The Role of Carbon Dioxide As a Safe Contrast Agent in Endovascular Treatment of Chronic Lower Limb Ischemia in Patients with Renal Impairment or Iodinated Contrast Allergy

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ABSTRACT

Background: *Peripheral arterial disease (PAD) is a common health problem and its risk is higher among patients with chronic kidney disease. The use of conventional iodinated contrast media (ICM) in angioplasty is associated with many hazards like contrast induced nephropathy and iodinated contrast allergy. The morbidity of contrast media is 5% and the mortality is 0.006%. CO_2 has emerged as an alternative or adjuvant to ICM in vascular imaging, as it has many advantages. It is non-allergic, lacks renal toxicity and is a highly soluble gas. When injected into the arteries, CO_2 acts as a negative contrast agent displacing the blood in the arteries and imaging devices identify the density difference between the gas and the surrounding soft tissues. The homemade plastic bag delivery system was introduced as a cheap and effective method for CO_2 delivery.* ***Aim of the work:*** *assessment of the procedural success and complications associated with the use of CO_2 angiography in endovascular treatment of chronic lower limb ischemia in patients with renal impairment or ICM allergy.* ***Patients and methods:*** *Thirty patients complaining of chronic lower limb ischemia, with lesions amenable for endovascular dilatation and have renal impairment or ICM allergy were treated by angioplasty using CO_2 as a main contrast agent, complemented by iodinated contrast when needed. CO_2 angiography was done using he homemade plastic bag delivery system. Patient demographics, clinical details, preoperative and postoperative renal function were recorded. After the procedure the patients were observed for 24 hours for any clinical incidents or endovascular complications. ABI was measured 24 hours following the endovascular procedure. All patients had regular follow up visits at one week and one month for evaluation of the procedure according to Rutherford guidelines.* ***Results:*** *The clinical presentation of the studied cases varied between intermittent claudication in 10 patients and critical limb ischemia in the remaining 20 patients (either as rest pain in 9 patients or trophic changes and minor tissue loss in 11 patients). The angiographic images obtained by CO_2 were of accepted quality to guide the decision in angioplasty procedures in all cases. Hemodynamic success was achieved in all cases with increase of mean ABI from 0.54 ± 0.25 SD before the procedure to 0.91 ± 0.12 SD after it. The mean amount of ICM used was about 13.75 ml ± 5.58 SD and the median was 10.5 ml. Three cases, had ICM allergy, were performed exclusively by CO_2 without the use of ICM. In the 30 angioplasty procedures performed, we encountered 41 arterial lesions, which were classified into iliac, femoral, popliteal or tibial regions by a percentage of 4.9%, 36.6%, 9.8% and 48.7% respectively. We succeeded to dilate 39 of those lesions, so technical and anatomical success was achieved in 95% of lesions. We had no complications related to air embolism in the studied 30 cases. As regard renal function, there was significant decrease in the mean serum creatinine value from 3.35 mg/dl ± 1.36 SD pre-procedural to 3.07 mg/dl ± 1.35 SD post-procedural. Intraoperative nausea and vomiting occurred in two patients which were simply managed by antiemetic drugs with no sequel post-operatively.* ***Conclusion:*** *CO_2 can be used as an alternative to or adjuvant to ICM in patients with renal impairment to decrease the risk of CIN associated with the use of large amounts of ICM and to prevent anaphylactic reactions that may be fatal in patients with ICM allergy.*

Key words: *CO_2 angiography - angioplasty – chronic lower limb ischemia.*

INTRODUCTION

Peripheral arterial occlusive disease is a common problem affecting large sector of the population. According to the National Health and Nutrition Examination Survey (NHANES), the overall prevalence of PAD "defined as an Ankle Brachial Index (ABI) < 0.9" was 4.3% [(1)]. Most of those patients are asymptomatic, while symptomatic patients may present by intermittent

claudication or critical limb ischemia (CLI) in the form of rest pain or tissue loss and gangrene. The risk of PAD is higher among patients with chronic kidney disease (CKD), as patients with CKD are at increased risk for atherosclerosis and cardiovascular diseases. In a study of "The Prevalence and Correlated Factors of Peripheral Artery Disease in Patients with Chronic Kidney Disease"[(2)], it was found that the prevalence rate of PAD in CKD patients is about (17.7%).

