Accuracy of CO_2 Angiography in Vessel Diameter Assessment: A Comparative Study of CO_2 versus Iodinated Contrast Material in a Porcine Model

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PURPOSE: To compare, with use of intravascular ultrasound (IVUS) as an internal reference standard in a porcine model, arterial diameters measured from arteriograms obtained with use of CO_2 to those obtained with use of iodinated contrast material (ICM).

MATERIALS AND METHODS: In nine pigs, digital subtraction angiograms (DSAs) were obtained in the aorta and iliac arteries to compare vessel diameters measured with use of CO_2 to those measured with use of ICM. These measurements were divided by measurements made with use of intravascular ultrasound (IVUS) to yield a DSA/IVUS ratio. Differences between ICM and CO_2 were compared with analysis of variance to assess the effect of location (aorta vs iliac), contrast material used (ICM vs CO_2), and position (posteroanterior, right anterior oblique, or left anterior oblique). Secondary analysis compared measurements of dependent and nondependent iliac arteries and compared the use of hand-injected CO_2 to that of CO_2 injected by an injector.

RESULTS: The DSA/IVUS ratio was 70.7% ± 4.4% with ICM use and 69.6% ± 6.3% with CO_2 use, which did not represent a significant difference (P = .311). Animal position had no effect (P = .477). Underestimation was worse in the iliac arteries than in the aorta (67.4% ± 1.5% vs 71.4% ± 1.7%; P = .038). There was no difference in nondependent (P = .163) arteries, but CO_2 underestimated dependent iliac artery size more than ICM did (66.3% ± 4.8% vs 70.3% ± 5.4%; P = .051). Vessel diameter was underestimated more with the CO_2 injector than with hand-injected CO_2 (64.3% ± 2.3% vs 71.7% ± 1.7%; P < .0001).

CONCLUSION: There is no difference in diameter underestimation between CO_2 and ICM in this animal model. Hand-injection of CO_2 causes less underestimation of vessel diameter than does the CO_2 injector.

Index terms: Angiography • Carbon dioxide • Contrast media, comparative studies

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Abbreviations: DSA = digital subtraction angiogram, ICM = iodinated contrast material, IVUS = intravascular ultrasound, RAO = right anterior oblique

PRECISE measurements are required for safe and accurate arterial and venous interventions such as stent placement, angioplasty, and inferior vena cava filter placement in humans. Current measurements are based on iodinated contrast angiography images obtained with use of digital subtraction angiography (DSA) and an internal marking catheter. This allows precise measurement of luminal diameter for selection of stent size and balloon size for angioplasty.

However, a growing patient population is confronted with contraindications to the use of iodinated contrast material (ICM). The prevalence of acute adverse reactions to contrast material is reported as 5%–8% (1–6). In patients with baseline renal insufficiency who are not undergoing dialysis treatment, the administration of large volumes of ICM is considered a relative contraindication (7–9). The use of CO_2 in this patient population has been advocated as a means of assessing arterial lesions and planning for arterial intervention (10–16). With use of an aortic aneurysm flow model made of synthetic materials, Moresco et al (17) demonstrated that CO_2 overestimated vessel diameters compared to intravascular ultrasound (IVUS) and ICM. In this study, we compare

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Table 1
Diameter Measurements with Each Contrast Material and IVUS

	Contrast Material		
Location	CO_2	ICM	IVUS
Aorta	6.95 ± 1.11 (9)	7.17 ± 1.10 (9)	9.89 ± 1.28 (9)
Nondependent iliac	4.3 ± 0.64 (5)	4.11 ± 0.85 (5)	6.05 ± 0.72 (5)
Dependent iliac	4.25 ± 0.43 (5)	4.53 ± 0.56 (5)	6.45 ± 0.72 (5)
Overall	5.89 ± 0.75 (9)	6.03 ± 0.81 (9)	7.19 ± 0.75 (9)

Note.—Values expressed as means ± SD. Number of animals measured presented in parentheses.

CO_2 angiography to iodinated contrast angiography in a living system with use of IVUS as a reference.

