Observational Study

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# Feasibility and safety of automated $CO_2$ angiography in peripheral arterial interventions

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**Abstract**

Carbon dioxide ($CO_2$) gas is an established alternative to iodine contrast during angiography in patients with risk of postcontrast acute kidney injury and in those with history of iodine contrast allergy. Different $CO_2$ delivery systems during angiography are reported in literature, with automated delivery system being the latest. The aim of this study is to evaluate the safety, efficacy, and learning curve of an automated $CO_2$ injection system with controlled pressures in peripheral arterial interventions and also to study the patients' tolerance to the system.

From January 2018 to October 2019 peripheral arterial interventions were performed in 40 patients (median age-78 years, interquartile range: 69–84 years) using an automated $CO_2$ injection system with customized protocols, with conventional iodine contrast agent used only as a bailout option. The pain and tolerance during the $CO_2$ angiography were evaluated with a visual analog scale at the end of each procedure. The amount of $CO_2$, iodine contrast used, and radiation dose area product for the interventions were also systematically recorded for all procedures. These values were statistically compared in 2 groups, *viz* first 20 patients where a learning curve was expected vs the rest 20 patients.

All procedures were successfully completed without complications. All patients tolerated the $CO_2$ angiography with a median total pain score of 3 (interquartile range: 3–4), with no statistical difference between the groups ($P=.529$). The 2 groups were statistically comparable in terms of comorbidities and the type of procedures performed ($P=.807$). The amount of iodine contrast agent used ($24.60\pm6.44$ ml vs $32.70\pm8.70$ ml, $P=.006$) and the radiation dose area product associated were significantly lower in the second group ($2160.74\pm1181.52\ \mu Gym^2$ vs $1531.62\pm536.47\ \mu Gym^2$, $P=.043$).

Automated $CO_2$ angiography is technically feasible and safe for peripheral arterial interventions and is well tolerated by the patients. With the interventionalist becoming familiar with the technique, better diagnostic accuracy could be obtained using lower volumes of conventional iodine contrast agents and reduction of the radiation dose involved.

**Abbreviations:** µg = micrograms, $\mu Gym^2$ = micro Gray x square meters, AV = arterio-venous, $CO_2$ = Carbon dioxide, DAP = dose area product, DSA = digital subtraction angiography, F = French, IQR = interquartile range, mg = milligrams, ml = milliliters, PAD = peripheral arterial diseases, PAI = peripheral arterial interventions, USA = United States of America, VAS = Visual Analogue Scale.

**Keywords:** automated $CO_2$ system, $CO_2$ angiography, peripheral artery disease

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*All data generated or analyzed during this study are included in this published article [and its supplementary information files].*

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## 1. Introduction

Peripheral arterial diseases (PAD) affects almost 12% to 15% of the adult population and 20% of these patients are older than 70 years. With increasing older population and the growing number of patients with diabetes, the incidence and prevalence of PAD are increasing, with also an increase in the incidence of Stage IV disease of the Fontaine classification.[1] Endovascular minimally invasive revascularization methods remain the mainstay treatment in this group of patients, with lesser complication and morbidity rates and limb salvage in comparison to open surgery.[2]

Among most of these patients concomitant coronary artery disease, as well as advanced kidney disease, are not rare,[3,4] which places them at an increased risk of adverse events, particularly postcontrast acute kidney injury after traditional endovascular revascularization techniques.[5] In such patients and those with a known history of iodine contrast allergy, $CO_2$ angiography has been established as an effective alternative.[6–9]

The complications of $CO_2$ angiography include leg pain, abdominal pain, diarrhea, and very rarely lethal complications such as nonobstructive mesenteric ischemia.[9] Especially in case of peripheral arterial interventions (PAI), $CO_2$ angiography may be associated with severe leg pain. The pain associated may thus lead to further motion artifacts resulting in repeated digital subtraction angiography (DSA) runs, possibly contributing to higher radiation exposure. The $CO_2$ delivery during the angiography has developed tremendously in past decades, including hand injection approaches, bag reservoir delivery systems, and syringe systems. The newest development in this regard is the automated $CO_2$ delivery system with controlled pressure for arterial interventions and is proposed to be effective, safe, and with better image quality when compared to manual systems.[10–12] However, very few reports exist in literature with respect to the patients' tolerance to these systems.

