Accuracy of CO_2 Angiography in Vessel Diameter Assessment: A Comparative Study of CO_2 versus Iodinated Contrast Material in an Aortoiliac Flow Model[1]

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Abbreviation: IVUS = intravascular ultrasound

PURPOSE: Precise vessel sizing prior to endovascular intervention is critical to achievement of technical success. Diameter measurements obtained with CO_2 and iodinated contrast material in an aortoiliac flow model were compared.

MATERIALS AND METHODS: Aortoiliac flow was simulated in a compliant, silicone elastomer phantom of the aortoiliac system using an autoperfusion pump (flow volume, ~1100 mL/min; mean arterial pressure, 70–80 mm Hg at 80–90 cycles/minute) and a glycerol solution (40% by weight; viscosity 3.7 centipoise at 20°C). Digital subtraction angiography was performed with the phantom in the anteroposterior (AP) plane and in three oblique planes with both CO_2 and iodinated contrast material. Five sets of images for both CO_2 and iodinated contrast material were obtained for each projection. Two readers independently performed vessel diameter measurements at seven sites (distal abdominal aorta, bilateral proximal and distal common iliac, and mid-external iliac arteries). The model was then evaluated with intravascular ultrasound (IVUS) using a 20-MHz imaging catheter. Actual diameter measurements were taken from the inner wall to inner wall in orthogonal planes at the same locations within the model, as described previously. Analysis was performed to determine local difference in measurements (*t* tests), difference when compared to the standard AP projection with iodinated contrast material (Dunnett's test) and inter-reader variability (Pitman's test).

RESULTS: The contralateral iliac vessel segment did not opacify when imaging with CO_2 in the 45° obliquities; thus, 22 of 28 sites were available for comparison. At 18 of 22 (81.8%) sites, there was significant difference in vessel measurements ($P < .01$), with CO_2 yielding a significantly larger diameter at 17 of 22 (77.3%) of the sites. The difference in mean diameter ranged from -1.28 to 4.47 mm. With use of the AP iodinated contrast material run as the standard, there were significant differences ($P < .05$) in vessel diameter at 17 of 22 (77.3%) and four of 21 (19%) sites for CO_2 and iodinated contrast material respectively, with CO_2 tending toward greater diameter measurements. Significant differences ($P < .05$) in variance between the two readers were present but occurred primarily with CO_2 in the AP projection and iodinated contrast material in the 45° left obliquity. With use of IVUS as the standard, there were significant differences ($P < .05$) in the measured vessel diameters with CO_2 at nine of 22 (40.9%) of the sites and with iodinated contrast material at 17 of 28 (60.7%) of the sites. Of the measurements made with CO_2, seven of nine (77.8%) of the measurements were of larger diameter than those obtained with IVUS. By contrast, of the measurements made with iodinated contrast material angiography, IVUS measured larger diameters in 16 of 17 (94.1%).

CONCLUSION: CO_2 angiography consistently yielded significantly larger vessel measurements when compared to both iodinated contrast angiography and IVUS. These results have important implications in regards to planning intervention based solely on CO_2 angiography. Further evaluation is needed before recommending CO_2 for vessel sizing in clinical practice.

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A requirement of vascular intervention (ie, angioplasty, stent placement) is precise vessel sizing to achieve optimal technical success. Measurements based on iodinated contrast material angiography are the gold standard. Although proven safe for routine examination, a substantial number of patients have a contraindication to the use of iodinated contrast material (1–3). An alternative vascular imaging media is carbon dioxide (CO_2). It has been used to perform diagnostic angiography (4–6) and, more recently, to guide percutaneous interventions (5,7–10). Despite its use, no study has formally addressed the ability of CO_2 to accurately measure the target vessel diameter. If CO_2 can be shown to be accurate, there may be no need for confirmatory arteriography using iodinated contrast material or other unproven contrast agents prior to performing a vascular intervention.

Our hypothesis was that CO_2 angiography could yield measurement of vessel size similar to that of iodinated contrast material angiography.

