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RADIOLOGY—ORIGINAL ARTICLE

Comparison of intra-arterial digital subtraction angiography using carbon dioxide by 'home made' delivery system and conventional iodinated contrast media in the evaluation of peripheral arterial occlusive disease of the lower limbs

KS Madhusudhan,[1] S Sharma,[1] DN Srivastava,[1] S Thulkar,[1] SN Mehta,[2] G Prasad,[3] V Seenu[2] and S Agarwal[2]

Department of [1]Radiodiagnosis, [2]Surgery and [3]Anesthesiology, All India Institute of Medical Sciences, New Delhi, India

KS Madhusudhan MD; **S Sharma** MD, FRCR; **DN Srivastava** MD; **S Thulkar** MD; **SN Mehta** MS; **G Prasad** MD; **V Seenu** MS; **S Agarwal** MS.

Correspondence
Dr Sanjay Sharma, Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi 110029, India.
Email: drssharma@hotmail.com

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Summary

To prospectively compare the feasibility, safety and diagnostic role of carbon dioxide (CO_2) digital subtraction angiography (DSA) using a 'home made' delivery system with iodinated contrast medium (ICM) DSA in the evaluation of peripheral arterial occlusive diseases (PAOD) of lower limbs. Twenty-one patients (27 limbs; all men; mean age, 47.6 years) who presented with PAOD of lower limbs underwent DSA using both intra-arterial CO_2 and ICM. Conventional ICM DSA was performed first and used as gold standard. Carbon dioxide was then injected by hand using a locally improvised home made plastic bag delivery system. Patient tolerance was assessed subjectively. Arteries from aortic bifurcation to the ankle were independently evaluated by two radiologists and graded for stenosis using a five-point scale. For each patient, the quality of CO_2 DSA images were compared with the corresponding images of ICM DSA and an overall grade of 'good', 'acceptable' or 'poor' was assigned. Cohen's kappa coefficient was used to determine inter-observer agreement. Carbon dioxide opacified 86.2% (188/195) of major arteries and depicted stenosis adequately in 84.5% (191/226) of arterial segments. A good or acceptable image quality of CO_2 DSA was obtained in over 95% of patients. Infrapopliteal arteries were inadequately visualized. Mild pain was seen in six (28.6%) patients with both contrast agents; one patient developed severe pain during CO_2 DSA. Inter-observer agreement was good ($k > 0.75$) at 70% of the segments. Administration of CO_2 into lower limb arteries is well tolerated. Carbon dioxide DSA using the locally improvised home made delivery system is a feasible and safe alternative to ICM DSA in the evaluation of PAOD. It provides adequate imaging of arteries of lower extremities except infrapopliteal segments.

Key words: angiography extremity; carbon dioxide; contrast medium; digital subtraction angiography; peripheral vascular disease.

Introduction

Peripheral arterial occlusive diseases (PAOD) include a variety of conditions that cause narrowing of arteries, either acutely or gradually. Even though several non-invasive modalities can be employed for evaluation, the digital subtraction angiography (DSA) using iodinated contrast media (ICM) still remains the gold standard in mapping the extent and location of arterial pathology prior to revascularization procedures.[1] However, arteriography using conventional ICM DSA continues to be associated with small but significant risks of contrast-induced nephrotoxicity and allergic reactions. Elderly patients presenting with PAOD often have coexisting renal, cardiac and other medical illnesses that further increase the risk of these complications. Thus, in many patients, much of the risk associated with the management of PAOD is due to the iodinated contrast arteriography itself.

Carbon dioxide (CO_2) gas has been safely used for diagnostic purposes as early as 1914 in the evaluation of peritoneal and retroperitoneal organs.[2] It was subsequently used intravascularly into the right atrium to detect pericardial effusions.[3] Hawkins extrapolated from the venous work and attempted intra-arterial injection of CO_2 in animals and subsequently humans.[4,5] At present, CO_2 gas is used as an alternative to ICM in several diagnostic and interventional techniques.[4]

The gas produces negative contrast because of its low atomic number and density compared to the surrounding tissues. When injected into a blood vessel, CO_2 displaces the blood column, which allows vascular imaging. Digital subtraction angiographic (DSA) technique is necessary for optimal imaging.[5] Carbon dioxide is 20 times more soluble in blood than oxygen and hence dissolves rapidly and is eliminated by the lungs in the first pass. Intravascular CO_2 produces no allergic reaction and causes no nephrotoxicity.[5,6] Its solubility allows larger volumes to be used without adverse effects. It is 400 times less viscous than ICM making hand injections easy. It is also inexpensive. Although there are certain tribulations like explosive delivery of the gas, vapour lock phenomenon, insufficient filling of the arteries causing inadequate visualization and inadvertent injection of room air, these risks/limitations can be overcome by taking appropriate precautions and generally do not cause problems in imaging.[5,6] The use of CO_2 as a contrast agent for arterial imaging can significantly reduce the risk associated with DSA using iodinated contrast. Despite the advantages, the routine use of CO_2 is limited in the radiology community, the reasons being requirement of a proper delivery system, complex technique, less sharp images and tedious post-processing required to improve the appearance of the images.[7–10]

A dedicated CO_2 delivery system for DSA is commercially available (Coject; Angiodynamics, Glens Falls, NY, USA) but is relatively expensive for purchase by routine diagnostic imaging department. There have been sporadic reports of the use of locally improvised CO_2 delivery systems by some authors for vascular diagnostic and interventional work; however, a systematic comparative evaluation of PAOD by ICM and CO_2 DSA using a locally improvised CO_2 delivery system has not been reported.[11–14] The purpose of the present study was to prospectively evaluate the feasibility, safety and role of CO_2 DSA using our home made delivery system in the evaluation of lower extremity PAOD in comparison to the current gold standard of ICM DSA.

Methods

Patients

Over a period of 15 months, 21 consecutive patients (all male; age range 29-79 years; mean 47.62 years) with clinical diagnosis of PAOD, underwent arteriogram of lower limbs (27 total; 15 unilateral; 6 bilateral) using both CO_2 and ICM as contrast agents. The study was approved by the Institutional Review Board of our hospital. Prior written informed consent was obtained before the procedure was conducted in all patients.

All patients clinically suffered from calf or gluteal claudication and nine patients also had rest pain. Patients with cutaneous ulcer (without evidence of venous disease) and gangrenous changes in the limb were also included in the study. The exclusion criteria were severe chronic obstructive airway disease or pulmonary insufficiency, cardiac/renal dysfunction, aortic aneurysm, high prothrombin time (> 4 sec above control), high creatinine levels ($\geq$ 2 mg/dL), history of previous severe contrast reaction to ICM, current pregnancy and refusal to give consent.

