Carbon Dioxide Angiography in Lower Limbs: A Prospective Comparative Study with Selective Iodinated Contrast Angiography

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This was a prospective comparison of the accuracy and image quality of carbon dioxide digital subtraction angiography (CO₂ DSA) and iodinated contrast digital subtraction angiography (ICDSA) in evaluating lower extremity arteries and patient tolerance of the procedures. Selective DSA was performed in 14 Taiwanese patients who were diagnosed with peripheral artery occlusive disease (PAOD). Both contrast materials were administered through mechanical injectors. Post-processing of the image used pixel shifting. Images of vessels were divided into 22 anatomic segments and evaluated by two experienced radiologists. A four-point scale was used to classify diseased vessels. Two interpreters rated the CO₂ DSA image against the ICDSA image on a three-point scale. Patient tolerance was assessed from verbal descriptions. Cohen’s kappa was used to determine interobserver agreement and descriptive statistics were used to summarize patient experience. Interobserver agreement ranged from fair to excellent, with most being good or excellent. Three patients (21.4%) could not tolerate the whole procedure and nine patients (64.3%) reported discomfort during the CO₂ DSA procedure. CO₂ DSA image quality was better for the thigh than the distal runoff and pelvic regions. Our results showed that selective CO₂ DSA cannot replace ICDSA as a routine diagnostic tool for PAOD because it does not give images of comparative quality.

Key Words: digital subtraction angiography, contrast media, carbon dioxide, iodine, arterial occlusive diseases

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Iodinated contrast materials are considered the gold standard for conventional angiography to evaluate pathology in vascular structures. However, they can be associated with hypersensitivity and contrast material-induced nephrotoxicity, especially in patients who have a history of abnormal renal function and diabetes mellitus [1,2]. Because of these complications, carbon dioxide (CO₂) has been used as an alternative contrast material. CO₂ is a highly dissoluble natural gas (approximately 20 times more dissoluble than oxygen in serum) that can be rapidly dissolved in the blood and removed through the lungs [3]. Unlike iodinated contrast materials, CO₂ causes no hypersensitivity or nephrotoxic effects [4,5]. As a result, clinicians have used CO₂ digital subtraction angiography (DSA) in visceral, renal, and extremity arteries to detect aneurysms, renovascular stenosis, and extremity ischemia [6,7]. Back et al used CO₂ to optimize vascular imaging of neoplasms and assist in detecting occult gastrointestinal bleeding [8]. Others used CO₂ to facilitate intervention procedures such as transjugular intrahepatic portosystemic...
shunt procedures [9,10], angioplasty and stent placement [11,12], endovascular angioscopy, and laser recanalization [13,14].

This paper reports a prospective study that compared CO₂ DSA and iodinated contrast digital subtraction angiography (ICDSA) in patients who had peripheral artery occlusive disease (PAOD) in terms of diagnostic accuracy, image quality, and patient tolerance to the two contrast materials.

**MATERIALS AND METHODS**

**Patient population**
This study was conducted in a metropolitan area of Taiwan from April to October 2001. All patients had a clinical diagnosis of PAOD. None had intracardiac right-to-left shunting, severe chronic obstructive pulmonary disease, or diagnosis of PAOD. None had intracardiac right-to-left shunting, severe chronic obstructive pulmonary disease, or other contraindications to CO₂ DSA.

**Procedures**
All patients underwent both ICDSA and CO₂ DSA after they learned the details of the study, the potential risks, and gave informed consent.

ICDSA of the pelvic and lower extremity vessels was performed using a standard angiography unit (MultiDiagnost Image Intensified Fluoroscopic X-Ray System, Philips Medical Systems, Best, Netherlands). Because nonselective injection was expected to be inadequate for patients who had severe peripheral vascular disease, especially in the distal runoff [15–17], an optimized diagnostic angiographic procedure was adopted as the standard [17]. Each patient was given normal saline 50–100 mL/hour for 12 hours intravenously before and after the procedure to maintain adequate hydration. Bilateral lower extremity arteriography was performed after puncturing the common femoral artery on the right side. A 4-Fr Cobra catheter (Cook, Bloomington, IN, USA) or 4-Fr RIM catheter (Cook) was advanced through the aortic bifurcation into the common iliac artery and then into the common femoral artery to study the contralateral limb. Once this was completed, the catheter was pulled back for ipsilateral imaging.

