Unbiased and Efficient Estimation of the Volume of the Fibroid Uterus Using the Cavalieri Method and Magnetic Resonance Imaging

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Michael J. Thrippleton, PhD¹, Kirsty I. Munro, MRCOG²,
Graham McKillop, FRCR³, David E. Newby, DSc⁴,
Ian Marshall, PhD^{1,4}, Neil Roberts, PhD⁵,
and Hilary O. D. Critchley, MD²

Abstract

The aim of our study was to develop a reliable technique for measuring volume of the fibroid uterus using Magnetic Resonance Imaging. We applied the Cavalieri method and standard calliper technique to measure the volume of the uterus and largest fibroid in 26 patients, and results were compared with “gold-standard” planimetry measurements. We found Cavalieri measurements to be unbiased, while calliper measurements systematically underestimated uterine volume (-13.2% , $P < 10^{-5}$) and had greater variance. Repeatability was similar for the 2 techniques (standard deviation [SD] = 4.0%-6.9%). Reproducibility of Cavalieri measurements was higher for measurement of uterine (SD = 9.0%) than fibroid volume (SD = 19.1%), whereas the reproducibility of calliper measurements was higher for fibroid (SD = 9.1%) than uterine volume (SD = 15.9%). The additional measurement time for the Cavalieri method was approximately 1 to 2 minutes. In conclusion, the Cavalieri method permits more accurate measurement of uterine and fibroid volumes and is suitable for application in both clinical practice and scientific research.

Keywords

Magnetic Resonance Imaging, leiomyoma, fibroid uterus, volume estimation

Introduction

Uterine fibroids may be present in up to 70% of women of reproductive age,¹ resulting in significant symptoms, including heavy menstrual bleeding, pelvic pain, and urinary symptoms.² Surgery (hysterectomy and myomectomy) is the mainstay of clinical management for symptomatic fibroids but has inherent risks and contributes to fibroid-associated health care costs.³ Uterine artery embolization (UAE) is an alternative to surgery, although a subset of women undergoing this procedure will subsequently require hysterectomy, and UAE has only short-term advantages over surgery.⁴ Magnetic resonance-guided focused ultrasound is a further treatment option but is not yet widely used⁵ and there remains an unmet need for long-term effective drug treatments. A requirement shared by all nonsurgical interventions is the critical need to accurately evaluate uterine and fibroid volume in order to assess treatment outcome. Reliable techniques for volumetric assessment are also essential in research to better define the pathophysiology of fibroids, to identify factors that might prevent onset or retard progression,⁶ and to assess the effectiveness and safety of pharmacologic therapies.

Despite the wide use of uterine and fibroid volume as markers of disease progression and therapy response, the

optimal method of obtaining these measurements remains to be defined for use in both clinical practice and scientific research. The technique of exhaustive planimetric serial reconstruction (EPSR or “planimetry”) is considered to be the gold-standard for imaging-based measurements of volume. However, the method is time-consuming because the boundary of the uterus or fibroid is traced manually in successive imaging

¹ Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom

² MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, United Kingdom

³ Department of Radiology, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

⁴ Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom

⁵ Clinical Research Imaging Centre, (CRIC) University of Edinburgh, Edinburgh, United Kingdom

Corresponding Author:

Hilary O. D. Critchley, MRC Centre for Reproductive Health, The University of Edinburgh, The Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom.

Email: hilary.critchley@ed.ac.uk

Figure 1. Sagittal (a) and axial-oblique (b) images showing callipers used to estimate uterine volume, labelled as described in the text. The calliper measurements shown are 103(L) $\times$ 115(S) $\times$ 97(LR) mm.

sections throughout the whole structure, thus limiting its wider application.⁶⁻⁸ As a result, the most common image analysis approach used in clinical practice is the calliper method, in which one or more length measurements are combined to estimate the total volume assuming (typically) ellipsoidal shape.⁹⁻¹³

An alternative approach is to apply a stereological technique known as the Cavalieri method, which is less time-consuming than EPSR and avoids the assumption of the object of study having a specific shape that is required by the calliper method. The Cavalieri method has been applied successfully in the study of several organs including brain,¹⁴ liver,¹⁵ and heart¹⁶ but has been reported only once previously in the fibroid uterus.¹⁷ Importantly, volume estimates are unbiased and the measurement precision can be determined mathematically.