The aim of this retrospective study is to evaluate the safety, efficacy, and learning curve of a dedicated automated $CO_2$ injection system with controlled pressures in PAI indicated for $CO_2$ angiography. Focus is also given to evaluate the patients' tolerance to the automated $CO_2$ system and its quantification in the form of a visual analog scale (VAS). Furthermore, the effect of learning curve on the amount of iodine contrast used and the radiation dose involved is also studied.

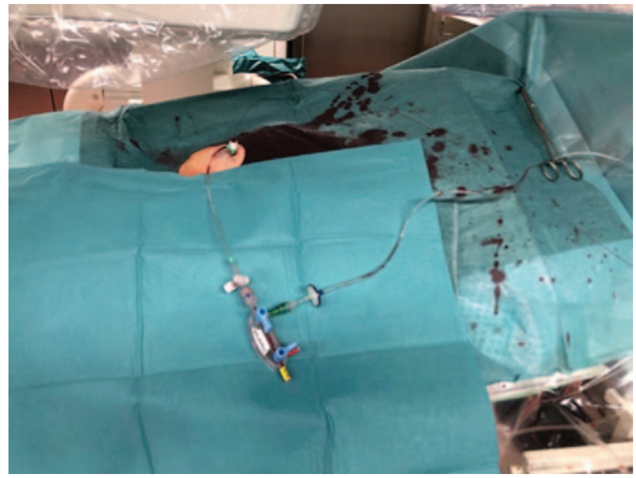

**Figure 1.** Figure demonstrating the setup during the angiography with automated carbon dioxide ($CO_2$) system.

## 2. Materials and methods

From January 2018 till October 2019, 40 consecutive patients with indications for $CO_2$ angiography were treated endovascularly using an automated $CO_2$ delivery system with controlled pressure and customized protocols (Angiodroid SRL, San Lazzaro du Savena, Italy). The indication for $CO_2$ angiography included renal impairment (reflected by serum creatinine values >1.3 mg/dl and glomerular filtration rate <55 ml/min), previous history of contrast allergy and renal transplant.

The patient group included those with PAD confirmed by clinical evaluation according to Fontaine classification as well as by Doppler ultrasound examinations. The indication for endovascular revascularization was established with the interdisciplinary consensus including angiology, interventional radiology, and vascular surgery.

### 2.1. Procedure details

All procedures were performed by a single interventional radiologist with extensive experience (>13 years) in interventional procedures with iodinated contrast agents. All procedures were carried out under local anesthesia in the angiography suite (Siemens Artis Zee) of the radiology department. Intravenous sedatives or analgesics were limited to a minimum to avoid masking the patient's reaction to the injection of $CO_2$. However, in minority of patients with severe back pain, procedures could only be carried out with pain medications (Maximal dose of 10 mg Piritramid intravenous). After attaining femoral access (antegrade or retrograde), the diagnostic angiography was performed using the automated $CO_2$ injector and the $CO_2$ procedural kit (Angiodroid SRL, San Lazzaro du Savena, Italy). With the connection of the procedural kit to the catheter sheath or introducer catheter, the dead space was always flushed with a small amount of $CO_2$ gas to eliminate air and attain a better image quality. Depending on the location of the target lesion, the $CO_2$ angiography was then performed according to customized protocols (Fig. 1, Table 1). DSA images were acquired using predefined protocols, specially developed for $CO_2$ angiography (Evenflow, Siemens, Frame rate of 7.5/s). From the images obtained, the indication for further intervention was established, which included recanalizations, angioplasties, and stent angioplasties. The use of conventional iodine contrast agent was considered, as a bailout option if the image quality was not sufficient to elicit the pathology or decision regarding the intervention was difficult. In patients with a previous history of contrast agent allergy, this was performed after preparing the patient with anaphylaxis prophylaxis (H1 antihistamines-Dimetindine 4 mg, Ranitidine 50 mg). A bolus of 5000 international units unfractionated heparin was administered intra-arterially in all patients to prevent thromboembolic complications. The results of the interventions were checked with further angiograms. If the image quality was not decisive, control angiograms with conventional contrast agents were performed. If the results were considered satisfactory, the procedure was finished by deploying a vascular closure device (Angio-seal 6F, Terumo Medical Corporation) or manual compression according to the operator's preference.

