Peripheral diagnostic and interventional procedures using an automated injection system for carbon dioxide (CO2): case series and learning curve

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ABSTRACT

Introduction: The administration of iodinated contrast media in doses sufficient for diagnosis and procedural guidance, when coincident with renal insufficiency, presents a considerable risk of exacerbating and hastening renal failure. Carbon dioxide has been proposed in the past as an alternative, but only recently dedicated injection systems have become available. We aimed to review our ongoing experience with an automated carbon dioxide injector for peripheral diagnostic and interventional procedures.

Methods: Details on 21 patients undergoing peripheral procedures with carbon dioxide angiography were systematically collected. An automated injector enabling customized and repeated carbon dioxide injections was used in all cases, with iodinated contrast media used only as bailout.

Results: No major or minor complications occurred in these patients, either during the procedure or up to discharge. Comparison according to phase of the learning curve showed that with accruing experience operators relied progressively more on carbon dioxide only, as there was a significantly reduced need for additional iodinated contrast media injections per procedure (from $2.5 \pm 2.1$ to $0.6 \pm 2.1$ injections per patient, $p=0.005$). Accordingly, in the second phase of our learning curve, iodinated contrast media were avoided in 91% of cases in comparison to 20% of procedures performed in the beginning of our experience ($p=0.002$). Concomitantly, no significant change in the duration of the procedure occurred.

Conclusions: Carbon dioxide-based angiography using an automated injection system is feasible and safe in patients undergoing diagnostic or interventional procedures for infra-diaphragmatic conditions, especially for transcatheter renal sympathetic denervation.

Keywords: angiography, angioplasty, carbon dioxide, peripheral artery disease.

INTRODUCTION

The burden of peripheral artery disease continues to increase worldwide. Given the favorable results of endovascular therapy in patients with PAD, also its role is increasingly important (1). Even patients undergoing surgical therapy or maintained on
maximal medical therapy only usually undergo invasive assessment with angiography relying on administration of iodinated contrast media (2). However, the safety of such iodinated media is less than satisfactory. Their adverse effects, especially contrast nephropathy, potentially undermine their diagnostic benefits (3). Accordingly, endovascular procedures may be limited in scope or aggressiveness in patients at high risk of contrast nephropathy, or avoided altogether in patients with severe allergic diathesis.

Alternatives to iodinated contrast media have been proposed over the decades, including ultrasound, gadolinium, and carbon dioxide (CO2). The latter has been proposed for digital subtraction angiography several years ago, given its high dissolubility and lack of hypersensitivity or nephrotoxic adverse effects (4). Indeed, for most diagnostic or interventional procedures, almost unlimited cumulative volumes of CO2 can be injected. Despite these theoretical and practical advantages, its use is until now very limited. Some of the main hurdles faced by physicians using CO2 as contrast medium are: suboptimal imaging yield, discomfort, and lack of dedicated automated and digital injection systems. Recently several non-digital (5) or homemade devices have been proposed (6). However, recent works suggest that dedicated injection systems with modifiable parameters are required to improve the diagnostic yield (7). In addition, the increasingly common performance of transcatheter renal sympathetic denervation, which requires invasive imaging of the renal arteries in patients who can be at high risk of iodinated contrast media because of refractory hypertension and chronic renal failure, calls for alternative invasive imaging approaches. A dedicated automated and fully digital injector for CO2 angiography has been recently developed. It builds upon prior less sophisticated ones,(8) and our cardiovascular catheterization laboratory has begun to use it. We hereby report our experience and learning curve, in order to provide guidance on adoption and improvement.

METHODS

*Design.* This study was a retrospective observational registry. All patients provided written informed consent for the procedure and data collection. Ethical approval was waived given the retrospective observational design.