The aim of this study was to measure the accuracy (in comparison to EPSR), time efficiency, and intra- and interobserver variability of uterus and fibroid volume measurements obtained using both the Cavalieri method and the standard calliper technique.

Materials and Methods

Thirty premenopausal women with symptomatic uterine fibroids and scheduled for hysterectomy were recruited from regional gynecology clinics as part of a clinical trial involving serial MRI¹⁸; all MRI data used in this study were obtained prior to the start of drug treatment. Each participant had at least 1 non-pedunculated fibroid (diameter ≥ 2 cm) or multiple small fibroids (total uterine volume ≥ 200 cm³) confirmed by ultrasound measurements at screening. All participants provided written informed consent and the study was approved by the local research ethics committee and was conducted in accordance with the Declaration of Helsinki.

Magnetic Resonance Imaging (MRI)

MRI was performed on a 1.5 T Siemens Magnetom scanner using body matrix and spine coil elements. The patients received 20 mg hyoscine butylbromide (Buscopan) prior to entering the MR scanner. The T2-weighted (T2W) MRI scans (repetition time/echo time = 4470-8480/84-104 ms, slice thickness/spacing = 4/5 mm, field of view = 250 $\times$ 250 mm, matrix size = 320 $\times$ 320, 2 signal averages) were acquired in the sagittal (Figure 1a) and axial-oblique (Figure 1b) planes (orthogonal to the uterine lumen and to the sagittal plane) using a fast spin-echo pulse sequence. A MR saturation pulse was applied anteriorly to reduce respiratory motion artifact and the number of slices was adjusted to obtain full coverage of the uterus.

Volume Measurements

Volumes of the uterus (excluding the cervix) and largest fibroid were obtained using the Cavalieri and calliper methods. Repeat measurements were obtained by the same observer and also by a second observer. The first observer also performed high-precision measurements using the EPSR method. The observers (a medical physicist and a gynecologist) were trained to measure uterine and fibroid volumes by an experienced radiologist. Repeated Cavalieri measurements were obtained using the same sections and with the point grids in the same positions and orientations; any variability is thus attributable to the observers and not to differences in the position and orientation of the point counting grids. Repeat measurements were performed blind to the results of previous measurements. Times required to select points (Cavalieri method), measure lengths (calliper method), and trace outlines (EPSR method) were recorded.

Figure 2. Five Cavalieri sections with point counting grids (the spacing between neighbouring points is 1.56 cm) used to calculate uterine volume using the imaging data shown in Figure 1. Yellow crosses indicate points within the uterus.

Cavalieri Method With Point Counting

Uterine and largest fibroid volumes were obtained on sagittal T2W images using the Cavalieri method in combination with point counting.^{19,20} Beginning from a random starting position within the chosen sampling interval, a systematic random series of images were sampled from the whole data set and an isotropic grid of test points was superimposed with random orientation and position over each image using the EasyMeasure program.²¹ Points within the structure were counted and an unbiased estimate of volume ($\tilde{V}$) was obtained:

$$\tilde{V} = T u^2 (P_1 + P_2 + \dots + P_n) \quad (1)$$

where T is the distance between sections, u is the grid spacing, P_i is the number of points counted in the section i , and n is the number of sections intersecting the object. The grid spacing and separation were modified according to the size of the structure to obtain a total point count of typically 50-150 points.

The coefficient of error (CE) for the Cavalieri method with point counting²²⁻²⁵ was estimated using the following equation:

$$CE^2 = \alpha(q) \cdot (3(C_0 - \hat{v}) - 4C_1 + C_2) \cdot \left(\sum P_i \right)^{-2} + \hat{v} \cdot \left(\sum P_i \right)^{-2}, \quad (2)$$

where $\alpha(q) = [\Gamma(2q+2) \cdot \zeta(2q+2) \cdot \cos(\pi q)] / (2\pi)^{2q+2} \cdot (1 - 2^{2q-1})$, with $C_k = \sum_{i=1}^{n-k} P_i P_{i+k}$ and $\hat{v} = 0.0724 \cdot S \cdot (n \cdot \sum P_i)^{1/2}$.