At the end of the procedure, the patients' perception of the procedural pain was routinely evaluated using a VAS score. The VAS is a 10-point scale that patients were asked to mark based on their pain and discomfort, with scores of zero indicating no pain and discomfort and 10 indicating the worst pain possible.

To evaluate our experience and learning curve with the automated $CO_2$ injection system, the patient group was divided

**Table 1**

**Customized protocol for $CO_2$ angiography depending on the location.**

| Location | $CO_2$ Injection Flush volume (ml) | Injection volume (ml) | Pressure (mm Hg) |
|---|---|---|---|
| Pelvis | | | |
| Vascular Sheath | 10 | 40 | 250 |
| Catheter | 20 | 40 | 350 |
| Above knee | | | |
| Vascular Sheath | 20 | 30 | 200 |
| Catheter | 30 | 30 | 240 |
| Below knee | | | |
| Vascular Sheath | 20 | 30 | 200 |
| Catheter | 30 | 30 | 240 |

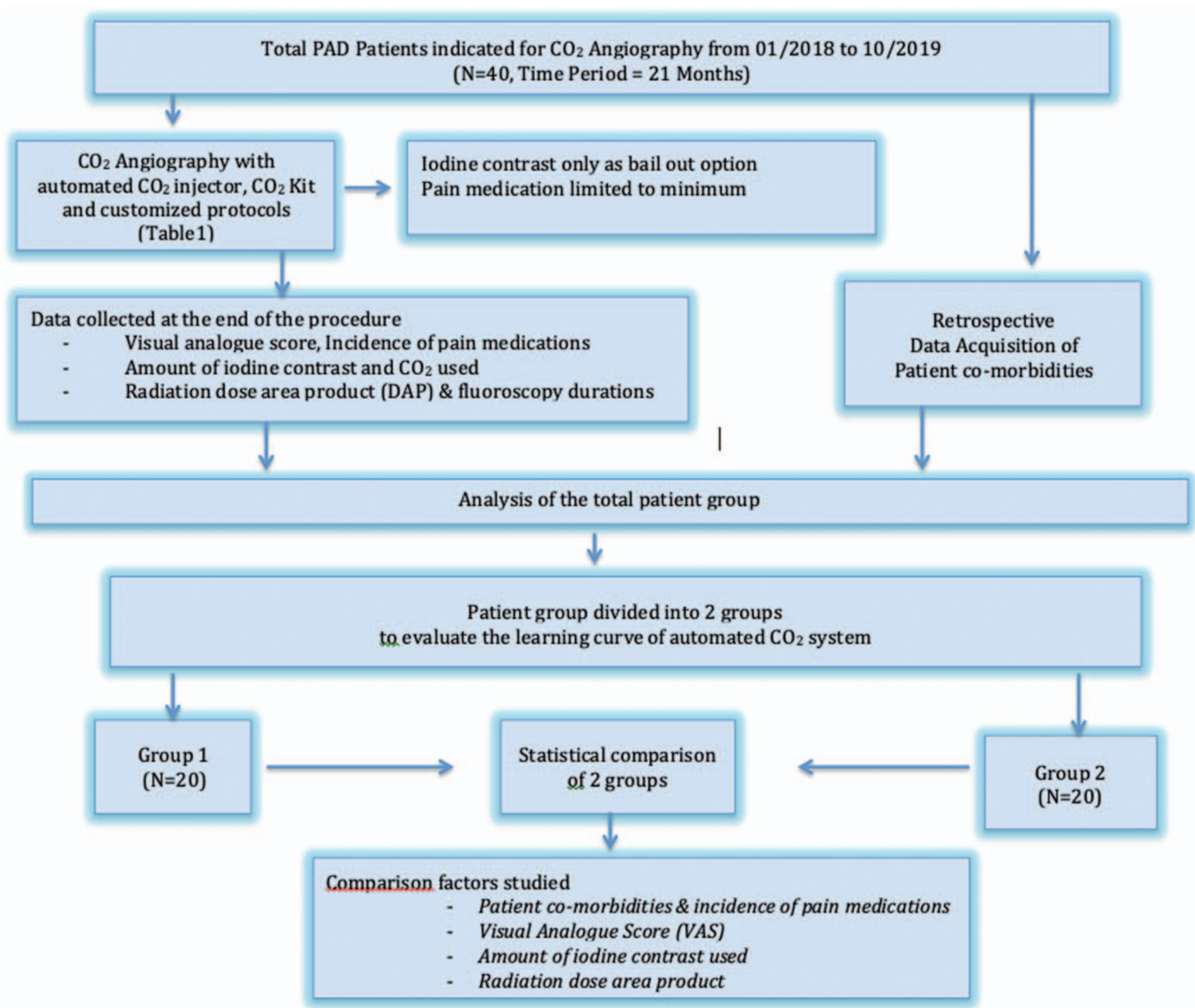


**Figure 2.** Schematic flowchart summarizing the main steps of the study. $CO_2$ = Carbon dioxide, PAD = peripheral arterial diseases.

into 2 groups, the first 20 patients and subsequent 20 patients. Patient data, including comorbidities and laboratory values and procedural data were retrospectively collected. These included the amount of iodine contrast and $CO_2$ used, number of injections with corresponding pressures, the radiation dose area product (DAP), given in $\mu Gym^2$ and fluoroscopy durations. A schematic flowchart summarizing the main steps of the study is illustrated in Figure 2. Informed consent was obtained from all patients and the local institutional review board approved this retrospective study. Complications were defined as intolerance and discontinuation of the procedure as well as other factors like access site complications, which eventually the prolonged hospital stays.

Statistical analysis was performed to estimate the differences between the 2 groups (SPSS, Statistical Package for Social Sciences, Version 23, Chicago, IL). For continuous variables, the analysis was performed using the Mann-Whitney *U* test, while Chi-Square test was used for categorical variables. A *P*-value of less than .05 was considered statistically significant.

## 3. Results

The median age of total patient group was 78 years (interquartile range [IQR]: 69–84 years, range: 52–91 years). The technical success rate of $CO_2$ angiography was 100%. All patients tolerated the complete course of $CO_2$ angiography, without discontinuation of the procedure because of pain or other technical problems. The median VAS in the total patient group was 3 (IQR: 3–4, range 2–6). The median VAS in the first group was 3.5 (IQR: 3–4) and in the second group 3 (IQR: 3–4), without statistical difference between the 2 groups ($P=0.529$). No procedural or postprocedural complications occurred in these patients during the procedure as well as until discharge. No prolonged hospital stay was observed.

