Research Article

Peripheral Angiography with Carbon Dioxide for Iraqi Patients with Chronic Kidney Disease: A Single Centre Study

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ABSTRACT

INTRODUCTION: Carbon dioxide angiography may provide the opportunity for a safe and successful outcome in patients with peripheral artery disease and chronic kidney disease.

OBJECTIVE: To describe the process and renal safety of CO2 peripheral angiography using a locally produced injector. Renal safety is measured by the rate AKI at 48 hours post-procedure according to the 2012 KDIGO-AKI guidelines definition.

METHODS: A single-centre, case series of 34 Iraqi patients with chronic kidney disease who underwent carbon dioxide angiography and intervention using a locally assembled CO2 delivery system. Patient and procedure-related characteristics were reported, along with pre-and two days post-procedural creatinine recorded to define AKI according to the KDIGO criteria.

RESULTS: Thirty-four patients, 18 females, were recruited. Their mean eGFR was 26.5 + 7.9 ml/min/1.73 m2. The mean delivered CO2 volume was 900 + 239.49 ml. The lesion site was below the knee in 24 patients (70%). Balloon angioplasty was the intervention of choice in 91,3% of the study group. Three patients (8.3%) had AKI 48 hours after the procedure and recovered with hydration. No patient needed renal replacement therapy.

CONCLUSION: CO2-DSA is a safe alternative to traditional iodinated contrast media DSA that could be used and well-tolerated during endovascular management of lower extremity arterial disease.

Key words: CO2 angiography, Peripheral vascular disease, Chronic Kidney disease, Iraq.

INTRODUCTION

In the 1920s, carbon dioxide (CO2) was used as a contrast agent to visualize retroperitoneal structures. In the 1950s, CO2 was used to delineate the right atrium to detect pericardial effusion. With the advent of digital subtraction angiography (DSA) in the 1980s, CO2 has evolved into a safe and useful agent for vascular imaging. [1]

The understanding of physiochemical characteristics of CO2 has led to its application in diagnostic radiology. CO2 constitutes 0.03 % of air, and its partial pressure is usually negligible. With its low density and atomic number, CO2 is regarded as a negative contrast agent compared to body structures used to visualize. Therefore, it absorbs X-rays to less extent than the surrounding blood and the vessel walls. It is highly soluble, 28 times more than oxygen, allowing injection below the diaphragm without clinically significant risks of gas embolism. It is less dense than the contrast media; thus, there would be minimal flow resistance. This makes easy injection through even microcatheters and side ports of the angiography sheath and the stent delivery system. [2]

With the availability of high-resolution DSA, and a reliable gas delivery system, CO2 can be easily injected and provide vascular information and possible intervention comparable to the iodinated contrast media (ICM). [3]

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Lack of anaphylactic response and renal toxicity on using CO2 made it the preferred alternative agent in patients with contrast allergy and renal insufficiency. The lungs would eliminate CO2 in a single pass, permitting nearly unlimited volumes of CO2 separated by 2-3 minutes between each injection. In terms of cost, CO2 is inexpensive in comparison to nonionic iodinated contrast media. [4]

CO2 angiography is limited in specific procedures like neuroimaging, thoracic aorta and coronary circulation because of the potential neurotoxicity and the possible risk of coronary artery gas embolism, myocardial ischemia and arrhythmia. The buoyancy of CO2 causes incomplete filling of the vessels, which may limit the required information. This depends on the vessel size and anatomical location of the area of interest. The compressibility of CO2 and the possible explosive delivery through the injector may contribute to a patient's discomfort and poor image quality. [5]

With these potential benefits and minimum risks, CO2 represented a valuable option for peripheral angiography when the traditional ICM are inapplicable or risky. Fujihara M et al reported a ~ 5% rate of acute kidney injury (AKI) in patients at risk.[6] The use of an automated CO2 injector, high-resolution DSA, and proprietary post-processing software make an image quality comparable to that of iodinated contrast media (ICM-DSA) for lower limbs femoropopliteal lesions.[3] A meta-analysis and systematic review by Ghumman SS et al. in 2017 concluded that CO2 use is associated with a modestly reduced rate of AKI. [7] A previous Egyptian report by Abdelbary et al. described the utility and safety of CO2- DSA for symptomatic peripheral vascular diseases (PVDs). [8] In our centre, this is the first study reporting the safety of CO2 as a contrast media in peripheral angiography. We failed to find any similar study from Iraq.

This study aims to describe the process of CO2 peripheral angiography using a locally produced injector system and measure its safety in a group of Iraqi adults with different degrees of renal insufficiency by measure the rate of acute kidney injury at 48 hours post-procedure.