The dimensionless shape factor S is defined as $\bar{B} / \sqrt{\bar{A}}$, where $\bar{B}$ and $\bar{A}$ are, respectively, estimates of the mean boundary length and mean area of the object over the sections. S was estimated using 5 data sets as 2.96 and 2.70 for uterus and fibroid, respectively. Γ and ζ denote the gamma function and the Riemann zeta function, respectively. The parameter q was estimated using the following formula:

$$\hat{q} = \max \left\{ 0, \frac{1}{2 \log 2} \cdot \log \left[\frac{3(C_0 - \hat{v}) - 4C_2 + C_4}{3(C_0 - \hat{v}) - 4C_1 + C_2} \right] - \frac{1}{2} \right\}, \quad n \geq 5 \quad (3)$$

When fewer than 5 sections were available, $q = 1$ was used as a reasonable approximation for quasi-ellipsoidal objects.

Worked Example Using the Cavalieri Method

Figure 2 shows a series of 5 Cavalieri sections through the uterus. The interval between sections $T = 2$ cm and grid spacing $u = 1.56$ cm on the test system used for point counting. The number of points determined to lie within the uterus was 30, 40, 40, 31, and 15 on successive sections, yielding a total point count of 156 and volume estimate of 762 mL. By using the method described previously, the total CE was estimated as 2.9%, with contributions of 2.3% due to finite intersection spacing and 1.8% due to finite grid point spacing.

Calliper Method

As illustrated in Figure 1, calliper measurements of the uterus were taken on sagittal T2W images from the internal cervical os to the most distant point of the uterus (L) and of the longest axis perpendicular to this (S); the maximum left-right (LR) dimension was taken on the axial-oblique T2W image. The volume of the largest fibroid was assessed similarly using measurements of the longest axis and the longest axis perpendicular to this in the sagittal image, together with the maximum LR measurement in the axial-oblique image. For both uterus and fibroid, the 3 orthogonal distances were combined to estimate volume assuming ellipsoidal shape ($V = \pi/6 \times L \times S \times LR$).

Exhaustive Planimetric Serial Reconstruction

To obtain volume measurements by EPSR, contours were manually drawn around the structures of interest on all sagittal T2W image slices using the ImageJ software (<http://rsb.info.nih.gov/ij/>). To estimate volume and CE for EPSR data, the same formulae were used as for Cavalieri data, with $\hat{v}$ set to 0, P_i to the area (in voxels) enclosed by the contours in successive sections, and u^2 to the in-plane voxel area.

Statistical Methods

Statistical analysis was performed using MatLab (MathWorks, Natick, Massachusetts) and PASW Statistics (IBM Corporation,

Figure 3. Comparison of methods for volume estimation of the uterus (a–c) and largest fibroid (d–f). (a) and (d) compare calliper volume estimates against gold-standard EPSR values, while (b) and (e) compare volumes obtained by the Cavalieri method against EPSR; lines of equality are shown. Error bars indicate $\pm 2SD$ (predicted) for Cavalieri volumes. Error bars for EPSR measurements are not shown since the sampling errors are too small to be clearly visible; for calliper measurements, error bars cannot be displayed as the sampling error is unknown. Boxplots in (c) and (f) compare measurement times of the first observer for the 3 methods, for uterus and fibroid, respectively; the medians and ranges for the calculated measurement precision are also indicated. EPSR indicates exhaustive planimetric serial reconstruction; SD, standard deviation.