**Table 2**

**Distribution of patient variables between the groups.**

| Patient variables | Overall (N=40) | Group 1 (N=20) | Group 2 (N=20) | *P* value* |
|---|---|---|---|---|
| Age | 78.13±7.98 | 77.45±9.35 | 78.80±6.51 | 0.904 |
| Female gender | 13 (32.5%) | 6 (30%) | 7 (35%) | 0.736 |
| i.v Analgesic administration | 9 (22.5%) | 5 (25%) | 4 (20%) | 0.705 |
| Risk factors | | | | |
| Smoking | 16 (40%) | 7 (35%) | 9 (45%) | 0.602 |
| Diabetes | 32 (80%) | 15 (75%) | 17 (85%) | 0.602 |
| Hypertension | 14 (35%) | 8 (40%) | 6 (30%) | 0.060 |
| Fontaine Status | | | | |
| II b | 3 (7.5%) | 1 (5%) | 2 (10%) | 0.362 |
| III | 2 (5%) | 1 (5%) | 1 (5%) | |
| IV | 35 (87.5%) | 18 (90%) | 17 (85%) | |
| Target lesion location | | | | |
| Suprapopliteal | 9 | 5 | 4 | 0.807 |
| Infrapopliteal | 15 | 8 | 7 | |
| Supra – and Infrapopliteal | 16 | 7 | 9 | |

* @ Chi-square or Mann-Whitney *U* tests. IQR = interquartile range.

The patient demographics of the two groups are depicted in Table 2. The median age of the first group was 78 years (IQR: 69–86, range 52–89 years, with a female incidence of 30% (6/20) and of the second group was 76 (IQR: 69–82.75, range 63–91 years) with a female incidence of 35% (7/20). The 2 groups were statistically not different in terms of age ($P=.174$) or gender ($P=.736$). Similarly, in relation to patient comorbidities including risk factors (smoking, diabetes, and hypertension), Fontaine status, and renal functions (serum creatinine, glomerular filtration rate), the 2 groups were not statistically different. The target lesion locations were also similar in 2 groups ($P$ value=.807, Table 2). Furthermore, the 2 groups were also not statistically different with regard to the number of patients who received analgesics ($P$ value=.705, Table 2).

The average amount of $CO_2$ gas used, with details regarding the number of injections and average pressure, the amount of conventional contrast used during the procedure and fluoroscopy duration with radiation DAP in the 2 groups are illustrated in Table 3.

In the first group of patients, repeated angiograms were required for eliciting the pathologies and the postprocessing of the images was also cumbersome. Additional conventional iodine contrast agents were often needed for the confirmation of pathology as well as for the decisions regarding the interventions. Similarly judging the rate of flow of $CO_2$ gas was rather difficult during the initial period.

With gaining more experience with the setup and the postprocessing, lesser amounts of iodine contrast were needed for eliciting the pathologies, and for interventional decisions. In the second group, better image quality of popliteal/infra-popliteal segments could also be attained with the use of longer catheter sheaths, allowing a better judgment of $CO_2$ flow-dynamics. The longer catheter sheaths thus resulted in a slightly lesser amount of $CO_2$ in the second group, although this was not statistically significant. It was noteworthy to mention that the average contrast agent amount used was significantly lower in the second group of patients (24.60±6.44 ml vs 32.70±8.70 ml, $P=.006$). The success of angioplasty could also be verified with $CO_2$ without the use of large amounts of iodine contrast agents. The diagnosis of dissections after balloon angioplasty, on the other hand, was difficult with $CO_2$ and this was mostly verified with iodine contrast. However, $CO_2$ revealed more arterio-venous fistulas after balloon angioplasties, which followed stent implantation in most of the cases (Fig. 3). The learning curve also showed a moderate influence in image acquisition, fluoroscopy duration and the radiation DAP, which was also slightly lower in the second group (2160.74±1181.52 $\mu Gym^2$ vs 1531.62±536.47 $\mu Gym^2$, $P=.043$).