Management of CLI involves surgical procedures, endovascular interventions or both (hybrid procedures). The role and the indications of endovascular interventions is increasing every day, as less invasive techniques with less hospital stay and less morbidity and mortality. The use of conventional ICM in angioplasty is associated with many hazards like contrast induced nephropathy (CIN) and dye allergies. The morbidity of contrast media is 5% and the mortality is 0.006%, with no significant difference between ionic and nonionic dyes. Although, CIN is a reversible cause of acute renal failure, it should not be considered as a benign disorder, because in 30% of patients, renal function would not be fully recovered. [(3)] Toprak et al. [(4)] reported that 13-50% of CIN patients who needed renal replacement therapy, may remain on dialysis for the rest of life. Even in cases of CIN with complete recovery of renal function, it will cause more morbidities including: prolonged hospital stay, increased resource utilization, increased risk of CKD and increased in-hospital and long term mortality rate. [(5, 6)] In patients with renal impairment and diabetes mellitus (DM), the nephrotoxicity of conventional contrast medium is increased, and the recommended maximum dose of iodine should not exceed 80 g. [(7- 10)] The risk of CIN increases by increasing serum creatinine. With serum creatinine more than 1.3 mg/dl and more than 1 mg/dl in men and women respectively the risk of CIN will significantly increase. It has been shown that by increasing serum creatinine from 1.2 to 2.9mg/dl the risk of CIN increases from 4% to 20%. [(11)]

Gadolinium was previously suggested as an alternative to ICM in patients with CKD, but after its association with the disease nephrogenic systemic fibrosis (NSF) in 2006, its use as a contrast agent in patients with CKD has significantly declined. [(12)]

Carbon Dioxide (CO_2) has emerged as an alternative to ICM in vascular imaging and in angioplasty, as it has many advantages. It is non-allergic, lacks renal toxicity and is a highly soluble gas. When injected into the arteries, CO_2 displaces blood and imaging devices identifies the density difference between the gas and the surrounding soft tissues. [(13, 14)] The use of CO_2 in radiology has a long history in the evaluation of peritoneal and retroperitoneal organs. Its first use intravascularly was by coincidence when Hawkins unintentionally injected 70 cc of room air into a patient instead of iodinated contrast during a routine celiac axis imaging. [(15)] The celiac axis and its branches were visualized as a negative image with no adverse effects to the patient. Due to his previous knowledge of CO_2 in venous imaging, Hawkins tried intra-arterial injection of CO_2 in animals and then humans. CO_2 is a nontoxic, nonflammable, buoyant (floating), compressible gas that has low viscosity and is produced endogenously. In comparison to O_2 and N_2, CO_2 has the highest molecular weight and is the most soluble gas (20 times more soluble than oxygen). As an endogenously produced gas, it doesn't cause allergy or renal impairment. When injected intravascularly, CO_2 tends to dissolve and is removed by the lung in one pass within about 30 to 60 seconds. Due to this property, there is no limit for the maximum amount of CO_2 that can be used in any angioplasty procedure; making it a very good alternative to ICM in patients with renal impairment or ICM allergy and also in endovascular procedures with high contrast loads in which the use of iodinated contrast has many limitations.

AIM OF THE WORK

The aim of the work was to study the use of CO_2 angiography in endovascular treatment of chronic lower limb ischemia in patients with renal impairment or ICM allergy as regards: success of the procedure and complications.

PATIENTS AND METHODS

This study was conducted at Alexandria Main University Hospital on 30 patients complaining of chronic lower limb ischemia, amenable for endovascular treatment and indicated for intervention (in whom ABI is lower than 0.9), with

associated renal impairment or ICM allergy. Patients were treated by angioplasty using CO_2 as a main contrast agent, complemented by iodinated contrast when needed. Preoperatively, all patients were evaluated by Duplex Ultrasonography of the arterial system. Patients were prepared by loading dose of clopidogrel 600 mg, if not already on clopidogrel.

- **Procedure**

Endovascular procedures were performed under local, regional or general anesthesia according to the patient general condition. The access used in all patients was transfemoral using the standard Seldinger technique. Patients were given 5000 IU heparin intravenous after securing the access before the start of the procedure. Imaging of the arterial tree was done using CO_2 as the main contrast agent complemented by small amounts of dilute ICM when needed; at the sites of lesions or when CO_2 angiograms were not clear enough to guide the decision. Traditional cast iron cylinder filled with medical grade CO_2 was used as source for CO_2 gas connected to a CO_2 regulator (used to control the exit of the gas from the cylinder) with its tap connected to a blood transfusion bag or transfer bag. The outlet port of the bag was then connected to the transfusion set consisting of the tubing and filter which allows passage of particles 0.2 µ or smaller. This tubing was then attached to an angiographic catheter through a single three-way tap assembly. The whole system was purged a couple of times with the delivery syringe before the final intravascular injection to be given by hand. [16] Figure 1 shows a diagram for the homemade delivery system used for CO_2 delivery.