Armonk, New York) software. Pearson R^2 values are shown on all scatter plots; however, agreement between pairs of measurements is more usefully characterized by the distribution of the differences. Thus, percentage relative differences (PRD) between Cavalieri and calliper measurements (V) and the gold-standard EPSR measurements (V_{EPSR}) were calculated as $\text{PRD} = 100 \times (V - V_{\text{EPSR}}) / V_{\text{EPSR}}$; agreement was assessed using the standard deviation (SD) and mean of the PRD. Repeated measurements using the same technique (V_1 , V_2) were compared using the modified equation $\text{PRD} = 100 \times (V_1 - V_2) / \frac{1}{2}(V_1 + V_2)$. Systematic differences between measurements (“bias”) were tested for using the one-sample t -test with the null hypothesis $\langle \text{PRD} \rangle = 0$. Differences in the measurement times between the methods were assessed using the Wilcoxon signed rank test.

Results

The MR images were analyzed for 26 of the 30 patients scanned; the remaining 4 patients were excluded from the analysis due to incomplete imaging coverage of the uterus.

Accuracy, Precision, and Efficiency

As shown in Figure 3 and Table 1, Cavalieri measurements were unbiased on average for measurements of both uterus (Figure 3b) and fibroid (Figure 3e) with mean differences relative to EPSR close to 0. The calliper measurements of the uterus (Figure 3a) showed significant average bias, underestimating the volume by an average of 13.2% ($P < 10^{-5}$) compared with gold-standard EPSR measurements. However, the average

Table 1. Mean (SD) of the Percentage Errors in Calliper and Cavalieri Volume Measurements Relative to Gold-Standard EPSR Values.

Method	Uterus	Fibroid
Calliper	−13.2 ^a (11.0)%	−3.7 (15.4)%
Cavalieri	+0.2 (4.6)%	−0.3 (9.0)%

Abbreviations: EPSR, exhaustive planimetric serial reconstruction; SD, standard deviation.

^a $P < 10^{-5}$.

bias for fibroid measurements obtained with the calliper technique (Figure 3(d)) was small and not statistically significant. The SDs shown in Table 1 (and the R^2 values shown in Figure 3) indicate greater inaccuracy for the calliper method than for the Cavalieri approach. As expected, the median estimated precision (ie, the predicted CE) for EPSR measurements was very high: 0.3% and 0.5% for uterus and fibroid, respectively. Corresponding predicted precisions for the Cavalieri measurements were 3.2% and 3.9%. Unfortunately, methods are not available for predicting the precision of the measurements obtained using the calliper technique. Median measurement times for the EPSR technique (17.8/9.3 minutes for uterus/fibroid) were prohibitively long for this approach to be used in routine clinical practice. However, Cavalieri measurement times (3.5/2.3 minutes for uterus/fibroid), shown in Figure 3(c) and (f), although longer than calliper measurements (1.7/1.2 minutes for uterus/fibroid), were short enough for potential incorporation in clinical practice.

Intraobserver Repeatability and Interobserver Reproducibility

Figure 4 shows intraobserver repeatability and interobserver reproducibility for Cavalieri and calliper measurements of uterus and fibroid volume, and Table 2 shows the level of agreement, indicated by the mean and SD of the PRD. Intraobserver repeatability for the 2 methods was similar (SD = 4.0%-6.9%) and showed less variance than interobserver reproducibility (SD = 9.0%-19.1%). For the uterus, interobserver reproducibility was better for the Cavalieri (SD = 9.0%) than for the calliper method (SD = 15.9%), while for the largest fibroid reproducibility the calliper method (SD = 9.1%) was better than the Cavalieri method (SD = 19.1%). Repeat measurements of uterine volume by the same observer using the Cavalieri method were slightly lower on average (2.9%, $P < 0.001$), while calliper measurements of fibroid volume differed on average by 4.7% between the 2 observers ($P < 0.05$).

Discussion

The aim of this study was to compare the Cavalieri method of volume measurement in the fibroid uterus with the calliper approach that is used routinely in radiological practice. The Cavalieri estimates were unbiased with respect to volumes measured by EPSR. In contrast, calliper measurements were biased, underestimating uterine volume by 13% on average.