*Patients.* Patients undergoing invasive angiography for peripheral artery disease or transcatheter renal sympathetic denervation with CO2 as contrast of choice were retrospectively identified in our institutional database, irrespective of whether other imaging modalities had been used as well. Carbon dioxide angiography was attempted in patients with decreased renal function (glomerular filtration rate <60 mL/min), when selective renal injection was envisioned, or whenever the diagnostic or interventional procedure was deemed to require >100 mL of iodinated contrast media. No patient was excluded, with the notable exception of those requiring only supradiaphragmatic angiography.

*Device.* Carbon dioxide was administered using a dedicated injection system (Angiodroid, Angiodroid Srl, Bologna, Italy). Angiodroid is a digital automatic injector, which ensures stable CO2 pressure and high accuracy of volumes, as well as a built-in control system to avoid air contamination. The Angiodroid workstation is movable on steerable wheels and it is similar in size to a iodinated contrast media injector. The main advantages over other approaches to CO2 injection, including hand injection or other CO2 injectors, are: digital volume dose settings, digital pressure in-
jection settings, fast automated reload (20 seconds) for repeatable injections, high accuracy of the set pressure injection, high accuracy of the set volume doses, dual microcontroller to ensure high safety and performance, safety limits to avoid errors and patient injury, remote controller to start injections, possibility to save injection settings for different vascular districts, and a touch screen control. Angiodroid is to date the first totally computerized CO2 injection system. Injections can vary between 1 and 100 mL in volume and between 45 and 700 mm Hg in pressure (respectively 6 and 93 KPa), with an accuracy for volume delivery of ± 1 mL and for pressure delivery of ± 1.5%. Notably, no specific injection parameters are recommended, as physicians choose the better dose, but they must remain within the above safety limits.

Once the injector has been prepared for use and activated, it automatically charges the required amount of CO2 from a 2 L CO2 cylinder. Afterwards, the injector must simply be connected through a disposable connecting tube to the diagnostic or guiding catheter or sheath of choice and injection is already possible without further delay. Thanks to the low viscosity of CO2, even 3 French catheters and 22G tubings or syringes can be used to obtain satisfactory angiographic images with digital subtraction angiography.

Despite its recent introduction into clinical practice, there are already favorable scholarly reports on the use of Angiodroid (9). Procedures. All procedures were performed by a single operator (A G) with extensive (>20 years) experience in peripheral diagnostic and interventional procedures with iodinated contrast media, performed according to the standard of care and using standard diagnostic and interventional materials. Carbon dioxide was administered using standard sheaths and catheters. After the first two cases, the CO2 delivery approach was modified, introducing a one-way check valve to prevent air aspiration and blood backflow. Since CO2 is very soluble in air and lighter than blood, air or blood could fill the delivery system for CO2 and make repeated CO2 injections cumbersome, or increase the risk of air embolism. In addition, in arteries with a reference vessel diameter of 10 mm or less, a 7 French Swan-Ganz catheter was used in order to reduce antegrade blood flow and increase CO2 opacification of the arterial lumen by maximizing blood displacement by CO2. For instance, when performing left lower limb arteriography, the Swan-Ganz was deployed uninflated through contralateral access up to the distal segment of the external iliac artery. Then, it was slowly and gently inflated before CO2 injection in order to minimize competitive blood flow and ensure almost complete filling of the vessels of interest with CO2.

Complete injections were administered at volumes ranging from 20 mL (for smaller vessels such as the renal artery) to 50 mL (for larger vessels such as the abdominal aorta), at a 350-400 mm Hg pressure. Scouts were instead based on 10 mL of CO2 delivered at 350 mm Hg. No pain medication or sedation was administered.

Definitions. Adequate image quality was defined as that enabling complete diagnostic appraisal of the anatomic structure of choice and, if pertinent, satisfactory guidance of the interventional procedure and eventual control of the angiographic results. Severe pain or discomfort was defined as the one requiring discontinuation of CO2 administration. Glomerular filtration rate was estimated according to the Modification of Diet in Renal Disease (MDRD) formula.