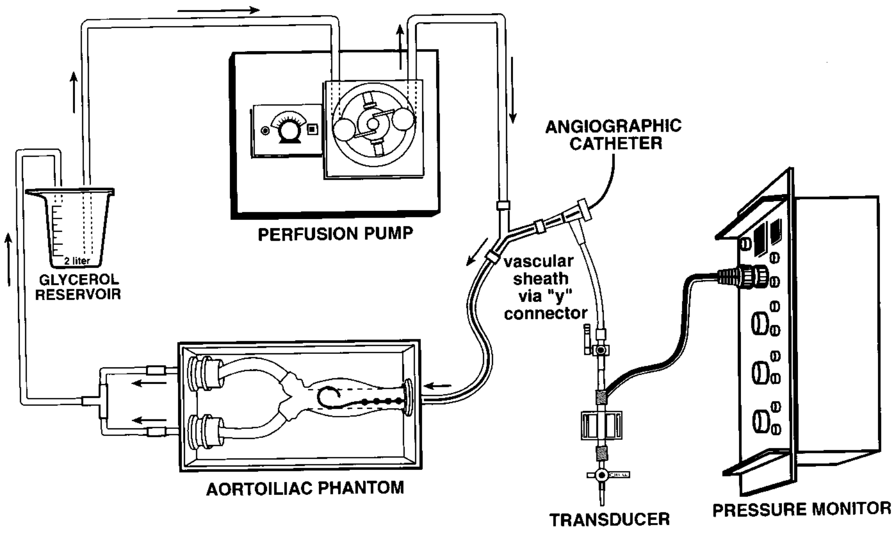


Figure 1. Aortoiliac flow model. The autoperfusion pump circulates glycerin solution through the phantom. A Y-connector inserted into Tygon tubing allows for the introduction of a sizing pigtail catheter. Simultaneous pressure monitoring is performed through the sidearm of the in-dwelling 10-F vascular sheath.