Methods

The pre-procedural work-up included a thorough clinical examination, complete blood count and baseline biochemical examination (blood urea, serum creatinine, blood glucose levels and prothrombin time). All patients were subjected electively to DSA after an overnight fast. In all patients CO_2 DSA was performed after ICM DSA in the same sitting. ICM DSA was used as a gold standard. As we did not have a standardized technique for performing CO_2 DSA in our department, we decided to perform ICM DSA first, followed by CO_2 DSA. The DSA was performed using a Seimens Polystar angiography unit (Seimens Medical Systems, Erlangen, Germany).

The access used in all patients was retrograde transfemoral using the standard Seldinger technique. The side with better volume pulse, less symptomatic or asymptomatic side was chosen for femoral puncture under local anesthesia. A 6F arterial sheath was inserted in all patients. Flush aortogram was first performed using a 5F pigtail catheter tip placed at aortic bifurcation. In unilateral limb disease, subsequent evaluation of infra-inguinal arteries was performed selectively using a 5F multipurpose or picard catheter introduced from the contralateral femoral arterial sheath. In patients with bilateral disease, the study was performed with the tip of the pigtail catheter at the aortic bifurcation for both ICM and CO_2 DSA. Subtracted images were acquired at various levels from the aortic bifurcation to the calf. The acquisition frame rate was two per second for above-knee evaluation and one per second for below-knee evaluation both for ICM or CO_2 DSA.

Iodinated contrast medium DSA

The iodinated contrast (Iohexol 300 and 350 mg/mL) was administered using a pressure injector (in bilateral limb evaluation with the catheter tip placed at the aortic bifurcation) or manually (in unilateral limb evaluation with the catheter tip placed selectively). The volume of contrast agent used per patient ranged from 50 to 140 mL (mean 87.4 mL) depending on the number of limbs studied.

Home made CO_2 delivery system

A sterile, disposable plastic bag delivery system was used to perform intra-arterial CO_2 DSA. This assembly is locally improvised and is depicted diagrammatically (Fig 1). It consisted of a regular disposable bag used to collect blood from donors at the Blood Bank. Because the bag is used to transport the gas from the operating room to the DSA suite, we call it the 'transfer bag.' It has a capacity of 300 mL and has inlet and outlet tubes. To fill the bag with CO_2, the inlet tube was connected to the tap of a laparoflator (used for laparoscopic delivery of CO_2 during laparoscopy), which in turn was connected to a cylinder filled with medical-grade CO_2. The laparoflator controls the pressure (fixed at 15 mmHg, equivalent to 1 atmospheric pressure) at which the gas fills the bag like a balloon. The gas was purged three to four times during collection to exclude room air from the bag. Once filled, the inlet port was tied securely with thin wire or tough silk thread before it was disconnected from the cylinder. More than one bag may be filled depending upon the requirement. The transfer bag was subsequently transferred to the DSA suite. It was then suspended on a regular drip stand keeping the tube port end dependent. This position theoretically enables heavier CO_2 to pass into the circuit in preference to air in case of accidental air contamination. The outlet port of this bag was then connected to the transfusion set consisting of the tubing and filter (Fig 1). The filter has pores of 200 μ diameter for the removal of any particulate matter that may be present in the gas obtained from the cylinder. The tubing of a regular intravenous set that comes without an attached filter, which is more easily available, can also be used instead of a blood transfusion set. This tubing was then attached to an angiographic catheter through a single three-way tap assembly. All connections were made carefully under a water seal. The three-way tap was kept strictly in a water bath both while aspirating gas from the bag and while injecting the gas into the patient. We liberally aspirated gas from the bag into a delivery syringe because underwater connections preclude all chances of air contamination. The catheter and tubing assembly were again purged a couple of times with the delivery syringe before the final intravascular injection was administered by hand. The CO_2 gas in the bag was promptly used to eliminate chances of contamination from diffusion by room air. We used the gas in the bag strictly within 30 min of its collection from the cylinder.

Technique of CO_2 injections through an angiographic catheter

All CO_2 DSA injections were made by hand. Initially approximately 10 mL of CO_2 was aspirated from the bag and expelled to fill the tubing with CO_2. Another 5 mL of the gas was used to purge the catheter with the gas to avoid explosive delivery. During injection, the nozzle of the syringe was tilted downwards. Table 1 shows the approximate rate and volume of CO_2 used per injection. The volume of injection mentioned is actually the amount of CO_2 which was aspirated to fill the syringe. A controlled hand injection of the gas in the syringe was made over 1 to 2 seconds.

The extreme buoyancy of the gas causes its accumulation in the non-dependent areas of the vessels. The limbs were therefore elevated by 15–20° above the horizontal to allow adequate filling and hence better visualization of the target vessels. Injections were spaced approximately 2 min apart and the extremities were returned to the horizontal position to improve clearing of

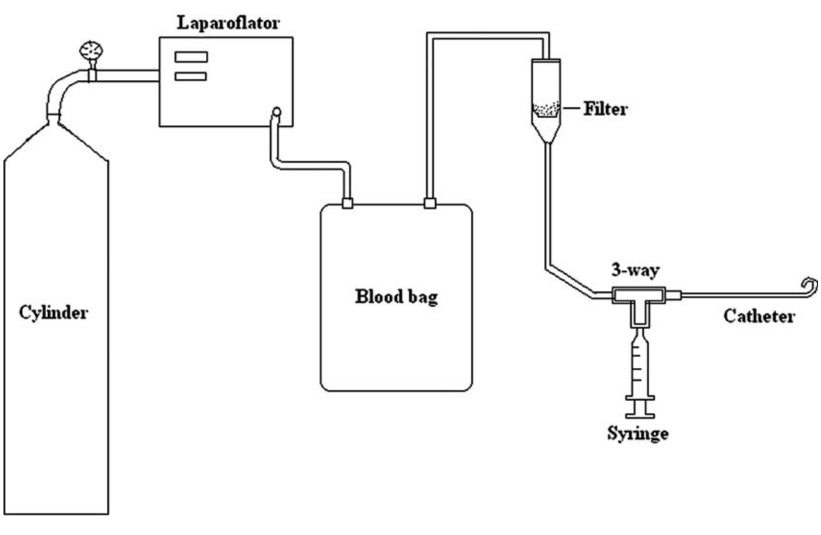

Fig. 1. Schematic line diagram of the simple 'home made' delivery system used for carbon dioxide angiography.