Analysis. Continuous variables are reported as mean ± standard deviation or n (%). Categorical variables are reported as n (%). In order to appraise the potential learning curve required to master CO2 angiography,
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the 21-patient case series was divided in two groups, the first 10 and the subsequent 11 patients. Statistical testing was performed with the Mann-Whitney U test for continuous variables, with the Fisher exact test for categorical variables when organized in two by two tables and chi-squared test when organized in larger tables. Statistical significance was set at the two-tailed 0.05 level. Computations were performed with SPSS 20 (IBM, Armonk, NY, USA).

RESULTS

Between March 2013 and February 2014, out of a total of 273 endovascular diagnostic or interventional procedures involving infradiaphragmatic vessels, 21 patients (8%) underwent CO2 angiography as part or whole of their diagnostic or interventional procedure (Table 1). Age was 67.9 ± 10.0 years and 12 (57%) were men. Procedures were performed in the aorto-iliac or femoro-popliteal district for diagnostic-only purposes in 3 (14%) cases and for angiography or interventions in 8 (38%) cases (Figure 1; Figure 2). Ten (48%) cases were transcatheter renal sympathetic denervations (Figure 3). In 2 (10%) procedures, which were performed at the beginning of our clinical experience, CO2-based angiography did not provide adequate quality images in the aorto-iliac and ilio-femoral district, due to lack of complete vessel filling with CO2. Thus, these procedures were mainly performed

Table 1 - Patient features.

| Feature                  | Overall (N = 21) | First cases (N = 10) | Following cases (N = 11) | P value* |
|--------------------------|------------------|----------------------|--------------------------|----------|
| Age (years)              | 67.9 ± 10.0      | 67.1 ± 6.1           | 68.6 ± 12.9              | 0.888    |
| Female gender            | 9 (42.9%)        | 3 (30.0%)            | 6 (54.5%)                | 0.387    |
| Hypertension             | 18 (85.7%)       | 7 (70.0%)            | 11 (100%)                | 0.090    |
| Dyslipidemia             | 6 (28.6%)        | 3 (30.0%)            | 3 (27.3%)                | 1.0      |
| Smoking status           |                 |                      |                          | 0.510    |
| Never                    | 17 (81.0%)       | 8 (80.0%)            | 8 (81.8%)                |          |
| Former                   | 3 (14.3%)        | 1 (10.0%)            | 2 (18.2%)                |          |
| Current                  | 1 (4.8%)         | 1 (10.0%)            | 0                        |          |
| Diabetes mellitus        | 9 (42.9%)        | 4 (40.0%)            | 5 (45.5%)                | 1.0      |
| Prior PTA                | 4 (19.0%)        | 2 (20.0%)            | 2 (18.2%)                | 1.0      |
| Left ventricular ejection fraction < 50% | 4 (19.1%) | 3 (30.0%) | 1 (9.1%) | 0.221    |
| Glomerular filtration rate < 60 mL/min | 5 (23.8%) | 3 (30.0%) | 2 (18.2%) | 0.635    |
| Fontaine class           |                 |                      |                          | 0.155    |
| 2A                       | 2 (9.5%)         | 1 (10.0%)            | 1 (9.1%)                 |          |
| 2B                       | 7 (33.3%)        | 6 (60.0%)            | 1 (9.1%)                 |          |
| 3                        | 0                | 0                    | 0                        |          |
| 4                        | 2 (9.5%)         | 1 (10.0%)            | 1 (9.1%)                 |          |
| NA                       | 10 (47.6%)       | 2 (20.0%)            | 8 (72.7%)                |          |
| Procedure                |                 |                      |                          | 0.102    |
| Angiography only         | 3 (14.3%)        | 3 (30.0%)            | 0                        |          |
| PTA ad hoc or after angiography | 8 (38.1%) | 4 (40.0%) | 4 (36.4%) |          |
| RSD                      | 10 (47.6%)       | 3 (30.0%)            | 7 (63.6%)                |          |

*at Fisher exact, chi-squared, or Mann-Whitney U tests.