MATERIALS AND METHODS

All aspects of the care and handling of the animals in this study conform to the recommendations of the National Institutes of Health's Guide for the Care and Use of Animal Laboratories, as well as state and institutional guidelines. Also, the experimental procedures were conducted under the Food and Drug Administration's Good Laboratory Practice for Non-Clinical Laboratory Study Regulations (21 CFR, part 58).

Ten outbred swine (mean weight, 33.3 kg; range, 23–42 kg) were sedated intramuscularly with 0.5 mL/kg of a solution of ketamine (1,000 mg/mL; Bristol Laboratories, Syracuse, NY) and xylazine (142 mg/mL; Miles Laboratories, Shawnee, KS). Anesthesia was induced with sodium thiopental (25 mg/kg; Fort Dodge Animal Health, Fort Dodge, IA). Anesthesia was maintained with 2%–4% Isoflurane (Schering-Plough, Rochester, NY) via endotracheal tube. One animal was excluded because of death from anesthesia-related malignant hyperthermia during the procedure. Animals were premedicated with Verapamil (2.5 mg intravenous; Abbott Laboratories, North Chicago, IL) to reduce spasm. Spasm encountered during the procedure was treated with nitroglycerine (Abbott Laboratories) and the procedure was halted until the spasm resolved. If the spasm failed to resolve, this was noted and the data were analyzed with the affected measurements included and excluded. All animals underwent heparin infusion (100 U/kg; Elkins-Sinn, Cherry Hill, NJ). The right neck was shaved, prepared, and draped in sterile fashion and an incision was made to expose the right carotid artery. An 8-F vascular sheath (Boston Scientific/Meditech, Natick, MA) was placed in the right carotid artery via surgical cutdown. Through the sheath, a 0.035-inch Bentson wire (Cook, Bloomington, IN) was advanced into the distal abdominal aorta and a graduated straight flush catheter (Cook) was positioned within the juxtarenal aorta. Six arteriograms were then obtained with the catheter in this position and the animal centered in the posterolateral (PA) position with use of a Toshiba 9800 angiography unit (source-to-image distance = 100, PID = 30, 12-inch image intensifier; Toshiba America, New York, NY). Three of these arteriograms were obtained with use of ICM (Isovue 300; Bracco Diagnostics, Princeton, NJ) at a rate of 8 mL/min for a total of 16 mL with a power injector (Medrad IV, Indianola, PA). Three were obtained with CO_2 injected either by hand (35 mL) or with a prototype CO_2 injector (AngioDynamics, Queensbury, NY) at a rate of 15 mL/min for 35 mL. Contrast material injection rates for CO_2 and ICM were optimized in an additional animal before commencement of the study. No data were recorded from this animal. The order in which contrast agents were chosen was randomized with use of a coin toss. After arteriography, the catheter was removed over a 0.035-inch guide wire, the distal tip of which was positioned down either the right or left iliac artery. Over this guide wire, a 12.5-MHz IVUS probe (Boston Scientific/Medi-tech) was advanced into the aorta. IVUS was performed throughout the aorta and both iliac arteries. A radiopaque ruler was placed below the animal to allow precise location of positions in the vessel to be correlated between angiography and IVUS. After IVUS in the PA position, the animal was turned to the RAO projection such that the right side of the animal was elevated above the left side, and the process was repeated with six arteriograms followed by additional IVUS. The animal was then positioned in the LAO position, with the left side above the right side, and the procedure was repeated. In the first experimental animal, the right and left iliac arteries were evaluated with use of IVUS in all projections. Wire manipulations to allow IVUS evaluation of the second iliac artery caused severe spasm. Therefore, the remaining animals had either the ipsilateral oblique iliac artery (left side in LAO position, right side in RAO position) or contralateral iliac artery evaluated with IVUS ($n = 4$ for each group).

Angiograms were printed with an unsubtracted view of the marking catheter and a digital subtraction image below it with the maximum contrast material volume filling the aorta and iliac arteries. The images were controlled by adjusting contrast and level to make the CO_2 images appear as close as possible to the iodinated contrast images. At the conclusion of the procedure, the animals were killed with Beuthanasia (Schering-Plough).