MATERIALS AND METHODS

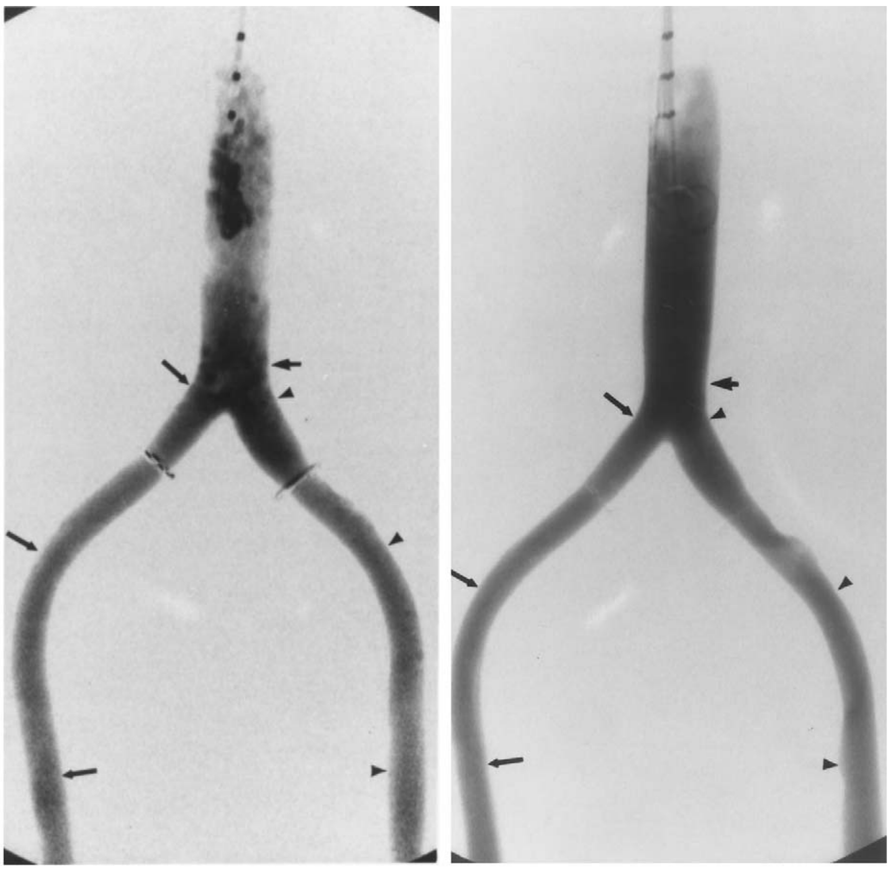
• Aortoiliac Physiologic Flow Model

An anatomic, silicone-based aortoiliac phantom was created for calibration of imaging modalities. Design and construction of the aortoiliac phantom has been described (11). A model that simulates aortoiliac arterial flow conditions within the phantom was then created **(Fig 1)**. The pump mechanism from an autotransfusion system (Model#ATS-F; Bently Laboratories, Santa Ana, CA) was used to generate flow within the phantom. Compliant Tygon tubing (Fisher Scientific, Pittsburgh, PA) was connected from the pump outflow to the cephalad inflow valve of the phantom. A glycerin solution (40% by weight; viscosity, 3.7 centipoise at 20°C; reference blood, 3.4 centipoise at 37°C) was circulated through the system from a 1.5-L reservoir. A 10-F vascular sheath was connected to the efferent tubing with use of a Y-adapter, allowing for catheter access into the system. A screw valve was fitted to the primary out flow tubing, which was used to vary the intraluminal pressure. Calculation of flow volume was performed by varying the pump flow rates at a fixed mean intraluminal pressure. The resulting flow volume was recorded.

• Study Design

Digital subtraction imaging of the phantom was performed using CO_2 and iodinated contrast material (50% diatrozoate meglumine [Hypaque 50]; Nycomed, Princeton, NJ). A 5-F, 70-cm graduated sizing catheter (Royal Flush II [Pig GSC]; Cook, Bloomington, IN) was introduction into the phantom through the vascular sheath. The catheter was positioned at the level of the mid-infrarenal aorta. Forty milliliters of CO_2 was delivered using manual bolus injection through a 60-mL syringe. Prior to actual imaging, reproducible quality of hand injection by a singe operator (K.P.M.) was achieved with practice CO_2 runs while monitoring intraluminal pressure. The iodinated contrast material was injected at a rate of 10 mL per second for a total of 15 mL (800 psi) with use of a standard contrast injector (Mark V plus; Medrad, Pittsburgh, PA). Determination of the rate and volume of each contrast agent injection was based on our routine imaging parameters, as well as numerous test injections to determine optimal opacification of the phantom lumen. The phantom was positioned under the image intensifier on the angiography table in the straight posterior-anterior (PA) projection. The phantom was then imaged in the 22° caudal and 45° right-anterior and left-anterior oblique projections with the aide of the respective-degree foam wedge placed beneath the phantom. Subject-to-intensifier distance (95 cm) and C-arm height (104 cm) were kept constant for all image acquisition sets. After each image set with iodinated contrast material, the entire circulating volume of glycerol solution was exchanged to minimize background effect.

All imaging was performed on a state-of-the-art digital angiography unit (Model DFP-2000A; Toshiba Medical Systems, Tochigi-ken, Japan). The x-ray control unit (automatic exposure control) determined



a. b.

Figure 2. CO_2 and iodinated contrast material angiograms. Large arrow marks the measurement location for the aorta. Small arrows and arrowheads mark measurement location for the proximal and distal common iliac and mid-external iliac arteries on the right and left respectively. **(a)** CO_2 angiogram obtained with the phantom in 22° of caudal angulation. **(b)** Iodinated contrast material arteriogram with the phantom similarly positioned on the angiography table.

the optimum imaging parameters (kV, mA, and pulse width) for each digital angiogram. Maximum values for kV and pulse width were set at 100 (kV and ms, respectively). A 14-inch-diameter image intensifier was used. The system's auto focus mode selected the focal spot size (small, medium, or large) based on the exposure parameters.