All CO_2 injections were made by hand. We tried to have fixed rate of delivery about 25 ml/sec in each CO_2 injection by using 50 ml syringe, luer lock, and injecting 50 ml over 2 seconds in each injection. The angiographic table was put in Trendelenburg position and the limbs were elevated by 15–20 degrees above the horizontal to allow adequate filling and hence better visualization of the target vessels, due to buoyancy of CO_2. Injections were spaced approximately 2 min apart to improve clearing of the gas and avoid vapor lock. Iodinated contrast, when needed, was diluted by normal saline in a ratio 1:2.

Heart rate, electrocardiogram, pulse oximetry and blood pressure monitoring were performed for all patients during the procedure. Any specific complaints from the patient during the procedure were noted.

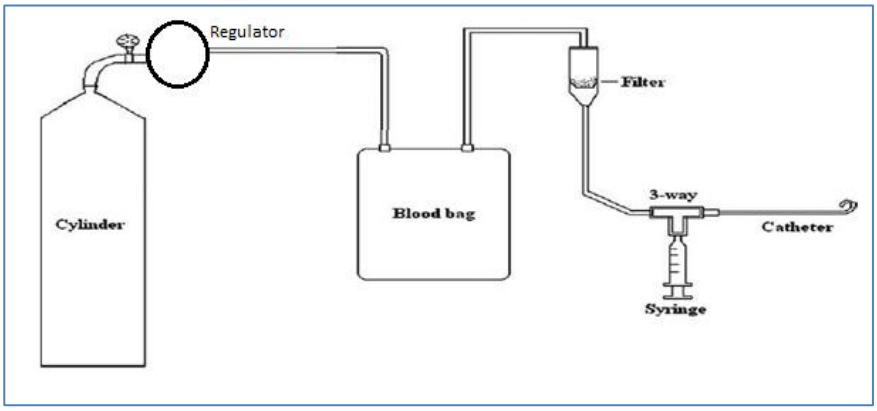

Figure (1): Diagram for home-made delivery system of CO_2. [17]

- **Follow up**

After the procedure the patients were observed for 24 hours and any clinical incidents were recorded. Patients were examined for endovascular complications as: puncture site hematoma, contrast extravasation, renal impairment and distal embolization and ischemia due to gas embolism following the procedure. ABI was measured 24 hours following the endovascular procedure. All patients had regular follow up visits at one week and one month. Evaluation of the procedure followed Rutherford guidelines as following:

- **Technical success**: defined as the presence of antegrade flow through the treated lesion at the termination of the procedure.

- **Anatomical success**: defined as the presence of less than 25% to 30% residual stenosis by angiography at the termination of the procedure.
- **Clinical success:** defined by an improvement by at least one category - if the patient is claudicant - or two categories - if there is any tissue loss- according to the Rutherford classification.
- **Hemodynamic success:** defined as an increase in ABI by 0.10 or greater.

RESULTS

The study was conducted on 30 patients; 19 males (63%) and 11 females (37%). Patients' age ranged from 49 to 70 years with a mean age 60.70 year. 18 patients (60%) were smokers, 26 (86%) were diabetic, 21 (70%) were hypertensive. The indication of CO_2 angiography was renal impairment in 27 patients (90%) and history of ICM allergy in 3 patients (10%). Risk factors in the study population are summarized in table 1.

Table (1): History of risk factors in the study group (n=30).

Risk factor	N (%)
Smoking	18 (60%)
Diabetes mellitus	26 (86%)
Hypertension	21 (70%)
Coronary artery disease	10 (33%)

10 patients presented by intermittent claudication (Rutherford category 3), while the other 20 patients had CLI "9 patients had rest pain (Rutherford category 4) and 11 patients had trophic changes and minor tissue loss (Rutherford category 5)". Of those eleven patients; five patients had gangrenous toe/toes and the other six patients had ischemic ulcers. Also, the mean pre-procedural ABI was 0.54 ± 0.25 SD.