However, while the mean error for calliper fibroid measurements was small (−3.7%), consistent with the observation that many fibroids possess the approximately ellipsoidal shape assumed by the calliper technique, the corresponding SD (15.4%) suggests that measurements of individual fibroids do have lower accuracy than corresponding Cavalieri measurements (SD = 9.0%). The Cavalieri method showed good intraobserver repeatability, and interobserver reproducibility was reasonable for uterine volume but poorer for fibroid volume; we suggest this may be due to the myometrium–fibroid interface, which is not always clearly defined on MR images compared with the well-delineated margins of the uterus itself. It is therefore important to establish reproducibility in future applications where multiple observers are used. Cavalieri measurements typically took 1 to 2 minutes longer than calliper measurements, although most were completed in less than 5 minutes which is very much faster than the gold-standard EPSR method. The Cavalieri estimates were obtained using a single 2-dimensional MRI acquisition, while for calliper measurements 2 sequences were required. Thus, the increased analysis time for Cavalieri measurements could potentially be offset by reductions in scan time. A further significant advantage of the Cavalieri approach is that the precision can be estimated from the point counts recorded in consecutive sections. In contrast, the precision of calliper measurements on individual patients cannot be readily predicted.

There are several reports of the application of the calliper technique for studying the fibroid uterus. For example, using gold-standard planimetry measurements, Broekmans et al⁷ reported that the calliper method gave “excellent performance” and recommended its use in studies of uterine volume. However, the data presented in Figures 1 and 2 of Broekmans et al’s article suggested that the calliper method may, in accordance with this study, underestimate the true uterine volume. In a recent study, Volkers et al²⁶ reported good reproducibility for calliper volume assessment of uterus and fibroids, but unfortunately did not address the accuracy of the method.

There is only one previous published investigation of the application of design-based stereology in the study of the fibroid uterus.¹⁷ Although the authors did not obtain “gold-standard” measurements, they report excellent interobserver reproducibility. In contrast to the Bland–Altman analysis performed in this study, the authors did not report SDs for the paired differences.²⁷ Although a small mean difference shows that there is little difference *on average*, the SD is required to quantify the likely disagreement encountered in individual cases. For the uterus, calliper measurements provided an overestimate of volume whereas in the present study calliper measurements provided an underestimate of volume. A possible reason for this is that the authors included the cervix in their measurements, which emphasizes the need for rigorous definitions in any study of what constitutes the structure of interest. Consistent with our results, the mean difference on average between calliper and stereological measurements of fibroid

Figure 4. Comparison of repeat measurements of uterine (left column) and fibroid (right column) volume by Cavalieri (a–d) and calliper (e–h) methods. (a and b) and (e and f) compare measurements by the same observer, while (c, d) and (g, h) compare measurements by 2 different observers; lines of equality are shown.

volume was not significant. Finally, Joe et al¹⁷ performed Cavalieri measurements using all image slices and with a comparatively dense point grid; as a result, the measurement times reported (5–15 minutes) are longer and the precision (not reported) is expected to be very high. In the present study,

we adjusted the spacing between slices and point grid density according to the size of the fibroid or uterus, resulting in sparser sampling as shown in Figure 2; as a result, fast measurements (around 3 minutes) were obtained with a precision (around 3%–4%) sufficient for most applications.

Table 2. Comparison of 2 Measurements Made by the Same Observer and of Measurements Performed by 2 Different Observers.^a

Method	Same Observer		Different Observers	
	Uterus	Fibroid	Uterus	Fibroid
Calliper	+1.7 (6.0)%	+0.2 (6.9)%	+3.7 (15.9)%	+4.7 ^b (9.1)%
Cavalieri	+2.9 ^c (4.0)%	+1.7 (5.8)%	−0.0 (9.0)%	+4.0 (19.1)%

Abbreviation: SD, standard deviation.

^a Mean (SD) of the percentage relative differences are shown.

^b $P < 0.05$.

^c $P < 0.001$.

In conclusion, the Cavalieri method permits unbiased and time-efficient estimation of uterine and fibroid volume, with many potential applications in the assessment of disease progression and treatment response. In contrast to calliper measurements, a single 2-dimensional MRI acquisition is sufficient for application of the Cavalieri method. Furthermore, controllable precision is an important advantage, providing the opportunity to establish an effective compromise between rapid low-precision measurements and time-consuming measurements with unnecessarily high precision.

Author's Note

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