• Data Collection

Five sets of images were obtained for both CO_2 and iodinated contrast material for each imaging plane from the same catheter position, with all variables remaining constant. For CO_2, the image acquisition was set at 10 frames per second with a 1,024 × 1,024 matrix for image storage. Image postprocessing was performed with use of the digital angiography system image-stacking software. First, each subtracted CO_2 angiogram was reviewed and the best image mask selected. Each run was then sectioned to include only those image frames in which the vessel(s) was opacified with CO_2. A functional (summed static) image was then constructed with use of the stored data and the contrast medium time-density curve. Image acquisition rate for iodinated contrast material was set at a rate of 5 frames per second with a 1,024 × 1,024 matrix for image storage. Similar image postprocessing was performed to obtain an image with uniform maximum opacification, although this was often not needed because of the slower, more uniform flow of the iodinated contrast material compared to the CO_2.

The two readers (K.P.M., N.P.) reviewed the final postprocessed images independently. Vessel diameter measurements at seven predetermined sites (distal abdominal aorta, bilateral proximal and distal common iliac, and mid-external iliac arteries) were obtained for each individual angiogram **(Fig 2)**. A standardized template was placed over each angiographic image, which marked the exact vessel location to be measured. Measurements were made directly from a hard copy image using an electronic digital caliper (Ultra-cal Mark III; Fowler, Newton, MA). All vessel diameter measurements were corrected for magnification using the sizing catheter. The opacified lumen was measured in a plane perpendicular to its longitudinal axis from the outer edge to outer edge. The actual and corrected diameter measurements were rounded to the hundredth of a millimeter and recorded.

Reference measurement of the model was performed with intravascular ultrasound (IVUS) using a 20-MHz imaging catheter (Sonicath Ultra 6; Boston Scientific Vascular, Watertown, MA). IVUS was performed after pressurization of the model to a mean intraluminal pressure of 80 mm Hg using a saline solution. Measurements were obtained at the same locations within the model, as described previously. Actual diameter measurements were taken from the inner wall to inner wall in orthogonal planes.

• Statistical Methods

For each angiogram and measurement location, the mean of the three direct measurements was corrected for magnification using the mean of the three sizing catheter measurements, and t tests were performed for each angle projection at all locations to assess differences between the observed values for both CO_2 and iodinated contrast

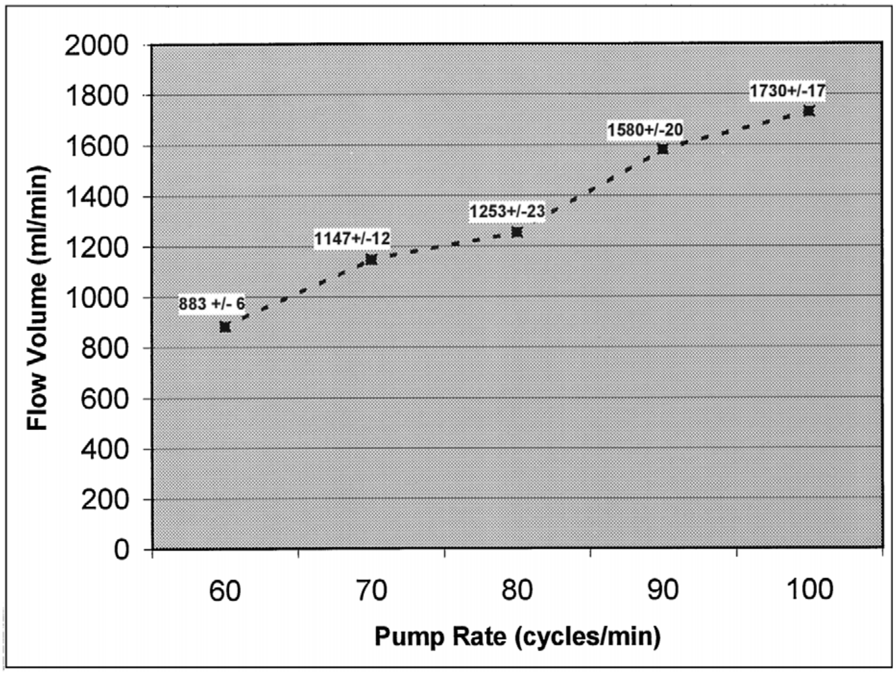


Figure 3. Flow volume versus autoperfusion pump rate. The volume of the glycerin solution circulated through the system was measured while varying the autoperfusion pump rate. All measurements were obtained while maintaining a constant, mean intraluminal pressure (80 mm Hg).