METHODS

Setting and Design: A descriptive cross-sectional study was conducted at the cardiothoracic and vascular surgery department and the radiology unit of the Surgical Specialties Hospital, the medical city of Baghdad, from June 2020 to December 2020.

Ethical consideration: The ethical committee of the Arab Board for Health Specialties-Iraq has approved the protocol of this study. And it was implemented according to the code of ethics of the Ministry of Health in Iraq, 2018 version. All study participants signed a consent form before being recruited for the study after being informed about the study's aims and the potential risks and benefits of the intervention going to be used.

Definition of the cases and exclusion criteria: All patients diagnosed clinically with peripheral artery disease and chronic kidney disease at our department and in need of peripheral angiography during the study period were included in this study. Our selection criteria defined chronic kidney disease as a glomerular filtration rate (FGR) of < 60 ml/min.[9] We excluded patients with cardiac septal defects, pulmonary hypertension, and COPD from this study. We also made sure that none of the participants were having COVID-19 during the time of the study and had no history of allergy to contrast media.

The Protocol:

Patients' evaluation: All patients were interviewed and examined by two certified vascular surgeons and a nephrologist. Then, a preprocedural colour doppler study was done for all participants. After reviewing the medical data and examining the patients, the team approved the need for diagnosing peripheral artery lesions with possible intervention. Testing for renal impairment made by renal function tests, blood

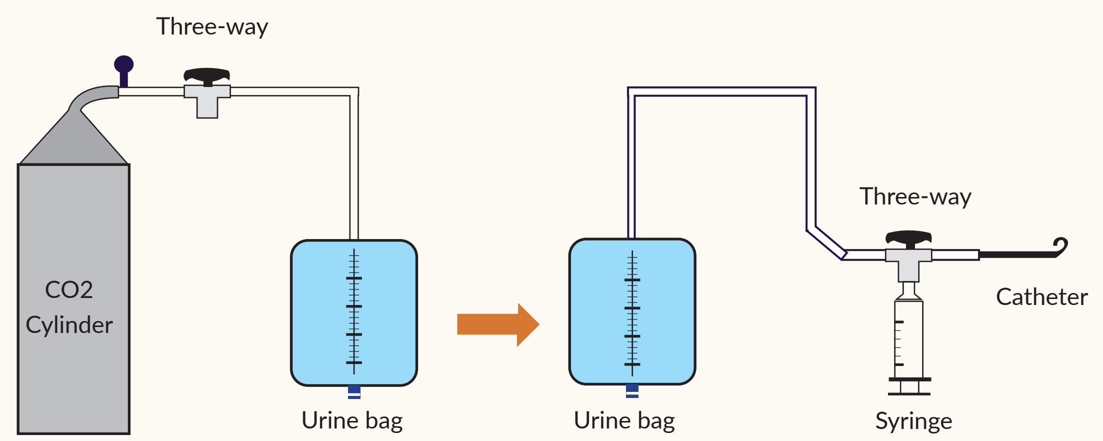

Figure 1 | Homemade CO2 delivery system

urea and serum creatinine, estimated glomerular filtration rate (eGFR), serum electrolytes, urine analysis, and abdominal ultrasound.

Patient Preparation: All patients were checked for any evidence of haemodynamic instability; checking blood pressure, doing ECG to exclude arrhythmias, and performing blood gas analysis. We did not use sedation or pre-medications before the procedure.

The procedure: an experienced vascular surgeon has conducted the procedure using a homemade CO2 delivery system. We did not use supplemental iodinated contrast media to enhance visualization in the study group.

Homemade Co2 delivery system: Currently there is one FDA approved specific CO2 delivery system.[10] It is usually assembled locally using specific sterile bags and a tubing system. Because importing CO2 delivery system is a lengthy and costly process in Iraq, we improvised a delivery system locally to perform intra-arterial CO2 DSA (see figure 1). First, We connected a urine bag to a three-way tap via a sterile intravenous line. The bag was filled with CO2 by connecting an inlet tube to the cylinder filled with medical-grade CO2. The gas was purged three times during collection to exclude room air from the bag. Second, we connected the bag to an angiographic catheter using an intravenous line with a three-way tap. Then, the gas liberally aspirated from the bag into a delivery syringe. Finally, the catheter and tubing system were also purged a couple of times with the delivery syringe before the final hand administered the intravascular injection. The CO2 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 minutes of its collection from the cylinder. [11]