Because interobserver variability was addressed in a previous study (17), a single reviewer performed all angiographic and IVUS measurements. The angiograms were measured from the level of the aorta above the renal artery through the iliac arteries in 2-cm intervals on each film of each animal. Each measurement was correlated with the IVUS measurement obtained with the animal in the same position at that same location. Vessel diameters were measured from the angiograms. Two diameters were measured on the IVUS measurements and these were averaged (**Fig 1**). The ratio of angiographic measurements (CO_2 or ICM) to IVUS measurements was calculated (DSA/IVUS).

Statistics

A generalized estimating equation model was fit to examine the effect of location (aorta vs iliac artery), contrast material (CO_2 vs ICM) and position (RAO,

Table 2
Percentage of IVUS Measurement Calculated by Dividing Contrast Measurement by IVUS Measurement and Multiplying by 100

Location	CO_2/IVUS	IC/IVUS	*P* Value
Aorta	70.4 ± 6.8% (9)	72.4 ± 4.5% (9)	.311
Nondependent iliac	71.4 ± 11.0% (5)	67.4 ± 6.8% (5)	.163
Dependent iliac	66.3 ± 4.8% (5)	70.3 ± 5.4% (5)	.051
Overall	69.6 ± 6.3% (9)	70.7 ± 4.4% (9)	.311

Note.—Values presented as mean ± SD with number of animals measured presented in parentheses.

LAO, and PA) on the DSA/IVUS ratio. The same model was also fit to exclude the LAO and RAO projections in one animal that had spasm that was unresponsive to nitroglycerine. The model was then fit separately for each level of any significant effects. The 95% CIs of the ratios, and for the difference between the ratios, were calculated for each level of any significant effects. A secondary analysis was performed to compare the ratios in hand-injected CO_2 studies to the ratios in CO_2 injector studies.

To examine the effect of measurements in dependent versus nondependent iliac arteries, a generalized estimating equation model was fit to use only the iliac measurements. The type of iliac measurement (dependent vs nondependent) was included in this model, in addition to contrast and position. Finally, to examine the contrast effect in dependent and nondependent iliac arteries alone, generalized estimating equation models were fit separately for measurements of dependent and nondependent iliac arteries.

RESULTS

Diameters measured angiographically with ICM were 70.7% ± 4.4% of corresponding IVUS measurements. Those measured with CO_2 were 69.6% ± 6.3% of corresponding IVUS measurements. There was no difference between CO_2 and ICM ($P = .311$). Animal position had no effect when analyzing all data ($P = .477$) or when analyzing only iliac measurements ($P = .499$). Contrast material underestimation (with either ICM or CO_2) was slightly worse in the iliac arteries than in the aorta (67.4% ± 1.5% vs 71.4% ± 1.7%; $P = .038$). There was no difference between ICM and CO_2 underestimation of nondependent ($P = .163$) or dependent iliac arteries, but CO_2 angiography tended to more greatly underestimate vessel size in the dependent iliac artery (66.3% ± 4.8% vs 70.3% ± 5.4%; $P = .051$). Exclusion of data in the one animal that had unresponsive spasm in the iliac arteries did not change these results. The CO_2 injector underestimated vessel diameter by an additional 7.4% ± 2.9% compared to hand-injected CO_2 (64.3% ± 2.3% for the injector, 71.7% ± 1.7% for hand injections; $P < .0001$).