Table 1. Approximate rates and volumes of carbon dioxide (CO_2) injected

Position of catheter tip	CO_2 injected	
	Rate (mL/sec)	Volume (mL)
Aortic bifurcation	25–30	60
Femoral/popliteal artery	15–20	40

the gas and avoid vapour lock. The total volume of CO_2 used from the bag per patient ranged from 150 to 280 mL (mean 213.3 mL).

Complications

Heart and respiratory rates, electrocardiogram and blood pressure monitoring were performed for all patients during the procedure. Any specific complaints from the patient during the procedure were noted. After the investigation the patients were observed for 24 hours and any clinical incidents were recorded.

Evaluation and comparison

A laser printer was used to make hard copies of all representative images. The CO_2 DSA images were post-processed for contrast, brightness and edge enhancement to improve the appearance.

Evaluation and comparison of ICM DSA and CO_2 DSA were conducted independently by two radiologists who did not perform the arteriography procedure.

The arteries of the lower limbs were grouped into five segments: iliac (pelvic); femoral; popliteal; anterior tibial and posterior tibial. Each segment was then graded (I, normal; II, stenosis <50%; III, stenosis $\geq$50% <75%; IV, stenosis $\geq$75% <100%; V, complete occlusion) according to the percentage of stenosis. This was obtained by comparing the vessel diameter at the stenosis to that of the adjacent normal segment excluding any region of post-stenotic dilatation. When multiple lesions were present in a single segment, only the most severe (occlusion > stenosis > normal) was recorded (Fig. 2).

The presence of collaterals and reformation of the artery distal to the obstruction were also assessed. An arbitrary score of 0, 1 or 2 was given for non-visualization of collaterals, visualization of few collaterals and visualization of many collaterals respectively.

The results obtained by CO_2 DSA were then compared with ICM angiography with respect to the quality of images (Fig. 3). The CO_2 DSA images of each patient were given an overall subjective grade of 'good', 'acceptable' or 'poor'. It was considered 'good' when the anatomical details shown were comparable to ICM DSA. An 'acceptable' grade was given when there was some loss of anatomical details, but did not affect the interpretation and assessment of true extent of the abnormality. It was considered 'poor' when there was significant loss of anatomical details, affecting the interpretation.

Statistical analysis was performed using χ^2 test, which provided the sensitivity, specificity and accuracy of the results. The overall quality of the scores was also compared using this method. The inter-observer agreements were estimated based on Cohen's kappa coefficient.

Results

Adverse events

Figure 4 shows the incidence of complications. No major complications requiring intervention were observed during ICM and CO_2 DSA. Mild pain in the limb was seen

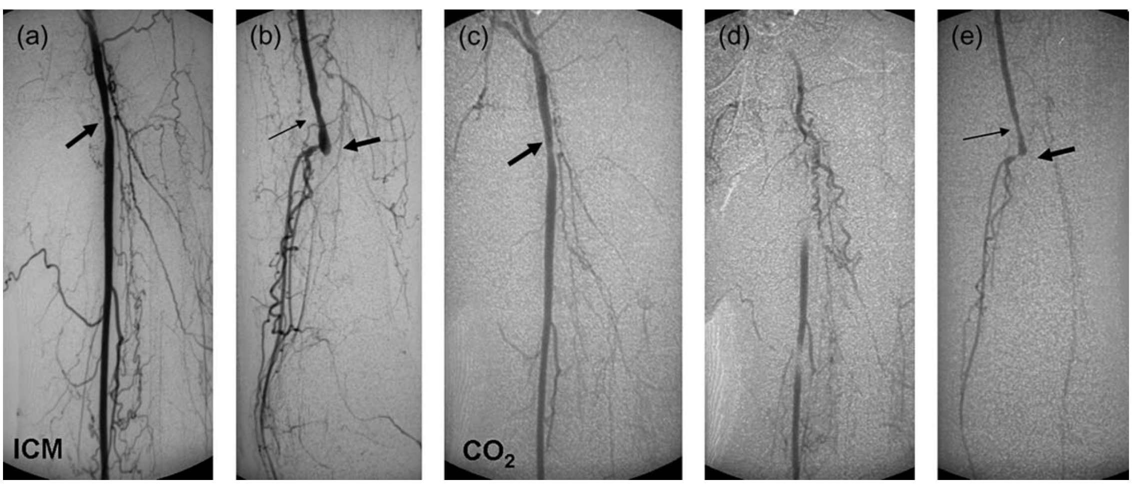

Fig. 2. (a) Iodine contrast digital subtraction angiography (DSA) of a 48-year-old male presenting with intermittent claudication in the left heel and calf of 6 months duration depicts grade III narrowing (arrow) of the proximal superficial femoral artery with corkscrew collaterals. (b) Complete occlusion of distal superficial femoral artery (thick arrow) with collaterals is demonstrated. Note mild irregularity of the artery proximal to the occlusion (thin arrow). (c,d,e) Carbon dioxide DSA of the same patient provides the same diagnostic information.