Iodinated contrast medium was administered by a mechanical injector (Angiomat 6000; Liebel-Flarsheim, Cincinnati, OH, USA). Because selective injection of contrast medium can improve image quality and a suitable lower contrast material concentration can reduce movement artifacts [17], we used 35% non-ionic contrast medium (Iopamiro 370, Bracco, Milan, Italy; or Ultravist 300, Schering, Berlin, Germany) diluted with normal saline at a 1:1 ratio. Table 1 gives information on the contrast volume, injection rates, and injection sites. While filming the feet, the X-ray beam was perpendicular to the interosseous membrane to splay the arterial trifurcation. No external bandage was applied to the lower extremities, thus avoiding pseudo-occlusion of the arteries. Appropriate collimation and edge filters were also chosen, but no peripheral vasodilator was used.

CO₂ DSA was performed immediately following ICDSA, using the same angiographic machine. The imaging procedure was similar to that of ICDSA, except that CO₂ gas was injected using a different mechanical injector (Inspect 2005-R; Daum Medical, Schwerin, Germany) at three frames per second. With this injector, users can control CO₂ volume (10–100 mL) and output gas pressure (250–2,000 mbar) during each injection. The injector shows the injection duration by volume and pressure. For a given gas volume and injection duration, users can calculate the flow rate of CO₂ gas. In this study, the gas volume and pressure were adjusted according to vascular segments, image quality, and patient reaction during the examination (Table 1). The rest interval between each injection was 1 to 2 minutes. Because of the characteristic buoyancy of CO₂ gas, patients’ feet were elevated at an angle of 18° to 20° during the CO₂ injection period. Post-processing used pixel shifting.

**Data collection**
In this study, we focused on three areas: diagnostic accuracy, image quality, and patient tolerance of the two contrast materials. For diagnostic accuracy, after masking each patient’s identification, CO₂ DSA and ICDSA images were evaluated by two experienced radiologists. The lower extremity vessels were separated into 22 segments: bilateral common, internal and external iliac, profunda and superficial femoral, popliteal, anterior and posterior tibial, peroneal, dorsalis pedis, and plantar arteries. The two radiologists rated the arterial pathology in each arterial segment as follows: 1 = normal appearance; 2 = stenosis of less than 50% of vessel diameter; 3 = stenosis of 50% or more of vessel diameter; and 4 = total occlusion or no visible vessel. When multiple lesions were present in a single segment, only the most severe lesion was recorded. The two interpreters scored image quality for three anatomic levels: aortofemoral, femoropopliteal, and below the knee. Using ICDSA images as the reference, the interpreters rated CO₂ DSA images on a three-point scale: 0 (equal to ICDSA); –1 (worse than ICDSA but can provide diagnostic information); and –2 (worse than ICDSA and cannot provide diagnostic information).

All discomfort and complications that occurred within the first 2 days after the procedures were recorded. Patient
discomfort is a subjective experience. Thus, only patients’ comparative feelings for both contrast media were recorded. Patients were asked to describe their feelings as well as rate their comparative feelings on a three-point scale: –1 = more discomfort during the CO\textsubscript{2} DSA examination; 0 = equal for both examinations; and 1 = more discomfort during ICDSA examination. Because CO\textsubscript{2} DSA was performed after ICDSA, only the period of acquiring each image was considered to be the examination time. The time spent on puncture, catheterization, and compression after the procedure was excluded.

**Statistical analysis**

Descriptive statistics (%) were used to summarize patient tolerance. Cohen’s kappa was used to assess the two radiologists’ agreement on ratings for diagnostic accuracy and image quality. This statistical approach documents point-by-point agreement and is considered the most stringent in determining observer agreement (or reliability).

**RESULTS**

Fourteen patients were enrolled, nine males and five females, with a mean age of 74.6 years (range, 62–82 years). Patients were able to complete the entire DSA examination process. However, due to intolerance to severe pain, three patients did not complete the CO\textsubscript{2} DSA on one distal leg. Thus, only 11 patients’ images were available to assess image quality at the distal runoff level.