DISCUSSION

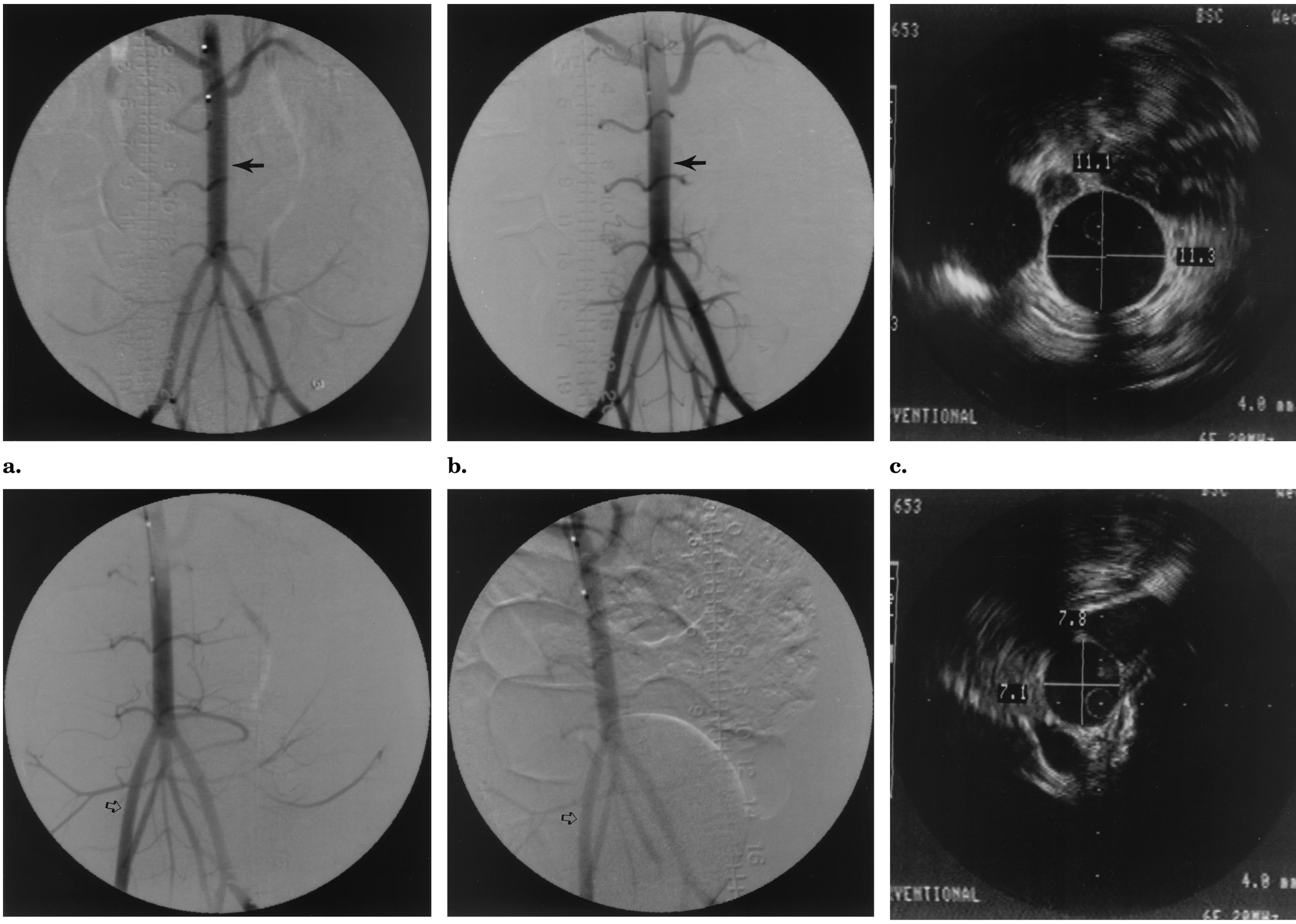
In current practice, vessel measurements for planning arterial intervention are most commonly based on contrast angiography measurements. This is often performed with an internal marking catheter as a calibration guide. Previous studies have evaluated the accuracy of contrast angiography compared to IVUS for the purposes of measuring vessels for intervention. Although several studies indicate that angiography underestimates vessel size compared to IVUS (18–21), Froelich et al (22) demonstrated a slight increase in diameter measurements with angiography compared to IVUS and perfusion fixation measurements. In previous studies with phantom models, IVUS demonstrated excellent correlation to actual phantom measurements (23,24). For this reason, we chose to use IVUS rather than perfusion fixation as our reference standard.

