Quantification of Coronary Artery Lumen Volume by Digital Angiography

In Vivo Validation

Sabee Molloi, PhD; Ghassan S. Kassab, PhD; Yifang Zhou, PhD

Background—Coronary artery lumen volume may potentially have several advantages over the commonly used variables, such as percent stenosis or minimal lumen diameter, in the assessment of coronary artery disease. The goal of this study is to validate a quantitative assessment of lumen volume using a video densitometry technique.

Methods and Results—Coronary arteriography was performed in 9 swine (body weight 20 to 55 kg) after power injection of contrast material (2 mL/s for 3 seconds) into the left main coronary artery. Phase-matched subtracted images were used to quantify regional lumen volume by a video densitometry technique. The in vivo volume measurements were validated by a polymer cast of the coronary arterial tree made at physiological pressure. The measured cast volume ($V_C$) and video densitometric regional lumen volume ($V_{VD}$) were related by $V_{VD} = 1.06 V_C - 0.01 \text{ mL} \ (r=0.99)$. The root mean square and systematic errors for these measurements were 17% and 3%, respectively.

Conclusions—A video densitometry technique for quantification of coronary lumen volume was validated both in vitro and in vivo in a swine animal model. The present results demonstrated the feasibility and potential utility of the video densitometry technique for accurate measurement of regional lumen volume in vivo. This study contributes to the understanding of the angiographic methods used for the assessment of coronary artery disease and indicates that this technique can potentially be used for quantification of diffuse coronary artery disease during routine coronary arteriography. (Circulation. 2001;104:2351-2357.)

Key Words: arteries • angiography • coronary disease • imaging

Progression and regression of coronary artery disease have been assessed by measurement of lumen diameter and cross-sectional area after repeat coronary angiography in clinical trials. A commonly used variable in the assessment of atherosclerosis has been percent stenosis. Percent stenosis, however, is a relative measurement that relies on a reference segment, which may be affected by disease. Another proposed variable is the minimal diameter of stenosis, which is an absolute dimension measurement and does not rely on a reference segment. The minimal diameter stenosis, however, takes into account only the changes of a single point in an arterial segment. Furthermore, the arterial lumen often includes noncircular cross-sectional areas at the site of atherosclerotic lesions, which introduces image projection angle−dependent error.

Unlike diameter measurements, volume accounts for all changes in lumen geometry over an arterial segment, and it is not dependent on the imaging projection angle. Intravascular ultrasound (IVUS) and angioscopic techniques have been used for lumen volume reconstruction. An inherent limitation of IVUS, however, is the wedging of the ultrasonic catheter in the case of severe stenosis and in small vessels. This restricts the application of 3D IVUS to large vessels without severe stenosis.

Digital angiography can be used to measure lumen volume by geometric and video densitometry techniques. The geometric techniques consist of vessel diameter measurement and arterial length measurement by 3D reconstruction of the arterial centerline. These techniques require biplane images and assume a circular or elliptical cross section, which does not apply in the presence of obstructive atherosclerosis. Video densitometry techniques do not require any assumptions regarding the geometry of the vessel cross section and do not require a 3D reconstruction of the coronary arterial tree. There have been reports of video densitometry techniques for lumen volume measurement in physical phantoms and human coronary casts. In vivo volume measurements using video densitometry techniques have been hampered, however, by the nonlinearity due to physical degradation factors in the image intensifier television imaging chain and the lack of knowledge about blood iodine concentration. We have previously developed techniques that
address these limitations. In the present investigation, a video densitometry technique for quantification of coronary artery lumen volume has been validated both in vitro and in vivo in a swine animal model.