**Diagnostic accuracy**

Cohen’s kappa showed that most interobserver agreements were within the range of 0.6 to 1.0 (Table 2), which suggested good to excellent agreement between the two radiologists. The lowest agreement was in the ratings for ICDSA images of the plantar and posterior tibial arteries (κ = 0.51–0.56) and for CO\textsubscript{2} DSA images of the plantar and internal iliac arteries (κ = 0.51–0.52). The kappa results suggest fair agreement between the two radiologists for these two areas.

**Image quality**

For most comparisons at the aortofemoral level, there was good to excellent agreement (κ = 0.61–0.80). The image quality with CO\textsubscript{2} DSA was comparable to that with ICDSA (Figure 1). However, at the distal runoff level, agreement was lower (κ = 0.23–0.78) (Figure 2). The femoropopliteal level had the greatest proportion of good-quality CO\textsubscript{2} DSA images (64%, 18/28). ICDSA was reportedly superior to CO\textsubscript{2} DSA in 18 of 28 arteries (64%) at the aortofemoral level, 10 of 28 (36%) at the femoropopliteal level, and 16 of 22 (73%) at the distal leg level. Using ICDSA as the standard, CO\textsubscript{2} DSA had a tendency to overestimate stenosis (Figure 3).

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**Table 1. Parameters of carbon dioxide digital subtraction angiography (CO\textsubscript{2} DSA) and iodinated contrast digital subtraction angiography (ICDSA)**

<table>
<thead>
<tr>
<th>Location and projection</th>
<th>Catheter tip</th>
<th>CO\textsubscript{2}</th>
<th>Iodinated contrast medium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Volume (mL)</td>
<td>Gas pressure (mbar)</td>
</tr>
<tr>
<td>Pelvic vessels, PA projection</td>
<td>Common iliac</td>
<td>80–100</td>
<td>700–1,000</td>
</tr>
<tr>
<td>Common and upper femoral, PA projection</td>
<td>Common iliac</td>
<td>80–100</td>
<td>600–800</td>
</tr>
<tr>
<td>Lower superficial femoral, PA projection</td>
<td>External iliac</td>
<td>50–100</td>
<td>400–600</td>
</tr>
<tr>
<td>Popliteal artery and trifurcation, PA projection</td>
<td>External iliac</td>
<td>50–100</td>
<td>400–600</td>
</tr>
<tr>
<td>Distal leg, PA projection</td>
<td>External iliac</td>
<td>50–100</td>
<td>400–600</td>
</tr>
<tr>
<td>Ankle and foot (dorsalis pedis and plantar), true lateral</td>
<td>External iliac</td>
<td>50–100</td>
<td>400–600</td>
</tr>
</tbody>
</table>

PA = posterior–anterior.
Figure 1. Right lower leg images, from common femoral artery to trifurcation, in a 74-year-old man with the chief complaint of right leg claudication. CO₂ DSA (right) shows similar image quality to that of ICDSA (left). Arrows = correspondent narrowing; arrowheads = overestimate of narrowing in CO₂ DSA; white arrow = misdiagnosed as patent vessel due to incomplete pixel shift.

Table 2. Cohen’s kappa for diagnostic accuracy

<table>
<thead>
<tr>
<th>Artery</th>
<th>Interobserver agreement (Reader 1 vs 2)</th>
<th>Intraobserver agreement (ICDSA vs CO₂ DSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICDSA</td>
<td>CO₂ DSA</td>
</tr>
<tr>
<td>Common iliac</td>
<td>0.70</td>
<td>0.69</td>
</tr>
<tr>
<td>External iliac</td>
<td>0.87</td>
<td>0.64</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>0.85</td>
<td>0.51</td>
</tr>
<tr>
<td>Profunda femoral</td>
<td>0.74</td>
<td>0.71</td>
</tr>
<tr>
<td>Superficial femoral</td>
<td>1.00</td>
<td>0.86</td>
</tr>
<tr>
<td>Popliteal</td>
<td>0.72</td>
<td>0.86</td>
</tr>
<tr>
<td>Anterior tibial</td>
<td>0.74</td>
<td>0.91</td>
</tr>
<tr>
<td>Peroneal</td>
<td>0.69</td>
<td>0.67</td>
</tr>
<tr>
<td>Posterior tibial</td>
<td>0.56</td>
<td>0.89</td>
</tr>
<tr>
<td>Dorsalis pedis</td>
<td>0.95</td>
<td>0.82</td>
</tr>
<tr>
<td>Plantar</td>
<td>0.51</td>
<td>0.52</td>
</tr>
</tbody>
</table>

ICDSA = iodinated contrast digital subtraction angiography; CO₂ DSA = carbon dioxide digital subtraction angiography.