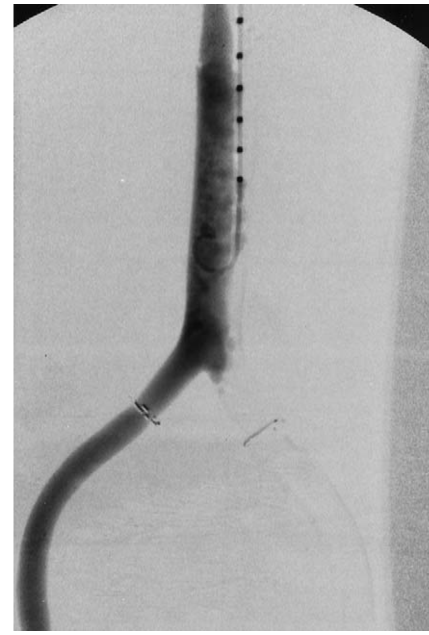


Figure 4. Aortoiliac phantom in the 45° right anterior oblique position. Because of its buoyant nature, CO_2 flows along the nondependent surface and fails to opacify the contralateral iliac system.

material. In addition, with use of the AP projection with iodinated contrast material as the gold standard, all other angle projections and contrast agent combinations were compared to it using Dunnett's test (12). Dunnett's test is a multiple comparison test used to compare treatment means to a control. To test if the variances for the two readers across the five runs from a given angle and contrast agent combination were the same, Pitman's test (13) for correlated variances was used. Means and standard deviations of the IVUS diameter measurements were calculated. Dunnett's test was also used to compare all angle projections and contrast agent combinations to the IVUS measurements.

RESULTS

The described aortoiliac flow model achieved physiologic flow conditions similar to those of the human infrarenal abdominal aorta and iliac arteries. Magnetic resonance arteriography of a healthy volunteer (M.S.J.) measured flow in the human infrarenal aorta at ~1,200 mL/min. At a rate of 80 cycles per minute, with the mean intraluminal pressure set at 80 mm Hg, a flow volume of ≥1,200 mL/min was achieved through the phantom **(Fig 3)**. Multiplanar angiography, using both CO_2 and iodinated contrast material, was successfully performed with only mild, transient increase in the intraluminal pressure. The system reservoir allowed for easy exchange of the fluid contents. This was necessary because of background noise from circulating contrast material when performing repeated angiography with iodinated contrast material.

The iodinated contrast material runs showed adequate opacification at all segments of interest. The contralateral iliac vessel segment did not opacify when imaged with CO_2 in the 45° obliquities **(Fig 4)**. Thus, only 22 of 28 (78.6%) sites were available for direct comparison. At 18 of 22 (81.8%) sites, there were significant differences in vessel diameter measurements ($P < .01$), with CO_2 yielding a significantly larger vessel diameter at 17 of 22 (77.3%) of the sites **(Table 1)**. The differences in mean vessel diameter ranged from -1.28 to 4.47 mm. With use of the AP run with iodinated contrast material as the standard, there were significant differences ($P < .05$) in the measured vessel diameter for CO_2 at 17 of 22 (77.3%) sites and for iodinated contrast material at four of 21 (19.1%) sites **(Table 1)**. CO_2 angiography had an overall tendency toward greater diameter measurements. Significant differences ($P < .05$) in variance between the two readers were present for 13 of 50 (CO_2, five of 50 [10%]; iodinated contrast material, eight of 50 [16%]) measurement locations **(Table 2)**. This was primarily limited to measurements made in the AP projection for CO_2 and the right-anterior oblique and

Table 1
Means and Standard Deviations for Contrast Agents at all Projection Angles and Sites