We performed 30 lower limb angioplasty procedures in 30 patients. Those patients had 41 arterial lesions, as some patients had a lesion at a single level, others had lesions in two or three levels. These lesions were classified into iliac, femoral, popliteal or tibial regions. Lesions included 2 iliac stenotic lesions. Also, we had 15 lesions of the superficial femoral artery (SFA), 10 of them were SFA stenosis and the other 5 were short segment of chronic total occlusion (CTO) ≤ 5 cm in length. Only 4 lesions of the popliteal artery were identified, 3 of them were popliteal stenosis, while the other lesion was short segment of CTO < 3 cm. Lastly, 20 lesions of the tibial arteries, 13 of them were stenosis and the other 7 lesions were long CTO ≥ 4 cm. Table 2 shows the sites of lesions according to the arterial segment involved.

Table (2): Distribution of the studied cases according to the site of lesion.

Site and type of lesion	N (%)
Iliac	2 (4.9%)
SFA	15 (36.6%)
Popliteal	4 (9.8%)
Tibials	20 (48.7%)

The angiographic images obtained by using CO_2 as a contrast agent were of very good quality in most of the regions mainly at the sites without arterial lesions. The image quality was better in the iliac and femoral segments and the quality decreased as going distally in the popliteal and tibial segments. The images obtained in one of the studied cases for a patient who had total occlusion in the popliteal artery are reviewed in (figures 2-8) showing that CO_2 can be used as an alternative to ICM in areas without lesions. Also, the segments at which we obtained angiograms by both contrasts showed that CO_2 angiograms are comparable to ICM angiograms.

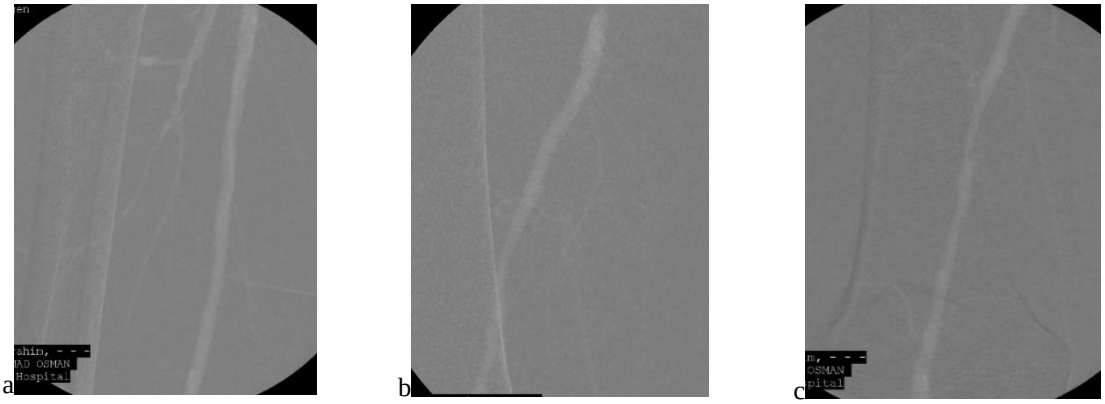

Figure (2): CO_2 digital subtraction angiography of (a) the upper thigh, (b) the middle thigh, (c) the lower thigh; after injection through a sheath in the ipsilateral common femoral artery showing the superficial femoral artery and profunda femoris artery. The arterial tree was well delineated with no lesions, so we didn't take an image with ICM.

Figure (3): CO_2 digital subtraction angiography of the popliteal artery showing total occlusion of the infra-genicular popliteal artery down to the bifurcation, with good delineation of the distal runoff.

Figure (4): passage of the wire in the popliteal artery through the lesion to the anterior tibial artery.

Figure (5): images obtained during inflation of the balloon showing waist of the balloon at the site of total occlusion of the popliteal artery in CO_2 angiogram