Methods

Animal Preparation

Fasted swine (20 to 55 kg, n = 9) were sedated with acepromazine (1.0 mg/kg IM), atropine (0.11 mL/kg IM), ketamine (20 mg/kg IM), and xylazine (1.0 mg/kg IM). The animals were anesthetized with halothane (1% to 2%) and ventilated with 100% O2 with a Harvard respiratory pump. Ventilator settings were adjusted during the experiments to maintain PO2 and PCO2 within normal ranges. A peripheral vein was used for the administration of medication and intravenous fluid. Arterial pressure was measured in the right carotid artery with a calibrated pressure transducer (TSD104A, Biopac Systems, Inc). Standard techniques were used to cannulate the left main ostium with a 7F multipurpose diagnostic catheter under fluoroscopic guidance. The ECG, femoral artery blood pressure, and x-ray tube voltage (kV) were continuously recorded (MP100, Biopac Systems, Inc). The University of California–Irvine Animal Research Committee approved the procedures used in this study.

Each animal was positioned under the image intensifier, and the projection was optimized for separation of the left anterior descending coronary artery (LAD) and left circumflex artery (LCx) and maintained at a 30° right anterior oblique angle. Coronary arteriograms were then obtained after power injection of 6 mL of contrast material (Omnipaque, Nycomed Amersham) with an iodine concentration of 350 mg/mL and an injection rate of 2 mL/s. To minimize the effect of ventilation, the respirator was turned off at the end of full expiration during image acquisition. An iodine calibration phantom was imaged over the chest of the animal for system calibration purposes.16 The system iodine calibration was repeated if any of the imaging parameters were changed. After completion of the in vivo coronary arteriograms, we then proceeded to the postmortem studies.

Isolated Heart Preparation

A midline sternotomy was performed, and anticoagulation was induced with heparin (100 U/kg). An incision was made in the pericardium, and the heart was supported in a pericardial cradle. The animal was heavily anesthetized, and the heart was arrested with a saturated KC1 solution given through a jugular vein. The heart was then excised with the ascending aorta clamped to keep air bubbles out of the coronary vessels. The right coronary artery (RCA), LAD, and LCx were cannulated under saline to avoid air bubbles. The coronary arteries were then immediately perfused with an osmotic, cardioplegic rinsing solution to maintain the myocardium relaxed and the vasculature vasodilated.16 Cardioplegic solution was continuously infused into the arteries at 100 mm Hg until the solution hardened, and cut into 5 to 9 segments at the bifurcation on the main trunk of the arteries. The bifurcations were chosen as landmarks for exact correspondence between casts and coronary arteriograms. Lumen volume was calculated from the weight and the known density (0.99 g/cm3) of the casts.

Image Acquisition and Processing

All images were acquired by use of a conventional x-ray tube (Dynamax 79-45/120, Machlett Laboratories), a constant-potential x-ray generator (Optimus M200, Philips Medical Systems), a 23/15-cm CsI image intensifier, a focused grid (8:1 grid ratio, 36 lines/cm), and a CCD camera (Multicam MC-1134N, Texas Instruments Inc). An adjustable aperture controlled the light intensity in front of the camera. The video signal was linearly digitized to 640×480×8-bit precision with a Matrox Pulsar frame grabber (Matrox Electronics Systems Ltd) and a Pentium III computer.

The images were acquired with the 15-cm image intensifier mode and a large (1.2-mm nominal) focal spot. Corrections were made for the spatially varying scatter and veiling glare. A convolution-filtering technique was used to estimate scatter-glare distribution in images without the need to sample the scatter-glare intensity for each experiment.17 This technique uses the exposure parameters and the detected intensity distribution to estimate scatter-glare intensity by predicting the total thickness at every pixel in the image. The thickness information is used to estimate scatter glare on a pixel-by-pixel basis.

Volume Measurement in Physical Phantoms

Phantom studies were made to determine the accuracy of the imaging system for volume measurement. Cylindrical vessel phantoms were constructed of plastic tubing with inside diameters of 1.3 to 4.7 mm to produce known lumen volumes of 0.06, 0.13, 0.21, 0.26, 0.39, 0.41, 0.52, 0.57, and 0.78 mL. The tubes were filled with 100% contrast material and sealed on both sides. Images were acquired by placing all the tubing over a humanoid chest phantom. A region of interest (ROI) approximately outlining the visible contrast material was drawn manually. The integrated video densitometry signal was directly converted to iodine mass by use of the system iodine calibration curve.18 Iodine mass was converted to volume by use of the known iodine concentration of the contrast material.