**Table 3**

**Amount of contrast agent and dose area product (DAP) in both groups.**

| | Overall | Group 1 | Group 2 | *P* value |
|---|---|---|---|---|
| Average $CO_2$ amount (ml) | 320.25 | 350.75 | 289.75 | .114 |
| Average contrast amount (ml) | 28.65 | 32.70 | 24.60 | .006 |
| Average pressure (mm Hg) | 249.68 | 241.30 | 258.06 | .043 |
| Fluoroscopy duration (min) | 18.45 | 20.67 | 16.22 | .030 |
| DAP ($\mu Gym^2$) | 1846.18 | 2160.74 | 1531.62 | .043 |

## 4. Discussion

The most recognized indication of $CO_2$ angiography as an alternative to conventional iodine contrast agents is the high risk of postcontrast acute kidney injury, which constitutes the third leading cause of hospital-acquired renal failure.[13] Another indication for $CO_2$ angiography is the previous history of contrast agent allergy. Further indication for $CO_2$ angiography is where $CO_2$ actually outperforms the conventional iodine contrast agents.[7,14]

The use of $CO_2$ permits the unlimited intraprocedural angiographic guidance during interventions and the physical properties of $CO_2$ make it attractive as an intravascular contrast agent. It is highly compressible, has very low viscosity, and is approximately 20 times more soluble in blood than oxygen. The majority of the circulating $CO_2$ is eliminated by the lungs in a single pass.[15] It is also not nephrotoxic and is nonallergic, eliminating the possibility of a fatal hypersensitivity reaction.[16] On the other hand, the disadvantages include buoyancy, neurotoxicity, and mild ischemic effects because of the displacement of blood during angiography.

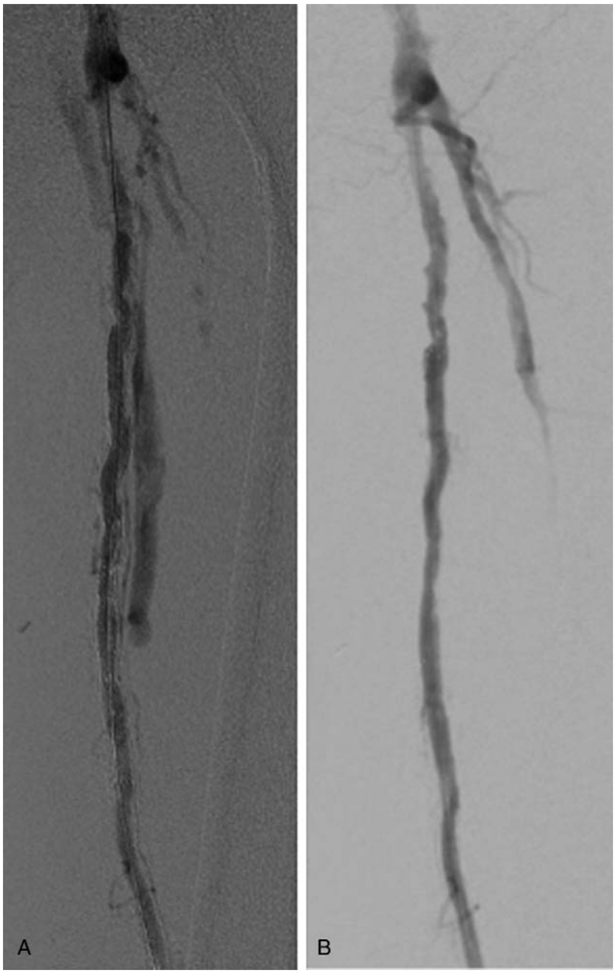


**Figure 3.** (A) $CO_2$ angiogram after percutaneous transluminal angioplasty (PTA) showing relevant arterio-venous fistula (B) angiogram with conventional iodine contrast agent after implantation of a covered stent (Viabahn Endoprothesis, W.L Gore & Associates, Inc., Flagstaff, Arizona, USA).