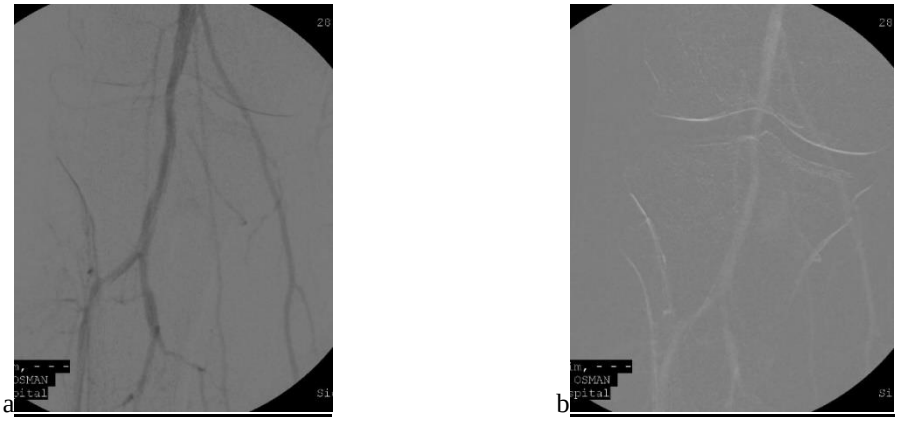

Figure (6): digital subtraction angiography of the popliteal artery bifurcation after balloon dilatation of the occluded segment (a) using ICM angiography (b) using CO_2 angiography

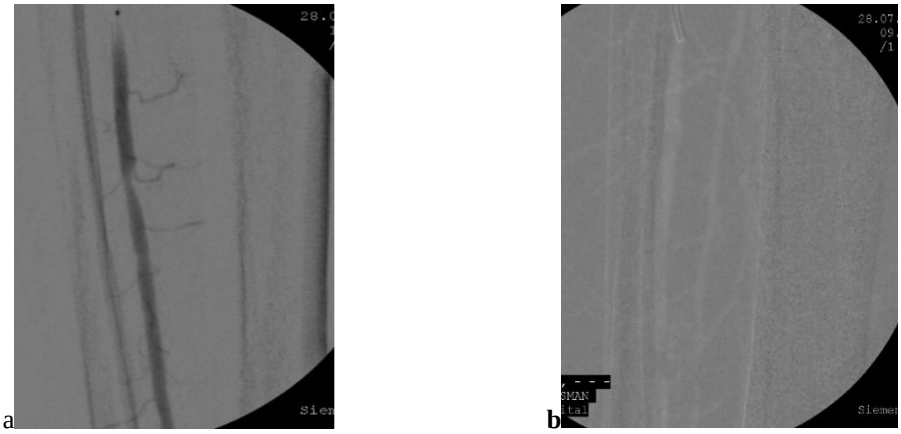

Figure (7): digital subtraction angiography of the middle third of the leg by selective injection in the anterior tibial artery (a) using ICM angiography showing the ATA only (b) using CO_2 angiography showing ATA and peroneal arteries due to central reflux of CO_2.

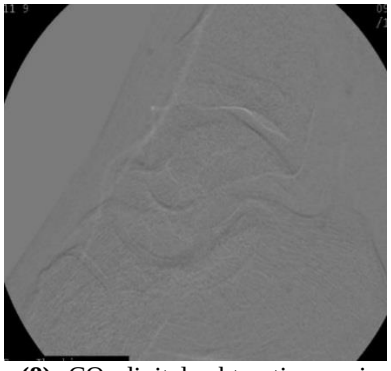

Figure (8): CO_2 digital subtraction angiography at the level of the foot by selective injection of CO_2 in the anterior tibial artery showing the opacification of the dorsalis pedis artery.

The mean amount of CO_2 used was about 386.0 ml ± 180.10 SD and the median was 375 ml, while the mean amount of ICM used was about 13.75 ml ± 5.58 SD and the median was 10.5 ml. Three cases, had ICM allergy, were performed exclusively by CO_2 without the use of ICM.

The measurement of ABI 24 hours following the endovascular procedure and its comparison with the pre-procedural ABI showed ***hemodynamic success*** in all cases. The mean pre-procedural and post-procedural ABI were 0.54 ± 0.25 SD and 0.91 ± 0.12 SD respectively. During the follow up visits, we have found that ***Clinical success*** was achieved in all cases as rest pain disappeared in those who had rest pain, while patients who had debridement of gangrenous

ulcers or amputation of gangrenous toes showed healed or healing wounds. Of the 10 claudicant patients, 7 patients reported disappearance of their claudication and the other 3 patients showed significant increase in the pain free walking distance, as well as, maximum walking distance. Of the 41 arterial lesions presented, we succeeded to achieve ***technical and anatomical success*** in 39 lesions by a percentage of 95 **%**. One patient had total occlusion in the anterior tibial artery that could not be dilated and perforation occurred, but this patient had also SFA stenosis which was successfully dilated and well opacified posterior tibial artery. So, failure to dilate the anterior tibial artery didn't affect the hemodynamic and clinical success in this patient. Another patient had single vessel runoff in the peroneal artery with multiple stenotic segments that were dilated and total occlusion of the posterior tibial artery at its middle third in which passage of wire failed.