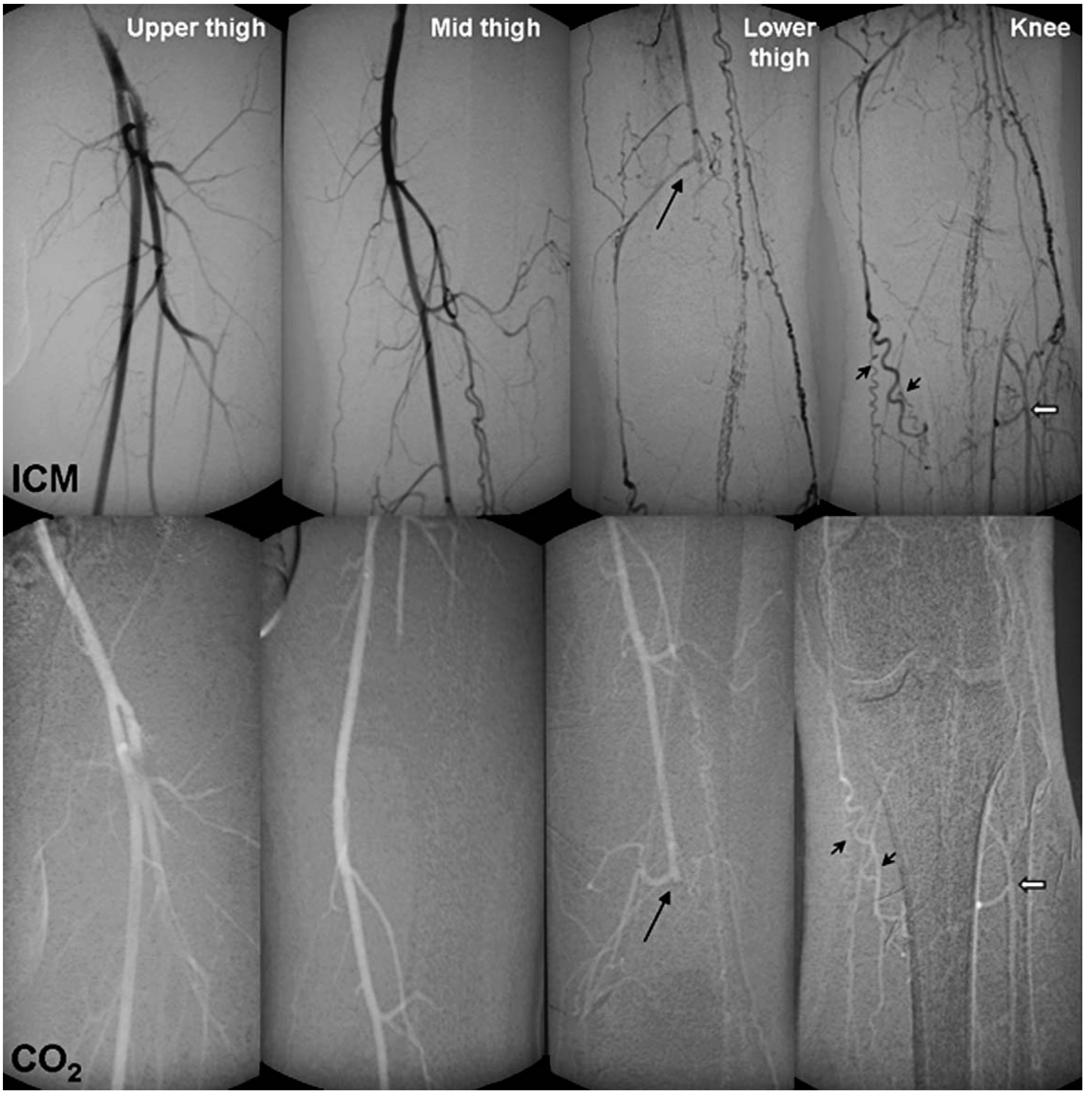

Fig. 3. Angiograms of a 40-year-old male smoker with an ulcer on the dorsum of the left foot of 6 months duration. There is complete occlusion of the distal superficial femoral artery (arrow) on both studies. The segment is faintly opacified by iodinated contrast medium. However, the opacification is better by carbon dioxide due to more selective injection. Corkscrew collaterals (short arrows) and reformed anterior tibial artery (block arrow) are noted on both angiograms.

in six (28.6%) patients during both ICM and CO_2 DSA. Severe pain in the affected limb was noted transiently in one (4.8%) patient during the injection of CO_2, which improved with subsequent injections.

Image quality

Of the 195 major named arteries evaluated (common, external and internal iliac, superficial and deep femoral, popliteal, and anterior and posterior tibial), ICM opacified 188 (96.4%) and CO_2 opacified 168 (86.2%). This excluded segments which were not adequately opacified either due to the presence of arterial sheath, or proximal complete occlusion. The result was statistically significant (Student's *t*-test showed *P*-value of < 0.05).

A total of 113 arterial segments of 27 limbs were evaluated. As these were evaluated by two observers, the total observations made were 226 (113×2). The difference in stenosis grade between CO_2 and ICM DSA at each arterial segment levels are tabulated in Table 2. The table shows that 180 (79.7%) segments were graded the same by both the techniques; 35 (15.5%) were evaluated better by ICM and 11 (4.9%) were demonstrated more clearly by CO_2 DSA. In all, 191 (84.5%) segments were adequately demonstrated by CO_2 DSA. If the infrapopliteal segments are excluded, 145 (91.8%) of the 158

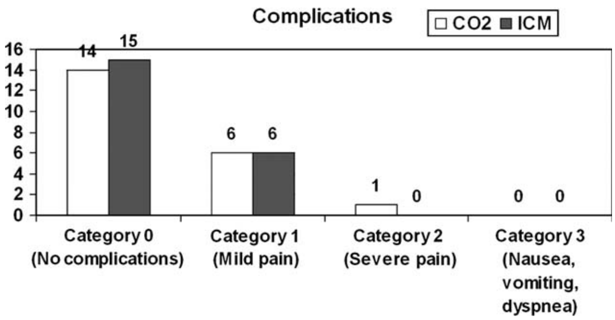

Fig. 4. Bar chart showing the incidence of various complications with carbon dioxide (CO_2) and iodinated contrast medium (ICM) digital subtraction angiography.

Table 2. Score difference between carbon dioxide (CO_2) and iodinated contrast medium (ICM) digital subtraction angiography (DSA) at different segments

Segmental level	Score difference						
	−2	−1	0	+1	+2	+3	+4
Iliac	0	3	63	6	0	0	0
Femoral	0	0	52	0	0	0	0
Popliteal	0	3	24	1	5	1	0
Anterior tibial	0	0	21	4	3	4	4
Posterior tibial	1	4	20	4	1	2	0
Total	1	10	180	15	9	7	4

A difference of 0 means the vessel grading by the two contrast agents was equal. A negative value means that CO_2 graded the vessels better than ICM and a positive value means that ICM graded the vessels better.

segments were effectively evaluated by CO_2. Figure 5 shows that significant stenosis (defined as stenosis of 50% and more) was seen in 42% (95/226) segments on CO_2 DSA and in 34.1% (77/226) on ICM DSA. If infrapopliteal segments are excluded, the percentages of significant stenosis demonstrated on CO_2 and ICM DSA are 24.3% (55/226) and 22.6% (51/226) respectively.

Reformation of the arteries distal to an occlusion was noted in 51.9% (28/54) of limbs on CO_2 DSA and in 50% (27/54) of limbs on ICM DSA. The visualization of the collateral vessels on both the studies is shown in Figure 6. It can be seen that collaterals were better demonstrated on ICM DSA than on CO_2 DSA (74.1% vs 55.6%) (Fig. 7). The overall diagnostic value of CO_2 DSA was as in Table 3. The difference in the overall value between the observers was not significant ($P = 0.41$).