Patient tolerance

Patients reported discomfort including a mild to moderate pricking in the lower limb (n = 4), a smarting sensation in the lower limb (n = 3), a hot sensation (n = 1), abdominal cramp (n = 1), and tenesmus (n = 1) with CO₂ injection. CO₂ DSA was stopped in three patients because they could not tolerate intense pain in the lower legs. In most cases, the discomfort diminished 30 to 60 seconds after injection of CO₂ was stopped. The patient who complained of tenesmus developed diarrhea about 2 hours after the examination. The patient with a moderate pricking sensation had mild leg swelling the following day, which resolved 2 days later. Nine patients felt more discomfort during CO₂ DSA than ICDSA. The other five patients felt no obvious difference except for a hot sensation during the ICDSA procedure. Overall, the examination time for CO₂ DSA was 10 to 15 minutes longer than that for ICDSA. No dyspnea or general reactions were noted after each injection of CO₂ gas, even in the patient who received a total of 1,300 mL. The total CO₂ gas volume given to each patient ranged from 760 to 1,300 mL, with an average of 920 mL.

Discussion

In this study, we examined CO₂ DSA and ICDSA images from 14 PAOD patients and the subjective experiences of patients during angiography to assess the potential of CO₂ as an alternative contrast material for angiography. Two deaths have been reported with CO₂ DSA, due to acute air pulmonary embolism caused by venous administration of
A major problem with CO₂ DSA in this study was that patients experienced a higher degree of discomfort than with ICDSA. Nine patients (64%) reported feeling discomfort, compared to discomfort rates of 10% or less reported in the literature [7,18]. Three patients experienced intense pain in the lower legs that caused termination of the procedure, similar to Diaz et al’s findings [19]. Patients in our study reportedly felt less discomfort when the volume of each injection of CO₂ gas was reduced from 80–100 mL to 40–60 mL, which is consistent with the literature [20].

CO₂ gas pressure and volume, and anatomic level influenced CO₂ DSA image quality. With an identical volume of 100 mL, the image quality with 600 mbar at the aortofemoral and femoropopliteal levels was better than that with 300 mbar. This difference may be caused by more gas fragmentation at low gas pressure. Nonetheless, there was no significant difference between 600 mbar and 800 mbar of CO₂ injection pressure (Figure 4). In contrast, no significant difference in image quality was found between high and low gas pressures in the regions below the knee. These findings seem to suggest that for high image quality, it is desirable to reach the gas pressure threshold. Kerns et al suggested that the key to acquiring good image quality with CO₂ DSA is to completely replace the intraluminal blood with CO₂ [3]. Fragmentation occurs when insufficient gas pressure cannot push the blood column out of the imaging vessel segment. This is why higher CO₂ gas pressure is needed to obtain good image quality in high blood pressure regions (e.g. aortofemoral and femoropopliteal). Our experience suggests that 600 to 700 mbar at a flow rate of 35 to 40 mL/second could be the pressure threshold for the upper anatomic levels, and 400 to 500 mbar at a flow rate of 26 to 30 mL/second for below the knee.

Figure 2. CO₂ DSA image quality according to anatomic levels (A) and readers (B). Image quality was assessed using the following scale: 0 = equal to ICDSA; –1 = worse than ICDSA but can provide diagnostic information; –2 = worse than ICDSA and cannot provide diagnostic information.

A large volume of CO₂ gas and room air contamination [18]. We found no general reaction with iodinated contrast medium or CO₂ injection. With injection of an average of 920 mL of CO₂ gas, no respiratory or neurologic abnormalities were noted in our patients. CO₂ angiography is probably a relatively safe procedure, especially when CO₂ gas is administered to arteries with a mechanical injector [8].