		Aorta		Rt Common Iliac		Rt Common/ External Iliac		Rt External Iliac		Lt Common Iliac		Lt Common/ External Iliac		Lt External Iliac	
		Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
22° caudal	CO_2	22.36*†	0.59	13.89*†	0.49	10.72*†	0.14	11.45*†	0.18	16.15*†‡	0.51	11.45*†‡	0.39	12.31	0.38
(model)	IC	18.80*‡	0.03	11.39*‡	0.08	9.28*‡	0.05	9.89*‡	0.07	14.00*	0.08	10.40*	0.10	12.36	0.10
AP	CO_2	23.24*†	0.23	13.99*†	0.12	11.31*†	0.14	11.87*†‡	0.08	16.71*†‡	0.18	10.92*†	0.08	12.40	0.17
	IC	18.77*‡	0.22	11.27*‡	0.19	9.18*‡	0.13	9.77*‡	0.13	13.88*	0.21	10.39*	0.16	12.28	0.10
LAO 45°	CO_2	19.94‡	1.32	NA	NA	NA	NA	NA	NA	16.79*†‡	0.41	11.57*†‡	0.35	11.94*	0.32
(model)	IC	19.53‡	0.28	11.79†‡	0.14	9.61†‡	0.08	9.75‡	0.16	14.32*	0.10	10.38*	0.14	12.53*‡	0.16
RAO 45°	CO_2	18.34‡	0.33	14.32*†	0.08	11.41*†	0.12	12.23*†‡	0.33	NA	NA	NA	NA	NA	NA
(model)	IC	19.62‡	0.24	11.69*†‡	0.11	9.41*†‡	0.03	9.94*‡	0.07	14.23	0.10	10.59	0.17	12.47	0.16
IVUS		22.60	0.57	13.60	0.89	10.83	0.67	10.85	0.44	14.33	0.54	10.58	0.33	11.80	0.44

Note.—Rt = right; Lt = left; STD = standard deviation; IC = iodinated contrast material; AP = anterior-posterior; LAO = left anterior oblique; RAO = right anterior oblique.
* *P* value from *t* test comparing observed values from CO_2 and IC for each angle projection at all levels < .05.
† *P* value from Dunnett's test treating AP-IC as gold standard < .05.
‡ *P* value from Dunnett's test treating IVUS as gold standard < .05.

Table 2
***P* Values from Pitman's Test of Interreader Variability**

		Aorta	Rt Common Iliac	Rt Common/ External Iliac	Rt External Iliac	Lt Common Iliac	Lt Common/ External Iliac	Lt External Iliac
22° caudal (model)	CO_2	.1998	.0679	.5809	.3411	.2004	.0625	.1507
	IC	.8957	.1998	.0955	.2810	.5751	.2597	.9986
AP	CO_2	.0005*	.0045*	.0024*	.0213*	.0278*	.1515	.0544
	IC	.7142	.4487	.8909	.3187	.6192	.7061	.1151
LAO 45° (model)	CO_2	.7882	NA	NA	NA	.7215	.3895	.8130
	IC	.0244*	.0129*	.0674	.0017*	.0418*	.0028*	.0235*
RAO 45° (model)	CO_2	.8698	.6396	.8445	.2148	NA	NA	NA
	IC	.1922	.2420	.3003	.2861	.1542	.0105*	.0402*

Note.—Rt = right; Lt = left; IC = iodinated contrast material; AP = anterior-posterior; LAO = left anterior oblique; RAO = right anterior oblique.
* *P* value < .05.

left-anterior oblique 45° projections for iodinated contrast material. For the 22° caudal angulation, no significant difference between the variances of the two readers was observed for either CO_2 or iodinated contrast material.

With use of IVUS as the standard, there were significant differences ($P < .05$) in the measured vessel diameters for CO_2 at nine of 22 (40.9%) sites, and with iodinated contrast material angiography at 17 of 28 (60.7%) sites **(Table 1)**. Of the nine significantly different measurements made when comparing CO_2 to those with IVUS, only the IVUS measurement of the aorta in both 45° projections (right- and left-anterior oblique) was of a greater diameter. For the remaining seven of nine (77.8%) sites, the CO_2 measurement was of a greater diameter.