The inter-observer agreement was calculated using the kappa test. There was good agreement ($k > 0.75$) between the observers at most segmental levels. The values were slightly higher for CO_2 DSA, but were not statistically significant.

Discussion

Carbon dioxide is a safe angiographic contrast medium. It is non-toxic, inexpensive, and non-allergic. The gas does not cause any changes in blood osmolarity, blood pH and blood gas values.[10,15] These properties allow it to be used effectively in patients with renal failure and patients who are allergic to ICM.

The delivery system that we use is simple, safe and can be developed easily. The components of the system are easily available in any hospital setup and are inexpensive. The laparoflator we used measured the pressure in the bag electronically, which we presumed to be more accurate than that measured by the mechanical regulator attached to the cylinder. The disposable, sterile, plastic CO_2 delivery bag is filled at a pressure of 15 mmHg (1 atm), at which the volume of CO_2 in the syringe would be equal to the capacity of the syringe and this prevents explosive delivery of the gas.[15] This principle was also applied by Hawkins *et al.*, who used a 1500 mL plastic bag as a reservoir for CO_2.[11] The authors incompletely filled it with gas from the cylinder to reduce its high pressure and keep its volume in the bag at approximately 1500 mL. To fill the reservoir bag with CO_2, we followed the technique described by Hawkins *et al.* [12] In their technique, after the bag was inflated with CO_2 it was emptied by manual compression. The filling/emptying cycle was repeated three times before the final filling with gas. This recycling was performed to remove any air present in the bag and to ensure that only CO_2 remained in the system. The gas in the syringe filled from the bag was also at one atmospheric pressure. However, during injection, as per Boyle's law, the pressure changes,

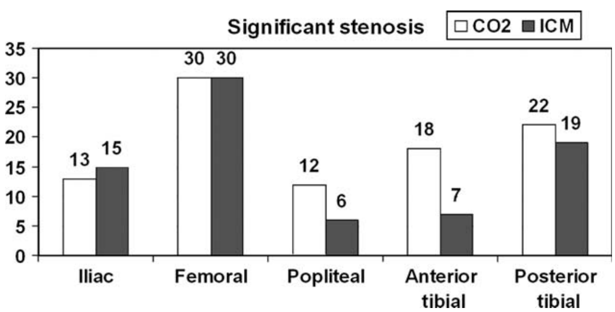

Fig. 5. Chart showing the number of limbs with significant stenosis at different arterial segments. CO_2, carbon dioxide; ICM, iodinated contrast medium.

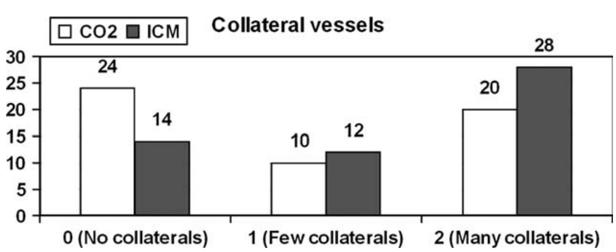

Fig. 6. Chart showing the number of limbs in which different grades of collaterals are demonstrated. CO_2, carbon dioxide; ICM, iodinated contrast medium.

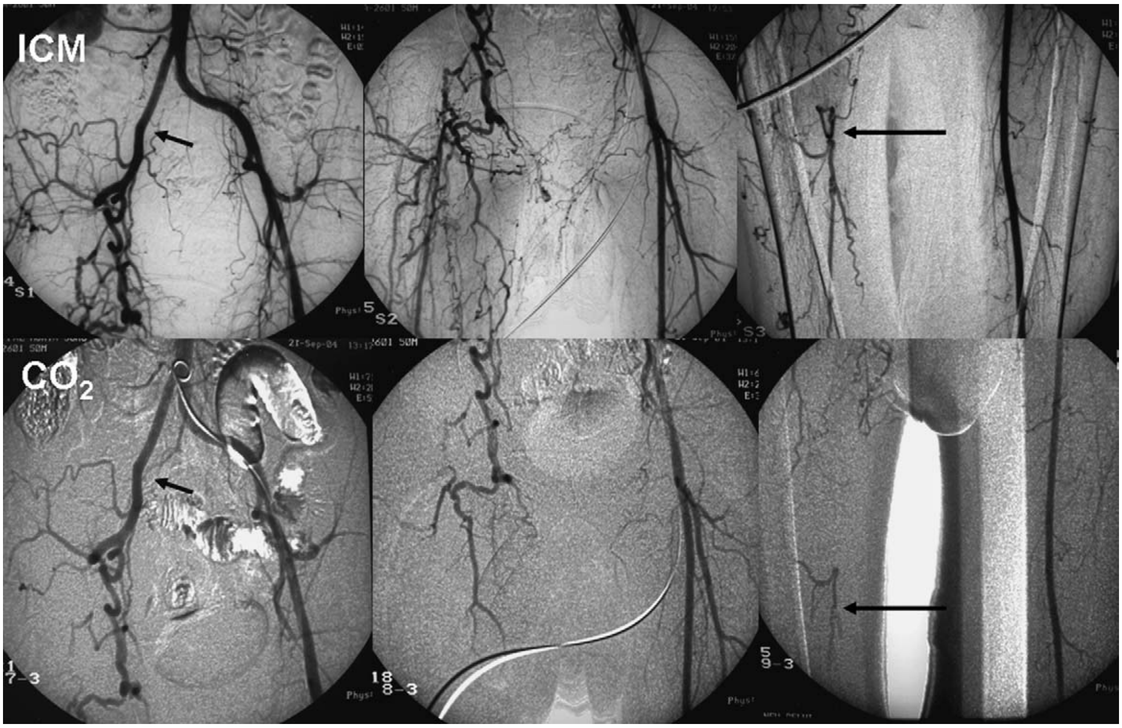

Fig. 7. Digital subtraction angiography (DSA) of a 50-year-old male chronic smoker suffering from rest pain in the right thigh and buttock for 6 months. Complete block of the right external iliac artery at its origin (arrow) with hypertrophied right internal iliac artery is noted on both contrast studies. Collaterals are noted in the right inguinal region, better shown by iodinated contrast medium (ICM) than by carbon dioxide (CO_2). Reformed right distal superficial femoral artery (long arrow) is diffusely narrowed on ICM DSA, but is faintly opacified by CO_2 (long arrow). Left superficial femoral artery is normal on both studies.

leading to a different injected volume. Nevertheless, we made an attempt to perform a controlled injection of the gas by hand.