PTA = percutaneous transluminal angioplasty; RSD = renal sympathetic denervation.
Figure 1 - Comparison between iodinated contrast media and carbon dioxide angiography for superficial femoral artery angiography and intervention: A) baseline iodinated contrast media angiography; B) baseline carbon dioxide angiography; C) iodinated contrast media angiography after stenting; D) carbon dioxide angiography after stenting.

Table 2 - Procedural features.

| Feature                                      | Overall (N = 21) | First cases (N = 10) | Following cases (N = 11) | P value* |
|----------------------------------------------|------------------|----------------------|--------------------------|----------|
| Arterial access                              |                  |                      |                          |          |
| Right femoral                                | 16 (76.2%)       | 6 (60.0%)            | 10 (90.9%)               | 0.149    |
| Left femoral                                 | 0                | 0                    |                          |          |
| Abdominal aortic injections performed with   |                  |                      |                          |          |
| CO2                                          | 1.1 ± 1.3        | 1.1 ± 1.4            | 1.1 ± 1.3                | 0.970    |
| ICM                                          | 0.1 ± 0.5        | 0.3 ± 0.7            | 0                        | 0.129    |
| Right renal injections performed with        |                  |                      |                          |          |
| CO2                                          | 2.5 ± 3.2        | 1.3 ± 2.3            | 3.6 ± 3.5                | 0.084    |
| ICM                                          | 0.4 ± 1.0        | 0.4 ± 0.7            | 0.4 ± 1.2                | 0.304    |
| Left renal injections performed with         |                  |                      |                          |          |
| CO2                                          | 3.6 ± 4.6        | 1.8 ± 2.4            | 5.3 ± 5.5                | 0.084    |
| ICM                                          | 0.3 ± 0.8        | 0.4 ± 0.7            | 0.3 ± 0.9                | 0.304    |
| Right lower limb injections performed with   |                  |                      |                          |          |
| CO2                                          | 3.0 ± 5.5        | 4.4 ± 6.6            | 1.6 ± 4.1                | 0.166    |
| ICM                                          | 0.3 ± 1.2        | 0.7 ± 1.6            | 0                        | 0.129    |
| Left lower limb injections performed with    |                  |                      |                          |          |
| CO2                                          | 1.8 ± 3.7        | 3.2 ± 4.8            | 0.6 ± 1.8                | 0.090    |
| ICM                                          | 0.3 ± 0.8        | 0.7 ± 1.1            | 0                        | 0.024    |
| Total injections performed with CO2          | 12.0 ± 5.7       | 11.8 ± 6.5           | 12.2 ± 5.2               | 0.972    |
| Total injections performed with ICM          | 1.5 ± 2.3        | 2.5 ± 2.1            | 0.6 ± 2.1                | 0.005    |
| No injection of ICM                          | 12 (57.1%)       | 2 (20.0%)            | 10 (90.9%)               | 0.002    |
| Use of unidirectional valve                  | 19 (90.5%)       | 8 (80.0%)            | 11 (100%)                | 0.214    |
| Use of Swan-Ganz catheter                    | 6 (28.6%)        | 5 (50.0%)            | 1 (9.1%)                 | 0.063    |
| Procedural duration                          | 98.6 ± 28.9      | 102.1 ± 30.4         | 95.1 ± 28.4              | 0.650    |

*at Fisher exact or Mann-Whitney U tests. CO2 = carbon dioxide; ICM = iodinated contrast media.
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In order to minimize CO2 washout due to blood flow during digital subtraction angiography when standard injection proved unsatisfactory, the Swan-Ganz catheter (Table 2; Figure 2) was added. This lead to improved imaging yield in these small-caliber vessels. Indeed, among the subsequent cases, many procedures could be completed without using any iodinated contrast. The remaining ones could be performed exploiting CO2 as main contrast agent, and reserving iodinated contrast administration only to exclude minor angiographic features such as post-procedural intimal dissection. No major or minor complications occurred in these patients, either during the procedure or up to discharge. Accordingly, no patient referred discomfort or pain, other than mild and transient symptoms.