In a previous study of CO_2 angiography versus angiography with ICM in a flow model, Moresco et al (17) demonstrated that CO_2 overestimated vessel measurements compared to IVUS. Also, CO_2 failed to opacify the nondependent iliac limb of the flow model. This is in contrast to previous results with contrast angiography in living systems (18–21).

Our results indicate that both CO_2 and ICM angiography underestimate vessel sizes compared to IVUS. In addition, there is no significant difference between CO_2 angiography measurements and ICM angiography measurements. Size underestimation was greater in the iliac arteries for both CO_2 and ICM. One explanation for this is that the marker catheter was in the aorta and not the iliac arteries. Because iliac arteries lie in a different plane than the aorta, magnifications for these vessels are different than the magnification of the marker catheter. Despite the significance of the difference ($P = .038$), the magnitude of the difference is very small (67.9% DSA/IVUS ratio for iliac arteries and 71.4% DSA/IVUS ratio for the aorta). Therefore, both CO_2 and ICM underestimated vessel diameter by approximately 30% in the iliac arteries and aorta.

With CO_2 injections, the size of the dependent iliac artery was more greatly underestimated than it was with ICM injections (66.3% ± 4.8% vs 70.3% ± 5.4%). This approached significance ($P = .051$) and can be explained on the basis of CO_2's buoyancy. CO_2 floats on blood, so it will tend to fill the nondependent vessels more so than the dependent vessels. However, in this experiment, CO_2 injections filled both the dependent and nondependent iliac arteries and the magnitude of the difference was very small. The CI for these data include 70% undersizing for both CO_2 and ICM.

It was notable that hand-injected CO_2 underestimated vessel size less than injections with a prototype CO_2 injector. We used the CO_2 injector in an attempt to standardize our injections. Hand injections were used because, midway through the experiment, the CO_2 injector failed to reliably inject contrast material without causing significant pain in the animals. We believed that it was because blood backed up into the tubing connected to the injector and caused the formation of carbonic acid, which can be painful on injection. When the catheter is maintained without saline solution in it, no water contacts the CO_2 to form carbonic acid, and therefore the injections cause no pain in the pigs. Despite this discovery, we were unable to reliably use the CO_2 injector in the last five pigs, so 35 mL of CO_2



a. b. c.

d. e. f.

Figure 1. Arteriography and IVUS measurements: CO_2 **(a)** and ICM **(b)** in the PA projection. Measurements were made every 2 cm from the renal arteries to the distal iliac arteries. As an example, measurements at position 8 (arrow) were 8.9 mm for CO_2 and 8.9 mm for ICM whereas the measurement with IVUS **(c)** was 11.1 mm × 11.3 mm. With the animal in the LAO position, CO_2 **(d)** and ICM **(e)** measurements were obtained. In the dependent iliac artery, the measurement was 5.3 mm at position 14 (open arrow) for CO_2 and 4.8 mm for ICM whereas the measurement with IVUS **(f)** was 7.8 mm × 7.1 mm.

was hand injected for each CO_2 study in these animals. With hand injections, CO_2 underestimated vessel size by 71.7% ± 1.7%, whereas the injector underestimated size by 64.3% ± 2.3%. This suggests an approximate 70% undersizing with hand-injected CO_2, which is not significantly different than undersizing with use of ICM.

In one animal, severe spasm was noted during the IVUS phase of the PA projection. This continued throughout the procedure. The analysis was repeated with these data excluded from the set and no significant change was noted in the data set or the difference between CO_2 or ICM.

In conclusion, CO_2 and ICM both underestimate vessel size by approximately 70% in this animal model. This suggests that CO_2 may be used as readily as ICM for measurements for the purpose of intervention. Both contrast agents underestimate vessel sizes compared with IVUS. Because CO_2 and ICM both underestimate vessel size by approximately 70%, no correction factor is needed to measure vessel size with CO_2 injections as long as the volume injected is sufficient to opacify the vessel to be measured.

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