The technique of CO2 injections through an angiographic catheter: All CO2 DSA injections were made by hand. Initially, approximately 10 mL of CO2 was aspirated from the bag and expelled to fill the tubing with CO2. Another 5 mL of the gas was used to purge the catheter with the gas to avoid explosive delivery. 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. Therefore, we elevated the limbs by 10–20° angle above the horizontal axis to allow the adequate filling to visualize the target vessels better. Injections were spaced approximately 2-3 minutes apart, and the extremities were returned to the horizontal position to improve the clearing of the gas and avoid vapour lock. The mean total volume of CO2 used from the bag was 900+ 239.49 ml. [11]

Imaging: This was done using digital subtraction angiography (DSA) with a 1024x1024 system and CO2 software program. The DSA equipment has a stacking software program that allows the integration of multiple images into a single composite image. The exposure rate was 3-6 frames per second. An experienced radiologist has evaluated the quality of the image and the presence of stenosis that mandates a decision for intervention.

Patient Monitoring: during the procedure, we monitor the patient by ECG, pulse oximeter, blood pressure. A significant vital sign change indicates air contamination or accidental delivery of excessive volumes of CO_2. Capnography was not used. After the procedure, the patients were checked for 24 hours for the vital signs, urine output, pain at injection sites, bleeding, arrhythmia, and neurological signs. Renal function test performed 48 hours after the procedure.

Outcomes: we used The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines definition for acute kidney injury (AKI) to define the occurrence of AKI after the procedure.[12] KDIGO defines AKI as any of the following:

- Increase in serum creatinine by 0.3 mg/dL or more within 48 hours or
- Increase in serum creatinine to 1.5 times baseline or more within the last 7 days or
- Urine output less than 0.5 mL/kg/h for 6 hours

The estimated glomerular filtration rate (eGFR) calculated using the MDRD equation: [13]

GFR (mL/min/1.73 m^2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American) Conventional units

Statistical Analysis: IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. were used for statistical analysis. Discrete variables are presented as numbers and percentages. Continuous variables are presented as means and standard deviations.

RESULTS

The study has recruited 34 Iraqi adult patients, 18 females; with a mean age of 62.83+9.94 years. There were no surgical complications post-procedure. Three patients had the diagnosis of AKI (8.33%) at 48 hours. There was no change in urine output; all recovered with good hydration and medical management. None of them mandated renal replacement therapy.

Table 1 | Characteristics of the study group (total no. 34)

Characteristics	Number (%)
Gender	
Male	16/47.1%
Female	18/52.9%
Age (Mean + SD) years	62 + 9.44
DM	20/58.8%
Hypertension	15/44.1%
Smoking	28/82.4%
Lesion site	
BTK	24/70.6%
SFA	5/14.7%
BTK + SFA	5/14.7%
Intervention	
Balloon Angioplasty	31/91.2%
Balloon Angioplasty and Stenting	3/8.8%
CO2 delivered volume cc	
Mean + SD	900 + 239.49
Range	1000
The stage of renal disease	
Stage III a	2
Stage III b	9
Stage IV	22
Stage V	1

BTK; below the knee segment, SFA; superficial femoral artery

Figure 2 shows a sample the quality of the angiography picture using CO_2 as a contrast.

DISCUSSION

Peripheral arterial disease (PAD) is a relatively common condition, with 220 million peo-

Table 2 | Renal data of the study group

Renal Data	Value
Mean eGFR ml/min/1.73 m^2	26.5 + 7.9
Mean S. Cr Pre-procedure (mg/dl)	2.30 + 0.56
Mean S. Cr Post-procedure (mg/dl)	2.28 + 0.46
AKI at 48 hours	3/34 (8.82%)

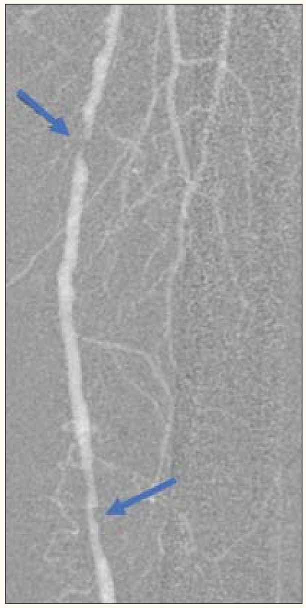

Figure 2 | Homemade CO2 delivery system. Blue arrows show stenosis at the femoral artery.

ple affected globally and an increasing prevalence worldwide. PAD represents a significant burden for patients' quality of life. The prevalence of patients with PAD is 25.2% and CKD is higher than that of myocardial infarction and stroke. The two key CKD measures, glomerular filtration rate (GFR) and albuminuria, are strongly associated with subsequent risk for PAD. [14, 15]