To simulate plaque in a vessel, Plexiglas rods (1.56 mm in diameter) were inserted into plastic tubing with inside diameters of 3.0 and 4.3 mm to produce known lumen volumes of 0.14, 0.18, 0.28, 0.33, 0.42, 0.51, 0.56, 0.69, 0.71, and 0.87 mL. The number of the Plexiglas rods was varied in different tubing to produce up to 50% area stenosis. The “stenotic” vessel phantoms were filled with 100% contrast and imaged in the anteroposterior (AP), 30° right anterior oblique (RAO), and 30° left anterior oblique (LAO) projections over the humanoid chest phantom. The volume measurements were performed with both the video densitometry and edge-detection algorithms.13 In the edge-detection algorithm, the vessel edges were defined relative to the first- and second-derivative extrema of the vessel profile.17 The diameter and length information measured with the edge-detection algorithm was used to calculate arterial volume assuming a circular cross section.

Analysis of the above measurements, linear regression analysis was performed for measured versus actual lumen volumes. The variance of the data points about the best-fit line reflects the precision of the measurements. A second variance was calculated, assuming that the data were fit to a line with unit slope and zero intercept (y = x line). The variance about the unit line reflects the accuracy of the measurements. The accuracy and precision of the edge-detection and video densitometry techniques were compared.

In Vivo Volume Measurement

Lumen volume measurements were made from contrast pass curves using phase-matched temporal subtraction images of the LAD and LCx. No in vivo angiograms were acquired from the RCA. An ROI approximately outlining the arterial segment of interest was drawn manually. A 3-pixel background shell was drawn just outside the
arterial ROI. The background ROI was used to estimate and correct for build-up of iodine signal in the myocardium included in the arterial ROI. Figure 1 shows a coronary arteriogram with an arterial ROI on the first diagonal branch of the LAD. The maximum in the integrated video densitometry signal in the contrast-pass curve was converted to lumen volume with the system iodine calibration curve and the known iodine concentration of the contrast material.15 An iodine calibration curve was generated by imaging a calibration phantom with known volumes of contrast material over the heart region. A correction was made for differential magnification between the calibration phantom and the coronary artery of interest. Regional volume measurements were made by drawing different arterial ROIs corresponding to arterial segments between bifurcation points on the main trunk of the LAD and LCx. The arterial tree was divided into 5 to 9 segments. The branches with visible overlap were not used.

To assess the reproducibility of the technique, regional volume measurements were made after 6 pairs of contrast injections in 2 animals. The contrast injections were separated by ~10 minutes. The arterial tree was divided into 5 to 9 segments. All the image acquisition and processing parameters were kept fixed. Additional studies were done in 2 animals to further challenge the reproducibility of the technique and to simulate repeated coronary arteriograms in a clinical setting. All the imaging parameters were recorded during the first coronary arteriogram. After the first study, the x-ray table was moved, and the image intensifier was rotated. All the imaging parameters were reproduced, and a separate system iodine calibration was made for the second coronary arteriogram. Two different operators analyzed the images. Regional volume measurements were made from 4 pairs of contrast injections. Each arterial tree was divided into 8 segments. The measured regional volumes from each pair were compared.

The accuracy of the technique was assessed by a comparison of the regional volume measurements by video densitometry and the volume of the casts in 3 animals. The regional volume measurements from 2 to 3 coronary arteriograms were averaged. The LAD and LCx casts were cut into 5 to 9 segments, corresponding to the previously chosen arterial ROIs. The bifurcation points were used as anatomic landmarks to determine the correspondence between cast and coronary arteriograms imaged over chest of humanoid phantom. Measured volumes by edge-detection algorithm (A) and video densitometry (B) are plotted with respect to known volumes. For volume measurements with edge-detection algorithm, 10 different measurements were made in AP projection, 8 in 30° LAO projection, and 8 in 30° RAO projection. For volume measurements with video densitometry algorithm, 5 different measurements were made in AP projection, 10 in 30° LAO projection, and 10 in 30° RAO projection. Results of linear regression analysis are shown in Table 1. Solid line represents line of identity.
nary angiogram. Regional volume was calculated from the weight and the known density (0.99 g/mL) of the casts. The measured regional volumes from video densitometry were compared with the volumes from the cast segments.