We had no complications related to air embolism in the studied 30 cases. Also, the other usual complications of percutaneous angiography were assessed, such as: puncture site hematoma either minor or major hematoma, pseudo-aneurysm, distal embolization and A-V fistula. Only three patients had minor hematoma at the puncture site, managed by local heparinoid creams. One patient had vessel perforation in the tibial vessels. As regard renal function, not only none of our patients had developed CIN, but also measurement of pre-procedural and post-procedural serum creatinine showed significant decrease in the mean serum creatinine value which changed from 3.35 mg/dl ± 1.36 SD pre-procedural to 3.07 mg/dl ± 1.35 SD post-procedural. Intraoperative nausea and vomiting occurred in two patients which were simply managed by antiemetic drugs with no sequel post-operatively. Summary of the complications is shown in table 3.

Table (4): Complications during and after the procedures in the studied cases (n=30).

Site and type of lesion	N (%)
Minor bleeding or hematoma	3 (10%)
Major bleeding or hematoma	0 (0%)
Pseudo-aneurysm	0 (0%)
Distal embolization	0 (0%)
A-V fistula	0 (0%)
Vessel perforation	1 (3.3%)
Renal impairment	0 (0%)
Intraoperative nausea and vomiting	2 (6.6%)

DISCUSSION

This study was conducted to test the application of CO_2 angiography for guiding endovascular intervention for treatment of patients with chronic lower limb ischemia with concomitant chronic kidney disease or iodinated contrast allergy. We focused mainly on the feasibility of the technique and its safety.

The use of iodinated contrast media in endovascular interventions carry the risk of contrast induced nephropathy, the third leading cause of acute kidney injury in hospitalized patients behind decreased renal perfusion and nephrotoxic medications. [18]

In the last two decades, different criteria for defining renal function deterioration were identified in clinical trials. The two most popular were: 25% relative increase of serum creatinine from baseline or an absolute increase of 0.5 mg/dl of serum creatinine from the base. [19] Not only none of our studied cases experienced any deterioration in renal function but also the follow up of the mean serum creatinine of the studied cases postoperatively showed that the mean serum creatinine decreased from 3.35 mg/dl ± 1.36 SD pre-procedural to 3.07 mg/dl ± 1.35 SD post-procedural. We suggest that this decrease in serum creatinine is mostly due to the preparation accompanying the angiographic procedure including good hydration of the patient. Early animal studies by Hawkins and others also showed that CO_2 as an intravascular contrast agent did not affect renal function. Hawkins [20] injected CO_2 into the renal arteries of dogs at a dose of 7 ml/kg to 54 ml/kg. The CO_2 injection decreased the renal blood flow by 11.86% but the renal blood flow returned to the baseline level after 24 hours, while the renal function remained unchanged. Hawkins later went on to demonstrate this in humans as well. Comparing iodinated contrast, gadolinium, and CO_2 in renal insufficient patients, CO_2 was the only agent not demonstrating an elevation in creatinine. [21]

Previous CKD is the most important risk factor for CIN, being the most important cause of delaying or cancelling angiographic procedures. Also, the risk of CIN correlates with the amount of ICM used during the procedure being the most important determinant of it. With the use of CO_2 angiography, there will be no need to postpone any angiographic intervention to improve the

renal functions and limiting the amount of contrast used in diagnostic and interventional vascular procedures will play a very important role in decreasing the risk of contrast induced nephropathy. CO2 angiography, due to its safety on the kidney, can play this role as an alternative to or an adjuvant to iodinated contrast angiography.

