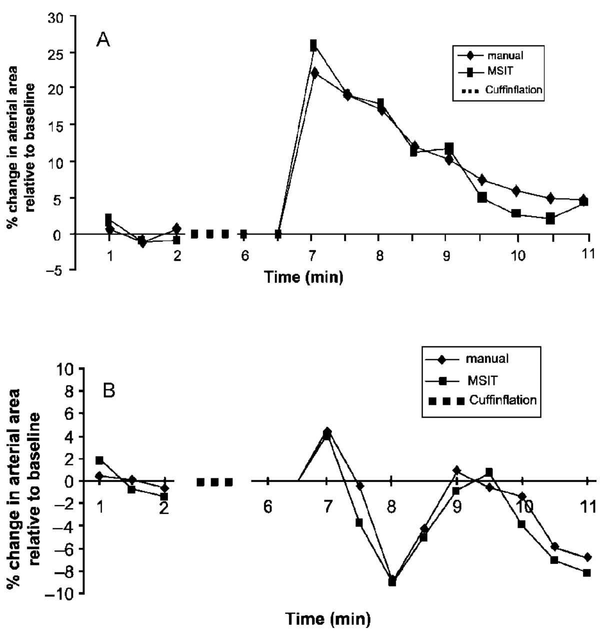

Figure 3. The comparison of manual and MSIT results from a normal individual (Panel A) and a participant with heart failure (Panel B). Each symbol represents averaged data from the three systolic frames of each sequence. As shown, the results generated with the automated MSIT technique are similar to those generated manually.

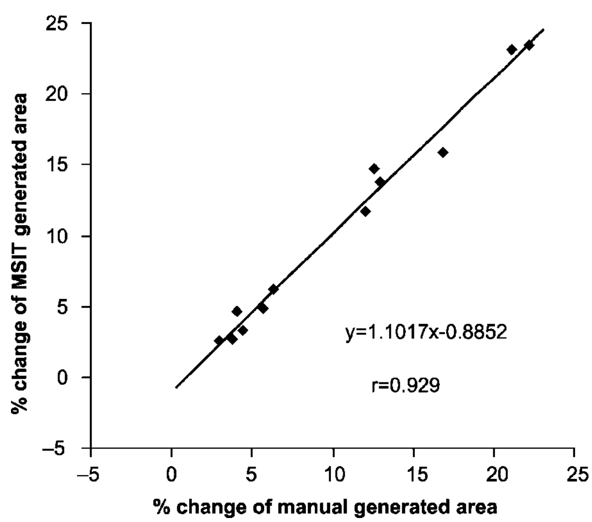

Figure 4. The relationship between manual (x-axis) and MSIT (y-axis) results in all the subjects. Each symbol represents the data from one patient. The regression line and equation are shown. There is good correlation between the manual and MSIT analysis methods.

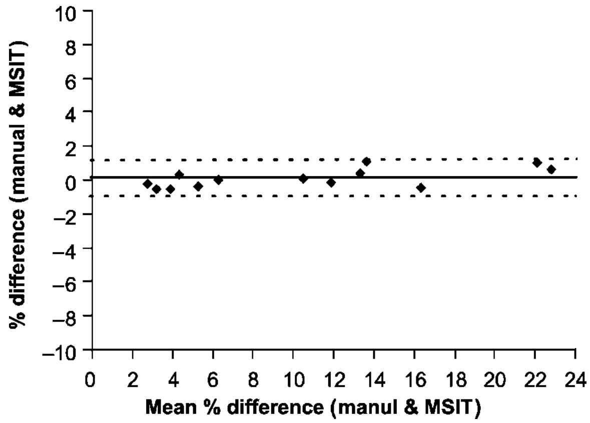

Figure 5. Mean percentage changes (x-axis) and the difference (y-axis) between the manual and MSIT methods of analysis for the 12 patients enrolled in the study. Each symbol represents data from one patient. The mean difference (solid line) and ±2 standard deviations from this difference (dashed lines) are shown. There is little difference in the limits of agreement between the manual and MSIT methods.