Figure 3. Distribution of narrowing estimation. Stenotic grade on CO₂ DSA was subtracted from that on ICDSA (stenotic grades 1 to 4, from normal to total occlusion). Negative values mean underestimation of the stenosis, positive values mean overestimation of the stenosis, and zero means no estimation difference using ICDSA as reference. CO₂ DSA tends to over-estimate stenosis. CIA = common iliac artery; EIA = external iliac artery; IIA = internal iliac artery; PF = profunda femoral artery; SF = superficial femoral artery; POP = popliteal artery; AT = anterior tibial artery; PER = peroneal artery; PT = posterior tibial artery; PED = dorsalis pedis artery; PLA = plantar artery.
Gas volume also affects image quality, and seems to have a greater impact than gas pressure for images of distal segments. We found that with the same gas pressure (500 mbar), a large CO₂ gas volume (100 mL) produced better image quality than a small volume (40–50 mL) in distal low-pressure regions (e.g. below the knee). The improvement in image quality is probably due to the fact that once gas pressure reaches its optimal level to replace the intraluminal blood, the larger the CO₂ gas volume (or the longer the injection duration of CO₂ gas), the longer the vascular segment occupied by CO₂ gas.

Another phenomenon observed in this study is that CO₂ DSA image quality in distal segments degrades more when there is longer segmental occlusion or more diffuse stenosis in the upper vascular segments (Figure 5). When a slow blood flow was noted (which could be due to poor cardiac output), the image quality of below-the-knee segments decreased. The same situation was observed even when there was only short segmental occlusion in the upper portion. The longer the intra-arterial CO₂ is in contact with the blood, the more it dissolves in the blood, resulting in decreased image quality [21]. This may also explain why there was relatively compromised image quality in the distal leg (27% equivalent image quality compared to ICDSA) in this study.

Bowel gas was also a factor that degraded pelvic CO₂ DSA image quality (36% equivalent image quality compared to ICDSA) (Figure 6). Two methods may improve the quality of images affected by bowel gas. First, intravenous administration of an anticholinergic drug, such as hyoscine-N-butylbromide, can inhibit bowel loop peristalsis. Second, application of an abdominal compression band pushes the bowel loops upward out of the pelvis.

Finally, CO₂ DSA had a tendency to overestimate stenosis in this study, which is consistent with the literature [19,21]. This might be due to incomplete CO₂ filling in the lumen of vessels and the fragment phenomenon. CO₂ DSA is influenced by movement, so the images for all patients were...
post-processed using pixel shifting and remasking. Although this modification is reasonable, it makes the CO₂ DSA post-processing time longer than that for ICDSA. As discussed earlier, a major problem with CO₂ DSA is patient discomfort during the examination. A rest period between each CO₂ gas injection is necessary to reduce discomfort, and elevation of patients’ legs is needed to obtain good image quality. A longer examination time for CO₂ DSA, even by only 10 to 15 minutes, is a shortcoming. All of these make CO₂ DSA a more complex procedure than ICDSA.

Limitations and future directions

Due to the small number of patients, the findings of this study cannot be generalized to every case. Further investigation with more patients is needed to confirm the relationship between the volume and pressure of CO₂ injection and image quality, and the relationship between CO₂ volume and patients’ pain tolerance. In addition, image stacking was not performed because the angiographic machines available at the time of the study did not have this capability. This might be partially responsible for the poor image quality in the distal runoff [8]. More recently, we have used a new angiographic machine equipped with the stacking function (Advantx LCN+; GE Medical Systems, Milwaukee, WI, USA) (Figure 7). With this machine, we were able to eliminate fragmentation and obtain good image quality with a smaller amount of CO₂ gas. The use of such a machine is worth further exploration since it reduces patient discomfort and the pain-induced leg motion artifact.

CONCLUSIONS

Selective CO₂ DSA using a mechanical injector does not yield images of comparable quality to ICDSA. It cannot replace ICDSA as a routine diagnostic tool for PAOD. Discomfort and the gas fragmentation phenomenon in below-the-knee regions and in severe stenosis are major limitations of CO₂ DSA. Overall, when administering CO₂ gas to arteries with a mechanical injector, CO₂ DSA is a safe procedure. It can serve as an alternative procedure and provide sufficient diagnostic information on femoropopliteal vascular segments, especially in patients who have poor renal function or allergic reactions to iodinated contrast medium.

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