**Postmortem Volume Measurement**

Postmortem coronary arteriograms were made to further validate the lumen volume measurement technique. Lumen volume measurements were made from temporal subtraction images of the LAD, LCx, and RCA. A total of 5 hearts were used for this purpose. Two animals were used for this purpose, in addition to 3 hearts from the above-described in vivo studies. The technique for regional volume measurement for the RCA was similar to the LAD and LCx, which was described in the above section.

**Results**

**Phantom Studies**

The results of volume measurements using cylindrical and stenotic vessel phantoms are shown in Figures 2 and 3. Linear regression results and the experimental variances representing precision and accuracy for these measurements are presented in Table 1. The volume measurements from the video densitometry technique showed a large improvement in precision and accuracy over the edge-detection algorithm.

**Postmortem Studies**

A comparison of regional arterial volume measurements from the casts and the video densitometry technique is shown in Figure 4. The lumen volumes measured from casts (VC) and video densitometry (VVD) were related by VVD=1.16VC−0.01 mL (r=0.97). The root mean square (RMS) and systematic errors for these measurements were 19% and 4% of the mean densitometry volume, respectively. The overestimation of lumen volume measurements is due to the poor image quality of the postmortem coronary angiograms, which is because contrast material is not completely washed out of the myocardium after repeated injections.

**In Vivo Studies**

The results of lumen volume measurements for repeated coronary arteriograms are shown in Figure 5. Figure 5A shows volume measurements for repeated contrast injections, where the first (Vf) and second (Vs) measured volumes were related by Vf=0.98Vs+0.001 mL (r=1.00). The RMS and systematic errors for repeated measurements were 9% and −1%, respectively. The results of volume measurements for repeated coronary arteriograms, with different operators to analyze the images, are shown in Figure 5B. Vf and Vs were related by Vs=1.00Vf+0.001 mL (r=0.99). The RMS and systematic errors for repeated measurements were 9% and 0.3%, respectively. The results of in vivo volume validation using cast data are shown in Table 2 and Figure 6. VC and VVD were related by VVD=1.06VC−0.01 mL (r=0.99). The RMS and systematic errors for these measurements were 17% and −3%, respectively.

**Discussion**

**Video Densitometry**

A video densitometry technique for the measurement of lumen volume is superior to geometric techniques, because it makes no assumptions regarding the geometry of the cross section. It also does not require 3D reconstruction of the arterial tree. In the present video densitometry technique, the integrated gray levels in an arterial branch or tree is converted directly to volume with an iodine calibration phantom. The results in this study represent the first in vivo measurement of

![Figure 4](http://circ.ahajournals.org/)

*Figure 4. Regional lumen volume measurements obtained from postmortem coronary arteriograms. Measured volumes using video densitometry are plotted with respect to cast volumes. Dashed line represents linear curve fit with regression analysis; solid line, line of identity.*
absolute lumen volume using single-plane coronary arteriograms.

Validation of the Method

The regional volume measurements were validated with a casting technique. Although the validation required matching between small segments of the coronary artery cast and the corresponding segments in the coronary arteriograms, the results show that reliable volume measurements can be made by this technique (see Figures 4 through 6). The reproducibility of the technique was verified by making regional volume measurements from repeated coronary arteriograms. It might be possible to further improve the reliability of the volume measurements by maximally dilating the epicardial coronary arteries with pharmacological agents such as nitroglycerin. It is also possible to further improve the technique by power injection of larger boluses at a higher injection rate. This will help minimize mixing of blood with the contrast bolus that enters the coronary arteries.