Of the 17 significantly different measurements made when comparing iodinated contrast material angiography with IVUS, IVUS yielded a larger diameter in 16 of 17 (94.1%). Only the left external iliac measurement obtained in the left-anterior oblique 45° projection was smaller for the IVUS. When comparing the measurements from the AP projection for iodinated contrast material angiography and IVUS, IVUS again yielded significantly larger diameters at four of seven (57.1%) of the measurement sites.

DISCUSSION

The use of CO_2 as an intravascular contrast agent has increased dramatically since the introduction of digital subtraction angiography. CO_2 possesses many of the characteristics of the ideal contrast agent. It is low in cost, readily available, and safe to use, with no reported risk of contrast-induced nephrotoxicity or allergic reaction. The efficacy of CO_2 to accurately portray vascular pathology has been postulated (4–8) but has yet to be proven in a randomized study. Many of the initial technical problems with CO_2 angiography have been overcome with the advent of improved digital imaging capabilities. The ability to perform image postprocessing, especially with the use of image stacking software, has resulted in superior quality images.

The injection characteristics of CO_2 have been studied (14). With use of a circulatory system model similar to that used in this study, the dispersion pattern of CO_2 from multiple catheter types was imaged with use of digital subtraction imaging. CO_2, when injected and thus compressed through an angiographic catheter, streams from a high- to a low-pressure region. Independent of the catheter type used, the CO_2 was found to rapidly flow toward the nondependent side of the tube. In general, the bubble under pressure from compression during injection expands into a large bubble, producing a uniform column. The profile of frontal motion was parabolic in its configuration, with increasing velocity toward the center of the bubble. When injected through an endhole catheter, CO_2 streams out as a single bubble. With a pigtail catheter configuration, the CO_2 is delivered into the vessel over the length of sideholes. The bubbles then float swiftly on the fluid and tend to move separately, resulting in a bubbly gas column. Because of the buoyant nature of the gas, even large injection volumes were not capable of displacing the slow-moving fluid layer along the dependent surface of the tube. This became more significant as the luminal diameter increased, with improved filling with increasing inclination of the tube.

Aside from diagnostic applications, an intravascular contrast agent must allow for accurate measurement of the vessel lumen to aid in the determination of the significance of a lesion, as well as to plan treatment of the vessel. There have been conflicting reports as to the accuracy of CO_2 compared to iodinated contrast material in assessing severity of stenosis (15,16). In a study comparing the accuracy of CO_2 and iodinated contrast material in the evaluation of hemodialysis fistulas, Ehrman et al (15) reported that CO_2 overestimated the number of cases of severe stenosis when graded on a visual inspection scale. This resulted in high sensitivity (94%) but poor specificity (58%) compared to iodinated contrast material. In a study using densitometric analysis of eccentric vascular stenoses in an ex vivo vascular circuit, CO_2 was found to be superior in accuracy to iodinated contrast material for en face stenoses measuring 50%, 60%, and 70% of the cross sectional diameter. The authors again found that CO_2 overestimated the degree of stenosis, whereas iodinated contrast material tended to underestimate the degree of stenosis. With such doubt as to the accuracy of measurements obtained with CO_2, many authors have chosen to initially image with CO_2 and, based on the preliminary finding, proceed with imaging with either iodinated contrast material or other alternate, and still unproven, contrast agents to guide interventions (8–10,14,17). This, in effect defeats the purpose of the initial use of CO_2, which is to avoid the risks inherent to iodinated contrast material.