Preexisting chronic kidney disease is the strongest patient-related risk factor for contrast associated nephropathy; the lower the kidney function level, the higher the risk. And ESRD patients have worse survival, limb salvage, and amputation free survival (AFS) outcomes following angioplasty and bypass for critical limb ischemia (CLI) than non-ESRD patients. [16,17]

Despite the evolution in the design of contrast agents, there was always a fear of renal risks about precipitating AKI. It was attributed to the direct and indirect effects of ICM on the kidney with intense intrarenal vasospasm and subsequent renal dysfunction.[18] Thus, the question was how to have a safe procedure in the context of renal impairment? Many medical interventions are trialled, and one of the options is to have another contrast agent, like CO2.

In this study, 34 Iraqi adults with CKD (Stages 3 and 4) underwent peripheral angiography and endovascular interventions using CO2 as a contrast agent. Three patients, 8.82%, had the clinical definition of AKI by 48 hours of the procedure.

Smoking is the single greatest modifiable risk factor for the development and progression of PAD. Patients with PAD experience smoking-related complications and increased mortality.[14] In this study, 82% of the patients were current or ex-smokers. Diabetes mellitus and hypertension are both risk factors for CKD and PAD. Both will amplify the risk of contrast associated nephropathy in patients with underlying CKD. 17,18 About two-thirds of the study participants were diabetic and hypertensives.

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) working group definition of contrast-induced nephropathy is the most widely accepted definition. Patient- and procedure-related factors also influence the risk of AKI after administering contrast material. Preexisting CKD is the strongest risk factor.[12,18] In a meta-analysis and systematic review by Ghumman SS et al, CO2 use was associated with a modestly reduced rate of AKI. In studies that use CO2 as the primary imaging agent, the average incidence of AKI remained high at 6.2%—supporting the concept that factors other than renal toxicity from ICM may contribute to renal impairment following peripheral angiography.[19] An Egyptian cohort of 18 patients showed a non-significant rise of serum creatinine levels. They concluded that in comparison to traditional ICM DSA, CO2 could be safely used as a tolerable option during endovascular management of lower extremity symptomatic arterial disease. [7]

CO2 also proved safe and useful in diabetic patients. It represented a viable option to significantly reduce (or eliminate) the use of iodinated contrast in diabetic CLI patients to preserve renal function. [20]

In this study, we didn't assess the image quality produced by CO2 DSA compared to ICM as per the study design. This is one of the limitations of our study. With the use of proprietary post-processing software, CO_2-DSA produced comparable diagnostic test and image quality to ICM-DSA, as proved in the recent report by Bürckenmeyer F, et al. [3]

No major complications occurred in this study that required active management. One patient complained of pain in the affected limb during injection of the gas. This is mostly related to the explosive delivery of the gas. This was consistent with Madhusudhan KS et al report described no serious complications. Seeger et al described complications in 1.6% of the 128 patients they studied. [11, 21]

There are different techniques for intravascular CO_2 injection. These include hand injection, pressure inflator and a dedicated delivery system.[11] Such delivery system is safe but it is expensive and not available in Iraq. This dedicated system ensures the lowest possible volume of the delivered gas. [22,23] The delivery system that we used in this study is simple and can be developed easily. The components of the system are easily available in any hospital setup and are inexpensive. The disposable, sterile, plastic CO_2 delivery bag is not available in Iraq. Hence, we used the disposable urine bag. There was no documented infection nor any air embolism secondary to air contamination in such a closed system. We used a larger volume compared to other studies. [7,11] A dedicated study needed to measure the effect of different injected volumes on image quality and complications.

CONCLUSION

CO_2-DSA is a safe alternative to traditional ICM DSA that could be used and well tolerated during endovascular management of lower extremity arterial disease. Further studies needed to assess image quality and to confirm the volume needed to produce good quality images.

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Abbreviations list: Acute kidney injury (**AKI**), Amputation free survival (AFS), Carbon dioxide (**CO2**), Chronic obstructive pulmonary disease (**COPD**), Corona Virus disease 2019 (**COVID-19**), Critical limb ischemia (**CLI**), Digital subtraction angiography (**DSA**), Estimated glomerular filtration rate (**eGFR**), Glomerular filtration rate (**FGR**), Iodinated contrast media (**ICM**), Kidney Disease Improving Global Outcomes (**KDIGO**), Peripheral vascular diseases (**PVDs**).

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