Physical phantoms were used to evaluate the accuracy of the video densitometry technique for assessment of lumen volume at the site of irregular coronary lesions. The results show that the video densitometry technique can accurately measure volume in vessel phantoms with irregular cross section (see Figure 3). Furthermore, the volume measurements were not dependent on the imaging projection angle.

Critique of the Method

A potential limitation of this technique for eventual clinical implementation is motion artifacts in the images. All the volume measurements in this study were made within 3 seconds after contrast injection. This means that the patient will have to hold his or her breath for a total of \(\approx 5\) seconds. A breath-hold for this short time interval should not be a limitation for the majority of patients.

Overlap of vessels is another potential limitation of this technique. This problem is an inherent limitation of the projection nature of radiographic images. It is possible, however, to choose a projection that will minimize those potential errors. A related source of error is the iodine accumulation in the myocardium and its contribution to the measured volume. This potential source of error was mini-

### TABLE 2. Comparison of Regional Lumen Volume from Video Densitometry of In Vivo Coronary Arteriograms and Cast Measurements

<table>
<thead>
<tr>
<th>Artery Information</th>
<th>Cast Volume, mL</th>
<th>Measured Volume, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal 1 (LCx)</td>
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<td>0.10</td>
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<td></td>
<td>0.05</td>
<td>0.05</td>
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<td>0.04</td>
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<td></td>
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<td>0.05</td>
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<td></td>
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<td></td>
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<td>0.01</td>
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<tr>
<td>Animal 2 (LCx)</td>
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<td></td>
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<td>0.53</td>
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<tr>
<td>Animal 3 (LAD)</td>
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<td>0.10</td>
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<td></td>
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<td>0.39</td>
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</table>

Figure 5. Regional lumen volume measurements obtained from repeated coronary arteriograms in pigs. Volume measurements were repeated after 2 contrast injections (A) without changing imaging geometry and repeated coronary arteriograms (B) using different iodine calibration curves and different operators for analysis. Dashed line represents linear curve fit with regression analysis; solid line, line of identity.
image data. The arterial branching angle and the imaging projection angle may cause some uncertainty in determining the exact arterial branching point in the image. This can potentially introduce error in the in vivo validation of the technique.

Clinical Implications

The present technique can be used to measure the progression and regression of atherosclerosis in an arterial segment or the entire coronary arterial tree from coronary arteriograms acquired in different time points. This will quantify the relative change of lumen volume in a specified arterial segment. Lumen volume measurements can also potentially be used for quantification of diffuse coronary artery disease. In this case, it is necessary to determine whether a given measured volume for an arterial tree or subtree is normal for the size of the myocardial mass it perfuses. We have previously shown that there is a power law relationship between the cumulative lumen volume and the sum of branch lengths in a coronary artery tree. Hence, it is possible to determine the extent of diffuse coronary artery disease by establishing the relationship between the lumen volume and the cumulative arterial branch lengths for normal human coronary arteries. Previous studies have also shown that there is a power law relationship between the diameter of a stem and the sum of coronary artery branch lengths. This relationship addresses the question of whether a measured vessel diameter is too small for the size of the myocardial mass it perfuses. Conversely, lumen volume gives global information for the entire coronary tree or subtree. Therefore, the volume and diameter relationships provide complimentary quantitative information regarding the extent of diffuse coronary artery disease. The diameter relationship is inherently more variable, however, than the volume relationship.

In conclusion, a video densitometry technique for quantification of coronary lumen volume was validated both in vitro and in vivo in a swine animal model. The present results demonstrated the feasibility and potential utility of the video densitometry technique for accurate measurement of regional lumen volume in vivo. Despite potential clinical limitations, this study contributes to the understanding of the angiographic methods used for the assessment of coronary artery disease and indicates that this technique can potentially be used for quantification of diffuse coronary artery disease during routine coronary arteriography.

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