In this study, CO_2 measurements were compared to those obtained from imaging with iodinated contrast material and IVUS. IVUS was used as the reference standard because, as a result of the manufacturing process, the actual internal phantom diameters are not known (personal communication Dr. J Unthank). IVUS is a tomographic imaging modality that displays the vessel lumen in cross section. This allows direct measurement of the luminal area and vessel diameter. IVUS measurements have been shown to have excellent correlation with the true vessel diameter in both in vitro and in vivo studies (18–22). Diameter measurements obtained when imaging with CO_2 differed significantly from those obtained with use of IVUS (41% of sites) and iodinated contrast material angiography (82% of sites). Overall, the diameter measurements were significantly greater with CO_2 when compared to both IVUS (31.8% of sites) and iodinated contrast material angiography (77.3% of sites), ranging upward of (+) 4 mm when compared to iodinated contrast material.

The results of this study have implications in regard to performing intervention based solely on imaging with CO_2. This is particularly true in regard to additional oversizing (10–20%), which is often used when planing an intervention based on measurements obtained from iodinated contrast material angiography. In this setting, the additional oversizing may be necessary because iodinated contrast material angiography tends to underestimate the true vessel diameter. This observation has been confirmed in comparative studies for diameter measurement using conventional iodinated contrast material angiography and IVUS (18–20). The problems related to vessel undersizing are more technical in nature, resulting in inadequate vessel dilation or stent undersizing and expansion, which may compromise the technical result. Such vessel undersizing may predispose to acute or subacute thrombosis, or early restenosis. These problems are correctable with additional interventions that can be performed to improve the technical result. The risk associated with oversizing of a vessel prior to an intervention can be dire and can result in severe vessel injury, such as acute rupture. The tendency for CO_2 to oversize the vessel may act to increase the risk of resultant vessel injury if an intervention is performed based solely on the results of the CO_2 angiography.

The fact that CO_2 yielded larger vessel diameters in the model may be due to the elastic nature of the walls and the expansive nature of the CO_2 as it exits the injection catheter. This would help explain the painful sensation reported by patients undergoing CO_2 angiography (23). As CO_2 exits the catheter after compression in the injection syringe, it expands intraluminally and the vessel dilates from its basal diameter. This activates the stretch receptors in the vessel wall and the patient experience pain, similar to when undergoing balloon angioplasty. As the bolus passes, the sensation subsides. Rolland et al (23) noted that the sensation was linked to the quantity of CO_2 injected. The authors were conducting a comparative of lower-limb angiography using CO_2 and iodinated contrast material. The patients were questioned as to tolerance for both contrast agents. Forty percent of patients reported a "more disagreeable" sensation after CO_2 injection. When the volume of CO_2 injected was decreased from 75 mL to 50 mL per injection, patient discomfort was also reduced. The diameter measurement may also be affected as a result of image postprocessing and the inherent decreased contrast differentiation between CO_2 and surrounding soft tissues. These two factors contribute to poor edge delineation of the vessel and thus a possible tendency to overestimate the luminal diameter. Despite this, there was no significant difference in reader variance between diameter measurements using CO_2 and iodinated contrast material.

A significant limitation of any in vitro study is the ability to translate the results obtained into in vivo applications. The aortoiliac phantom incorporated into the model used in this study is constructed of silicone elastomers set in a clear silicone gel (11). The phantom was created to be used as a calibration standard for various imaging modalities (ie, CAT scan, magnetic resonance imaging, and contrast angiography). The silicone elastomers making up the wall of the vessels in the model is a compliant material and truly simulates the elastic nature of the vessels being studied. Combining the model with the flow conditions produced by the described pump system allowed for rapid injection of CO_2 and iodinated contrast material in conditions that closely approximate human physiology. The results of the measurements obtained in this study correlate with other in vitro and in vivo studies regarding the tendency for CO_2 to overestimate vessel diameters, and the tendency of iodinated contrast material to underestimate diameters (compared with IVUS) (15,16,18–22). This acts to further validate the use of this physiologic model in such a comparative imaging study.

In summary, CO_2 angiography consistently yielded significantly larger vessel measurements when compared to both iodinated contrast angiography and IVUS. This has important implications when performing vascular interventions based solely on imaging with CO_2. Oversizing of the PTA balloon or stent might occur if vessel measurements are performed exclusively with CO_2. Further evaluation of CO_2 is required before its use to guide vascular interventions can be recommended.

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