The safety of CO_2 angiography has been proven in several studies with more than 30-year history of use in the vascular system. Although the main fear from CO_2 injection intravascularly is air embolization, we had no complications in the current study related to air embolism in the studied 30 cases. Caridi and Hawkins [(22)] studied CO_2 in diagnostic and therapeutic imaging in more than 1200 patients and they had very rare complications. Only 4 cases had complications due to trapping of CO_2 and subsequent vapor lock. One patient with a large infrarenal abdominal aortic aneurysm, required large volumes of CO_2, developed transient diarrhea (less than 24 hours) mostly due to vapor lock within a patent inferior mesenteric artery. Immediate sigmoidoscopy suggested ischemic changes, but mucosal biopsy was normal. After 3 weeks the patient had an aortobifemoral bypass surgery, during which no gross colonic abnormalities were noted. Another two patients had vapor lock in the right ventricular outflow tract during TIPS procedures. Malpositioning of stopcocks caused delivery of large volumes of CO_2 in one patient and room air embolization in another. Hemodynamic compromise, ECG changes and symptoms resolved within 1 minute after lateral decubitus position in each patient. This gives us a lesson that the CO_2 source should not be connected directly to the patient at any time during the procedure. One patient had transient neurologic changes during evaluation of axillo-femoral bypass graft when he raised his head during CO_2 injection, possibly due to cerebral embolization of CO_2. This situation can occur in any vascular bed in case of rapidly repeated injection of large volumes of CO_2 without repositioning and allowing sufficient time for dissolution of CO_2, thus preventing CO_2 from dissolving into adjacent blood. Spinosa et al [(23)] also reported a case of transient mesenteric ischemia in a female patient after CO_2 angiography of the abdominal aorta and iliac arteries. We also had one patient in our study who experienced intraoperative nausea and vomiting, which was simply managed by antiemetic drugs and had no sequel. We have no explanation for this and whether it is related to CO_2 injection or not. More severe complications of CO_2 angiography were reported by Rundback et al [(24)] who described the development of livedo reticularis, rhabdomyolysis, massive intestinal infarction and death after CO_2 angiography in a patient with congestive heart failure.

Besides its role to prevent or decrease the risk of CIN and ICM allergy, the angiographic images obtained by using CO_2 as a contrast agent were of accepted quality for our operators in most of the regions mainly at the sites without arterial lesions. We didn't make a special assessment for image quality in the present study, as we concentrated mainly on feasibility of the technique and its safety as mentioned before. Also, our studied patients had renal impairment or ICM allergy which didn't allow us to take angiographic images using ICM just for comparison of images obtained by both contrasts. The image quality of CO_2 angiograms in the present study was better in the iliac and femoral segments and the quality decreased as going distally in the popliteal and tibial segments. This could be improved by selective injection of CO_2 through a catheter or a balloon, by introducing the tip of the catheter as near as possible to the target area for imaging, by magnification of images and injection of vasodilators prior to injection of CO_2. This finding was similar to other studies in which image quality of CO_2 angiography was assessed. Vincent et al. [(25)] compared the diagnostic value of CO_2 to that of ICM for digital subtraction angiography of the abdominal aorta and lower extremities in a series of 35 patients and he found that CO_2 adequately opacified 89% and iodinated contrast 99% of vessels respectively. ICM images were more superior to that with CO_2 in both aorto-iliac and tibial arteries. Rolland et al. [(26)] studied the use of CO_2 angiography in a group of 30 patients in which he compared CO_2 with ICM angiography at five levels (Pelvis, thigh, knee, leg and ankle). The overall analysis of image quality showed that iodinated contrast images were superior in 35% of analyzed images, the image quality was equal in 61% of images and CO_2 angiography was superior in 4% of images. When they compared images by anatomic levels, it was found that image quality of CO_2 angiograms was comparable to ICM angiograms for the pelvis (93% of images) and it decreased distally scoring

74%, 43%, 53% and 53% at the levels of the thigh, the knees, the legs and the ankles respectively.

CONCLUSION

CO_2 angiography using homemade plastic bag delivery system is an effective, safe and cheap method which can be used in angiography of the aorta and lower limbs for evaluation of peripheral arterial disease; especially in patients with concomitant renal impairment or iodinated contrast allergy. CO_2 can be used as an alternative to or adjuvant to ICM in those patients to decrease the risk of CIN associated with the use of large amounts of ICM in patients with renal impairment and prevent anaphylactic reactions that may be fatal in patients with ICM allergy.