Contamination of an open syringe filled with pure CO_2 with room air occurs at a rate of 0.02–0.2 mL/sec.[6,16] With a closed system, which was used in our study, the chances of contamination with room air were presumed to be negligible. Peripheral arterial injection of CO_2 gas for arteriography also has the added safety factor of at least one and usually two (including the lung) capillary beds through which the gas must pass before reaching the coronary or cerebral circulation, which eliminates the likelihood of clinically significant gas embolism.[7] We did not encounter any complications related to air embolism in our study.

Various techniques are available for the injection of intravascular CO_2. These include hand injection,[15,17] Leveen pressure inflator[13] and dedicated delivery system by Coject (Angiodynamics, Glens Falls, NY, USA).[9,18,19] The latter equipment is expensive,[13] but reported to be safer.[7,19,20] Kerns *et al.* reported that a lower limit to the volume and rate of injection exists below which the bolus breaks up in the area of the imaging.[5] We used a lower rate and volume compared to other studies, which was probably a reason for inadequate opacification of few distal arteries in our study.[4,10]

As CO_2 produces contrast by causing complete displacement of the blood column in the vessel, each X-ray acquisition may not have the entire vasculature of interest opacified. In order to visualize the entire vasculature, post-processing techniques are often used to stack the individual images on top of another to form a single, composite image.[16] Stacking is a technique similar to maximum opacification wherein multiple negative pixels are integrated into a single composite image.[15] Fragmentation of the gas column is a known problem with the use of CO_2. This especially occurs in the central vessels with diameter exceeding 12 mm.[10,21] In our study, fragmentation of the gas column occurred in three (14.3%) patients (Fig. 8a,b). The reason for this break-up was increased distance between the site of injection and site of interest, which resulted in breaking of the CO_2 column.

Table 3. Overall diagnostic value of carbon dioxide digital subtraction angiography

Overall comparison	No. patients (n = 21)	
	Observer 1	Observer 2
Good	7 (33.3%)	8 (38.1%)
Acceptable	12 (57.1%)	13 (61.9%)
Poor	2 (9.5%)	0 (0%)

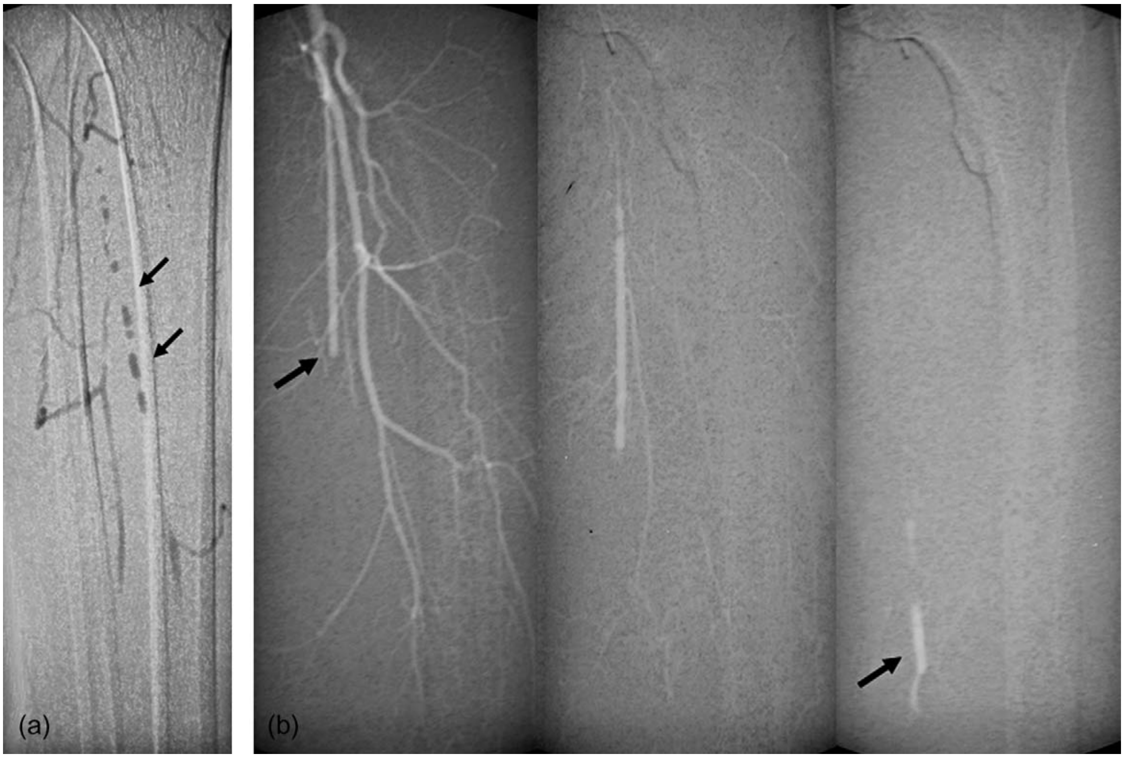

Fig. 8. (a) Fragmentation of the carbon dioxide bolus is seen within the anterior tibial artery (arrows). (b) Slow flow causing absorption of the gas bolus resulting in reduction of its size (arrow) and deterioration of the image quality.

No major complications occurred in our study which required active treatment. One patient complained of severe pain in the affected limb during initial injection of the gas while CO_2 DSA was performed. This could have been due to explosive gas delivery. Six (28.6%) patients complained of mild pain during both CO_2 and ICM DSA studies. However, our procedure was not affected. Seeger *et al.* experienced complications in only two (1.6%) of the 128 patients they studied; one patient with abdominal aortic aneurysm had watery diarrhoea and the other patient had septicemia and abdominal pain due to mesenteric artery ischemia.[7] Other studies also showed similar low incidence of complications attributable to CO_2 DSA.[4,17,19] Spinosa *et al.* described a case of transient mesenteric ischemia which occurred as a complication of intra-arterial CO_2 DSA.[22]