In spite of these attractive features of $CO_2$, there is a widespread assumption that it is time-consuming, produces inferior quality imaging, and may be associated with high radiation exposure. The way of delivery of $CO_2$ plays a vital role in the acquisition of the DSA images. Most commercially available systems deliver highly compressed $CO_2$ gas at high pressure, which is often associated with severe pain and patient intolerance. The automated $CO_2$ injector, as used in our patient cohort, delivers the $CO_2$ gas at reduced pressure and controlled manner, without the sudden release of $CO_2$ gas and this is better tolerated by patients. The average total pain score of 3.5 on the VAS and no discontinuation of procedures in our study group support these facts. Furthermore, pain reduction during the $CO_2$ delivery could be accomplished by administering 10 ml of 2% intra-arterial lidocaine,[17] if necessary.

From our results, we observed that the majority of the PAI could be accomplished efficiently with the automated $CO_2$ delivery system. This correlates very well with other reports in the literature.[11,12] At areas of turbulence or bifurcations, $CO_2$ fragmentation may occur resulting in a cobblestone-like appearance, which could be interpreted as relevant stenosis. With vessels below 8 mm in diameter, the reliability of $CO_2$ in the evaluation of stenosis is comparable to iodine contrast angiography and is reported to yield comparable densitometric analyses.[18] On the other hand, the low viscosity of $CO_2$ allows better detection of AV fistulas after angioplasties, as observed in our patient cohort. The low viscosity also enables the injection of gas directly into the sheath or interventional device, without the need to exchange to another catheter for the evaluation of the progress of intervention, which is termed as catheter-less delivery.[14]

Several adjunct procedures have been reported to enhance the image quality during $CO_2$ angiography. The use of longer sheaths and selective catheterization of the popliteal artery, as also observed in our patient cohort, is one of the methods to improve image quality. This not only aims at reducing the radiation exposure but also provides a better infra-geniculate filling of collaterals in attaining an overview of vasculature in the leg region. Similarly leg elevation of approximately 15 to 20 degrees and selective intra-arterial administration of 200 to 300 $\mu$g Nitroglycerine for vasodilation is reported to act as adjuncts to augment image quality.[19]

With regard to radiation exposure, our study demonstrated at least a trend in reduction of the radiation DAP in the second patient group as the interventionalist becomes familiar with the system. The higher radiation DAP of $CO_2$ angiography is associated mainly with image acquisition including increased frame rates. With super-selective imaging, the flow of $CO_2$ gas could be better judged and this along with increasing experience of the interventionalist could supplement measures in reduction of radiation exposure during $CO_2$ angiography.

There are several limitations to our study. This is a single-center observational study with only 1 interventionalist involved. The study sample is rather small and the study design is that of a retrospective design. Furthermore the changes in renal functions before and after the procedures were not investigated. However, the initial experience confirms the previous reports and this approach with a single interventionalist permits the assessment of learning curve effects in a small patient group. Automated $CO_2$ injection system was observed to be well tolerated by the patients. A larger group of patients with several interventionalists in a multicenter set-up could validate these results in the future.

## 5. Conclusion

Automated $CO_2$ angiography is technically feasible and safe for PAI and is well tolerated by the patients. There is a learning curve effect and better diagnostic accuracy can be obtained with training resulting in lesser use of conventional iodine contrast agents and reduction of the radiation dose involved.

## Author contributions

**Conceptualization:** Rohit Philip Thomas.
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**Formal analysis:** Rohit Philip Thomas, Simon Viniol.
**Methodology:** Rohit Philip Thomas, Irene Portig, Zaher Swaid.
**Resources:** Rohit Philip Thomas, Alexander Marc König, Irene Portig, Zaher Swaid, Andreas H. Mahnken.
**Software:** Simon Viniol.
**Supervision:** Andreas H. Mahnken.
**Validation:** Rohit Philip Thomas, Alexander Marc König, Irene Portig, Andreas H. Mahnken.
**Writing – original draft:** Rohit Philip Thomas.

**Writing – review & editing:** Simon Viniol, Alexander Marc König, Andreas H. Mahnken.

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