MSIT Performance

The MSIT algorithm searches three times with successively smaller threshold and grow limit values in order to detect the vessel boundary of the superficial femoral artery in the thigh. Using this technique, the first search covers most of the ROI area, and the two subsequent searches expand or reduce the dimensions of the ROI to match the true vessel boundary. We found three searches optimal for vessel boundary detection. If the algorithm searched only once using a single fixed threshold and grow limit, the boundary detected was irregular. If the algorithm searched the boundary more than three times, the analysis time was longer and the results were similar to those obtained after three searches. As our results indicate (Figs. 4 and 5), MSIT analyses of MRI derived FMAD assessments closely match those derived manually and they are performed in a fraction (1/20) of the time.

Comparison with Other Automatic Boundary Detection Algorithms

Several peripheral boundary detection algorithms, including methods incorporating threshold weighting (single intensity threshold) (Burkart et al., 1994; Chakraborty et al., 1996), wavelets (Chwailkowski et al., 1996; Furber et al., 1998), and simulated annealing (Kozerke et al., 1999), have been used to derive flow and area measurements in central and peripheral arteries (Gustavsson et al., 1997). Vessel boundaries are detected with the single intensity threshold technique by searching for a predefined gray level (Burkart et al., 1994); with the wavelet technique, by finding the smallest value of 4 summarized energy forces (Furber et al., 1998); and with simulated annealing by balancing the internal and external energy forces until the iteration limit is met for identifying the vessel boundary points (Kozerke et al., 1999). The single stage intensity threshold and the wavelet methods provide accurate measurements of area and flow in large vessels, such as the aorta or pulmonary artery (Burkart et al., 1994; Chakraborty et al., 1996; Gustavsson et al., 1997), but they have not been used to measure area or flow in smaller vessels such as the femoral arteries. It is unclear whether techniques incorporating wavelet boundary detection can differentiate the boundaries of small vessels from surrounding venous and nervous structures in the leg.

Simulated annealing works well when the iteration number is large (250 times, for instance); however, longer processing times are required (10 to 100 times longer than with the intensity threshold or wavelet techniques), and thus microprocessors of 2000 MHz (five times faster than a Sun Ultra 5 workstation) are needed to obtain results within 10 minutes. Our MSIT technique provides an accurate measurement of FMAD in a timely fashion on both Unix and Microsoft system platforms using 400–600 Hz microprocessors that are now widely available on Sun workstations or personal computers (both laptop and standard PCs).

Reproducibility

The MSIT algorithm exhibited excellent reproducibility when the initial spline covered 75% of the area of the lumen. This level of coverage (from which the mean gray level of the pixels within the spline area was derived) provided an adequate mean gray level sufficient for propagating the vessel boundary in the two subsequent searches. In this situation, the detected area differences in intra-observer and inter-observer testing were negligible.

Limitations

Our study has certain limitations. First, we are uncertain of the performance of this technique in patients with an irregular vessel lumen due to advanced arteriosclerosis. Second, our results are based on patients with regular heart rates and rhythm; it is unknown whether this technique will be useful when applied to images obtained from patients with an irregular rhythm such as atrial fibrillation. Third, our algorithm was tested only on superficial femoral arteries; the performance is uncertain in other vascular beds. Fourth, the intensity threshold values for boundary determination are based solely on the values within the ROI and do not consider the intensity of the surrounding tissue. This is reasonable in our application, since, with our scan technique, the femoral artery is surrounded by very low intensity pixels. However, in other applications with brighter surrounding pixels, the threshold values may need to be based on the intensity difference between the ROI and surrounding tissue. Finally, minor differences occurred between our vessel areas generated manually and automatically. For this reason, intermixing results generated manually and automatically may generate FMAD assessments that are disparate from those generated by using either technique alone.

CONCLUSION

Automated analysis of PC-MRI images of the femoral artery before and after cuff inflation with the multistage intensity threshold technique provides a rapid and accurate method for assessing FMAD in both normal and CHF patients. This technical advance may prove useful for the assessment of peripheral arterial endothelium function in patients undergoing clinical examinations of the cardiovascular system.

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