Internal iliac arteries formed a major share (16/27; 59.3%) of the arteries not opacified by CO_2 in our study. This was partly due to the vessel ostium pointing posteriorly and to image worsening by the overlying bowel gas. Glucagon or hyoscine butylbromide (buscopan) has been used by some workers to decrease the effects of bowel motion.[7,19,23] Our study shows that the iliac, femoral and most popliteal arteries were equally well demonstrated by CO_2 DSA as compared with ICM DSA. Over-grading was mostly seen at the infrapopliteal level. Suboptimal efficiency of CO_2 in evaluating infrapopliteal arteries is well documented in literature. In a study by Rolland *et al.* the imaging quality of CO_2 DSA was comparable to ICM DSA at the pelvis in 93% and at the thigh in 74% of 120 arteries studied.[4] Distally the same quality was achieved in only half of the cases. Oliva *et al.* found no significant differences in the mean stenosis values obtained with CO_2 or ICM in any segment for any of the observers.[19] Carbon dioxide inadequately opacified collateral vessels in our study. Although it has been described that CO_2 due to its low viscosity would show collaterals better than ICM, we did not find this.[7,15] Weaver *et al.* also found inadequate imaging of the collaterals and the arterial tree distal to severe lower extremity occlusive disease by CO_2 which forced them to use ICM.[17]

The reasons for inadequate opacification of the arteries and collaterals by CO_2 in our study could be that most patients had complete occlusion of the proximal vessels, which caused slow distal flow. Additionally, in patients in whom aortic injection of CO_2 was used for bilateral lower limbs evaluation, there was fragmentation of the CO_2 gas column, which deteriorated the image quality, especially of the infrapopliteal arteries. Also compared to other studies, the average volume and rates of CO_2 injection in our study were lower. Several authors [4,15,23] have suggested selective arterial injection in cases of suboptimal opacification due to fragmentation. Hawkins and Caridi suggested that the catheter be placed as close as possible to the lesion to improve the filling of the vessel with the gas.[15] They also reported that the use of vasodilators improved distal filling. In addition, in our study, CO_2 demonstrated stenosis in 84.5% of segments and in 91.8% when infrapopliteal segments were excluded. Although the stenosis prediction rate is slightly lower, this can be improved by using proper technique. We feel that in doubtful cases, a small amount of ICM can be used for better delineation of the distal vessels. By this complementary method, the requirement of ICM and hence its potentially toxic effects and costs can be reduced and a definitive treatment can be planned more confidently.

In our study CO_2 demonstrated stenosis in 11 segments (4.9%) better than ICM DSA. Of these, three segments were popliteal and five were posterior tibial assessed in two patients. Both were evaluated with the catheter at aortic bifurcation; one had bilateral proximal superficial femoral artery occlusion and the other had right external iliac artery occlusion. We presumed that the presence of proximal obstruction resulted in dilution of the ICM and consequently the distal arteries (popliteal and posterior tibial) were less clearly outlined and led to their over-grading. However, CO_2, due to its low viscosity, freely diffused across the collaterals and more clearly demonstrated the stenosis. Although ICM DSA was the gold standard in our study, contrast dilution distal to a stenosis is a limitation and may lead to poor opacification of distal run-off vessels.[24] This was an unusual observation in our study. The remaining three segments better graded by CO_2 were iliac arteries, which were better distended by the gas due to its intravascular expansion after exiting from the catheter. Such expansion is known to occur with CO_2 and some times it results in over-sizing of the vessels.[25]

Combining the results of both the observers, we found that over 95% of the CO_2 arteriograms were of good or acceptable quality. Observer 1 found two CO_2 DSA cases (9.5%) (one with external iliac artery occlusion and other with proximal superficial femoral artery occlusion) to be of poor quality due to complete absence of collaterals compared to ICM DSA; observer 2 found them to be of acceptable grade for management purposes. However, this difference was not statistically significant ($P = 0.41$). In a large study by Rolland *et al.*, performance of ICM was judged to be superior in 35%, image quality was identical in 61% and CO_2 angiography was superior in 4%.[4] In the series by Seeger *et al.* 91% of the arteriograms were judged to be of good or excellent quality by the two blinded observers.[7] Only one CO_2 study was found to be inadequate. Hawkins and Caridi obtained 92% diagnostic angiograms using CO_2 alone.[15] However, in the study by Diaz *et al.*, 17 (24.3%) of 70 CO_2 arteriograms were similar to or better than ICM studies as assessed by reader 1 while reader 2 considered eight (11.4%) CO_2 studies to be as good as the ICM DSA.[20]

In addition to CO_2, gadolinium is an important contrast agent used in patients with iodine contrast allergy and renal failure.[26] Gadolinium-based contrast agents have been used in lower-limb arteriography with satisfactory results.[27] Although at the usual low doses it is non-nephrotoxic, higher volumes may lead to osmolar load to the kidneys.[28] Further, there has been an increase in the recent reports of nephrogenic systemic fibrosis (NSF) in patients with renal failure who have been exposed to gadolinium.[29] This fact once again emphasizes the advantage of CO_2 in patients with renal dysfunction. Use of diluted concentrations of ICM (70, 140 and 200 mg/mL) produces diagnostic angiographic images and significantly reduces the incidence nephrotoxic effects.[28] Carbon dioxide, however, is cheaper than gadolinium, does not have the osmolar effects of gadolinium, and unlike diluted iodine contrast, can be used in patients who are allergic to iodine.

There were few limitations in our study. The number of patients in our study was relatively small. As ICM DSA was performed initially in all patients, CO_2 DSA was performed with a prior knowledge of the site and extent of vascular lesions. This led to some bias, which we tried to reduce, if not eliminate, by excluding the radiologist who had performed the study from comparing and evaluating the study after its completion. As injections were administered by hand, we did not have control over the pressure at which the gas was injected. Although ICM DSA was the gold standard, inconsistencies in comparison of DSA of two agents are bound to occur with hand injection and hence the gold standard may be fallaciously abnormal at times. The grading of stenosis in our study was subjective. The results of CO_2 DSA in isolation were not used as a basis for subsequent surgical reconstruction, endovascular intervention or non-operative management. Lack of stacking software in our angiography unit often resulted in tedious image processing. It also required comparison of two to three sequential images of a CO_2 acquisition with a single image of ICM run. The delivery system used resulted in loss of time due to transport of gas from the theatre to DSA suite. This can be avoided if the angio-suite has a CO_2 cylinder and laparoflator.

Conclusion

Carbon dioxide DSA using an inexpensive home made CO_2 delivery system is a safe and informative alternative technique in the evaluation of patients with PAOD of the lower limbs. Adequate opacification of the iliac and femoral arteries can be obtained with proper injection technique. We suggest that CO_2 be used as the initial contrast agent for the evaluation of PAOD in patients with renal failure and iodine contrast allergy. If there is inadequate depiction of a vessel despite selective injection, it can be supplemented with some amount of ICM for better visualization of the vessel in question. For infrapopliteal segment opacification we recommend selective injection as close to the target artery as possible. Delivery of CO_2 for angiograms by this technique is now acceptable amongst our referring clinicians and radiologists. Our study confirmed the previous research findings, but further studies without our limitations are required to firmly establish the role of CO_2 DSA in this subgroup.