REFERENCES

1. Selvin E, et al; prevalence and risk factors of peripheral arterial disease in the United States: Results from the National Health and Nutrition Examination Survey 1999-2000. Circulation 2004; 110:738-43
2. Ching-Ping Yang, Chin-Yen Tsai, Shu-Chuan Jennifer Yeh. The Prevalence and Correlated Factors of Peripheral Artery Disease in Patients with Chronic Kidney Disease. J Int Med of Taiwan 2010; 21(1): 48-55
3. Madyoon H: Clinical experience with the use of fenoldopam for prevention of radiocontrast nephropathy in high-risk patients. Rev Cardiovasc Med 2 (suppl 1) 2001; S26-S30.
4. Toprak O, Cirit M. Risk factors and therapy strategies for contrast induced nephropathy. Renal Fail 2006; 28: 365–381.
5. Gruberg L, Mintz GGS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary Procedure in patients with preexistent chronic renal insufficiency. J Am Coll Cardiol 2000; 36: 1542-1548.
6. Perazella MA. Radiocontrast-induced nephropathy: an update. Minerva Urol Nefrol 2009; 61: 215-233.
7. Shehadi WG, Toniolo G. Adverse reaction to contrast media: a report from the committee on safety of contrast media of the International Society of Radiology. Radiology 1980; 137:299-302.
8. Schwab SJ, Hlatky MA, Moms KG, et al. Contrast nephrotoxicity: a randomized controlled trial of a non-ionic and an ionic radiographic contrast agent. N Eng. J Med 1989; 320:149-53.
9. Parfrey PS, Griffiths SM, Burnett BJ, et al. Contrast material induced renal failure in patients with diabetes mellitus, renal insufficiency or both. N Eng. J Med 1989; 320:143-8.
10. Lang EK, Foremean J, Schlegel JU, Leslie C. List B A. Mc Cormic Pk. The incidence of contrast medium induced acute tubular necrosis following arteriography. Radiology 1981; 138:203-6.
11. Tepel M., Aspelin, P., & Lumiere, N. Contrast-induced nephropathy; A clinical and evidence-based approach. Circulation 2006; 113: 1799-1806.
12. Grobner T. Gadolinium- a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis. Nephrol Dial Transplant 2006; 21: 1104-1108.
13. Oppenheimer Mi, Durant DM, Stauffer HM, Stewart GH, Lynch PR, Berrera F. In vivo visualization of intracardiac structure with gaseous carbon dioxide: cardiovascular respiratory effects and associated changes in blood chemistry. Am J Phvsiol 1956;186: 325-34
14. Hawkins IF Jr. Carbon dioxide digital subtraction arteriography. AJR 1982; 139:19-24.
15. James G. Caridi, Kyung J. Cho, Christian Fauria, Navid Eghbalieh, Carbon Dioxide Digital Subtraction Angiography (CO2 DSA): A Comprehensive User Guide for All Operators. Vasc. Dis. Manag. 2014; 11(10): E221-E256.
16. Jason Q. Alexander.CO2 Angiography in Lower Extremity Arterial Disease: Techniques for improving safety and efficacy in the use of carbon dioxide as a contrast agent for evaluation and treatment of lower extremity arterial disease. J Endovascular Today 2011;
17. Madhusudhan KS, Sharma S, Srivastava DN, et al. Comparison of intra-arterial digital subtraction angiography using carbon dioxide by "homemade" delivery system and conventional iodinated contrast media in evaluation of peripheral arterial occlusive

disease of the lower limbs. J Med Imaging Radiat Oncol 2009; 53:40-9.
18. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002; 39: 930–936.
19. Sean W. Murphy, Brendan J. Barrett, Patrick S. Parfrey. Contrast Nephropathy. J Am Soc Nephrol 2000; 11: 177–182.
20. Hawkins IF Jr, Mladinich CR, Storm B, Croker BP, Wilcox CS, Akins EW, et al. Short-term effects of selective renal arterial carbon dioxide administration on the dog kidney. J Vasc Interv Radiol 1994; 5:149-154.
21. Spinosa DJ, Angle JF, Hagspiel KD, Kern JA, Hartwell GD, Matsumoto AH. Lower extremity arteriography with use of iodinated contrast material or gadodiamide to supplement CO2 angiography in patients with renal insufficiency. J Vasc Interv Radiol. 2000; 11(1): 35-43.
22. Caridi JG, Hawkins IF Jr. CO2 digital subtraction angiography: potential complications and their prevention. JVIR 1997; 8: 383-391.
23. Spinosa DJ, Matsumoto AH, Angle FH, Hagspiel KD, Hooper TN. Transient mesenteric ischemia: a complication of carbon dioxide angiography. JVIR 1998; 9: 561-564.
24. Rundback JH, Shah PM, Wong J, Babu SC, Rozenblit G, Poplansky MR. Livedo reticularis, rhabdomyolysis, massive intestinal infarction and death after carbon dioxide arteriography. J Vasc Surg 1997; 26: 337-340.
25. Vincent L. Oliva, Neil Denbow, Eric Therasse, Andrew A. Common, Claude Harel, Marie-France Giroux, Gilles Soulez. Digital Subtraction Angiography of the Abdominal Aorta and Lower Extremities: Carbon Dioxide versus Iodinated Contrast Material. JVIR 1999; 10: 723-731.
26. 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 Am J Roentgenol. 1998; 171(2): 333-337.