References

1. Hodgson KJ. Principles of arteriography. In: Rutherford RB (ed.) *Vascular Surgery*, 5th edn. WB Saunders, Philadelphia, 2000; 286–301.
2. Rautenberg E. Rontgenphotographie der Leber, der Milz, und des Zwerchfells. *Deutsch Med Wschr* 1914; **40**: 1205–8.
3. Paul RE, Durant TM, Oppenheimer MJ, Stauffer HM. Intravenous carbon dioxide for intracardiac gas contrast in the roentgen diagnosis of pericardial effusion and thickening. *AJR* 1957; **78**: 224–5.
4. Rolland Y, Duvauferrier R, Lucas A *et al*. Lower limb angiography: a prospective study comparing carbon dioxide with iodinated contrast material in 30 patients. *AJR* 1998; **171**: 333–7.
5. Kerns SR, Hawkins IF, Sabatelli FW. Current status of carbon dioxide angiography. *Radiol Clin North Am* 1995; **33**: 15–29.
6. Huber PR, Leimbach ME, Lewis WL, Marshall JJ. CO_2 angiography. *Catheter Cardiovasc Interv* 2002; **55**: 398–403.
7. Seeger JM, Self S, Harward TRS, Flynn TC, Hawkins IF Jr. Carbon dioxide gas as an arterial contrast agent. *Ann Surg* 1993; **17**: 688–98.
8. Caridi JG, Hawkins IF Jr. CO_2 digital subtraction angiography: potential complications and their prevention. *J Vasc Interv Radiol* 1997; **8**: 383–91.
9. Kerns SR, Hawkins IF Jr. Carbon dioxide digital subtraction angiography: expanding applications and technical evolution. *AJR* 1995; **164**: 735–41.
10. Bettmann MA, D'Agostino R, Juravsky LI, Jeffery RF, Tottle A, Goudey CP. Carbon dioxide as an angiographic contrast agent: A prospective randomized trial. *Invest Radiol* 1994; **29**: s45–6.
11. Hawkins IF Jr, Caridi JG, Kerns SR. Plastic bag delivery system for hand injection of carbon dioxide. *AJR* 1995; **165**: 1487–9.
12. Hawkins IF Jr, Caridi JG, Klioze SD, Mladinich CRJ. Modified plastic bag system with O-ring fitting connection for carbon dioxide angiography. *AJR* 2001; **176**: 229–32.
13. Snow TM, Rice HA. A simple gas injector of carbon dioxide angiography. *Clin Radiol* 1999; **54**: 842–4.
14. Cronin P, Patel JV, Kessel DO, Robertson I, McPherson SJ. Carbon dioxide angiography: a simple and safe system of delivery. *Clin Radiol* 2005; **60**: 123–5.
15. Hawkins IF, Caridi JG. Carbon dioxide digital subtraction angiography: 26-year experience at the University of Florida. *Eur Radiol* 1998; **8**: 391–402.
16. Back MR, Caridi JG, Hawkins IF Jr, Seeger JM. Angiography with carbon dioxide (CO_2). *Surg Clin North Am* 1998; **78**: 575–91.
17. Weaver FA, Pentecost MJ, Yellin AE, Davis S, Finck E, Teitelbaum G. Clinical applications of carbon dioxide/digital subtraction arteriography. *J Vasc Surg* 1991; **13**: 266–73.
18. Fermand M, Marzelle J, Cormier F, Cormier JM. Aorto-arteriography of the lower limbs using carbon dioxide. *Presse Med* 1994; **23**: 19–22.
19. Oliva VL, Denbow N, Therasse E, Common AA, Harel C, Giroux MF. Digital subtraction angiography of the abdominal aorta and lower extremities: carbon dioxide versus iodinated contrast material. *J Vasc Interv Radiol* 1999; **10**: 723–31.
20. Diaz LP, Pabon IP, Garcia JA, de la Cal Lopez MA. Assessment of CO_2 arteriography in arterial occlusive disease of the lower extremities. *J Vasc Interv Radiol* 2000; **11**: 163–9.
21. Konig T, Krasny T. Gas angiography: measurement of vascular gas filling and evaluation of parameters influencing gas injection using a circulatory system model. *Biomed Tech* 1991; **36**: 266–70.
22. Spinosa DJ, Matsumoto AH, Angle JF, Hagspiel KD, Hooper TN. Transient mesenteric ischemia: a complication of carbon dioxide angiography. *J Vasc Interv Radiol* 1998; **9**: 561–4.
23. Bees NR, Beese RC, Belli AM, Buckenham TM. Carbon dioxide angiography of the lower limbs: initial experience with an automated carbon dioxide injector. *Clin Radiol* 1999; **54**: 833–8.
24. Owen RS, Carpenter JP, Baum RA, Perloff LJ, Cope C. Magnetic resonance imaging of angiographically occult runoff vessels in peripheral arterial occlusive disease. *N Engl J Med* 1992; **326**: 1577–81.
25. Moresco KP, Patel N, Johnson MS, Trobridge D, Bergan KA, Lalka SG. Accuracy of CO_2 angiography in vessel diameter assessment: a comparative study of CO_2 versus iodinated contrast material in an aortoiliac flow model. *J Vasc Interv Radiol* 2000; **11**: 437–44.
26. Rieger J, Sitter T, Toepfer M, Linsenmaier U, Pfeifer KJ, Schiffl H. Gadolinium as an alternative contrast agent for diagnostic and interventional angiographic procedures in patients with impaired renal function. *Nephrol Dial Transplant* 2002; **17**: 824–8.
27. Kaufman JA, Geller SC, Waltman AC. Renal insufficiency: gadopentate dimeglumine as a radiographic contrast agent during peripheral vascular interventional procedures. *Radiology* 1996; **198**: 579–81.
28. Nyman U, Elrnstahl B, Leander P, Nilsson M, Golman K, Almen T. Are gadolinium-based contrast media really safer than iodinated media for digital subtraction angiography in patients with azotemia? *Radiology* 2002; **223**: 311–18.
29. Sadowski EA, Bennett LK, Chan MR *et al*. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007; **243**: 148–57.