Comparison according to phase of the learning curve (i.e. distinguishing the first 10 cases from the 11 following ones) showed that baseline patient features were similar in the two groups (Table 1). Conversely, analysis of procedural features showed that the overall number of ICM injections per procedure decreased over time (from $2.5 \pm 2.1$ to $0.6 \pm 2.1$, $p = 0.005$). A similar trend was found also for the number of injections of ICM required for lower limb procedures (from 0.7 to 0, $p = 0.024$). Accordingly, in the second phase of our learning curve, iodinated contrast media

Figure 2 - Angiography with solely carbon dioxide to diagnose and treat a significant stenosis of the left common iliac artery: A) baseline angiography with a standard JR 4 diagnostic catheter to also image the carrefour; B) baseline angiography with an inflated 7 French Swan-Ganz catheter (arrow) to increase image quality in the distal vessel; C) final angiographic result after stenting.

Figure 3 - Angiography with solely carbon dioxide to perform transcatheter renal sympathetic denervation: A) baseline angiography in the right renal artery; B) ablation with the Simplicity catheter (Medtronic, Minneapolis, MN, USA); C) control angiography after 6 ablation runs.
DISCUSSION

This case series, reporting on the clinical use of the Angiodroid automated injection system for CO2 in patients with peripheral artery disease or undergoing transcatheter sympathetic renal denervation, has the following implications: a) CO2 injection for infradiaphragmatic diagnostic and interventional procedures appears feasible; b) despite an obvious learning curve, imaging accuracy could be improved with the use of simple ancillary devices, such as the Swan-Ganz balloon-tipped dual lumen catheter; c) CO2 may be particularly appealing as a contrast medium in patients undergoing transcatheter sympathetic renal denervation, given its adequate imaging yield and lack of renal toxicity; d) based on our learning curve analysis, we may tentatively speculate that experienced endovascular specialists after only 10 cases could be confident to rely only or mostly on CO2 for their diagnostic or interventional procedures in infra-diaphragmatic vessels.

Despite ongoing improvements in the safety of iodinated contrast media in the last decades, even current generation agents are associated with adverse events, in particular with the risk of contrast nephropathy and anaphylactic reactions (10). Alternatives to iodinated media include CO2, which is already produced throughout the body and can be easily expelled by the lungs. Indeed, CO2 was proposed instead of iodinated media several decades ago, but being a gas it is more difficult to manage in the catheterization laboratory (4). Moreover, while iodinated contrast media may opacify a vessel even if it is not completely filled, CO2 needs to displace all or most of the blood to achieve adequate images (7). In addition, digital subtraction angiography with summation is usually required. Accordingly, CO2 angiography is hitherto available only in few centers, and even in those institutions with a specific expertise in CO2-guided procedures, it is used very selectively.

Most probably, the main hurdle for a more widespread use of CO2 in peripheral invasive procedures is the difficulty in handling this gas, due to the lack of user-friendly digital automated injection systems, until recently (5). Indeed, the present work is built upon prior experiences with other dedicated injection systems, showing that such means to deliver CO2 is particularly effective.

We found that, on top of sophisticated imaging algorithms, the use of the Swan-Ganz catheter improves the ease and imaging yield. In addition, we found that adding a simple one-way valve to the injection tubing remarkably improved the ease of use of the system, by reducing blood backflow inside the tubes themselves. Accordingly, this contrast media appears attractive for infra-diaphragmatic invasive procedures, especially in those with or at risk for contrast nephropathy or other contraindications to iodinated contrast media. Moreover, our preliminary experience suggests that CO2 may be useful in patients with resistant hypertension undergoing transcatheter renal sympathetic denervation.

Similarly favorable results have been recently reported by other authors. For instance, Criado et al. have reported favorable data on CO2-guided endovascular abdominal aneurysm repair in 114 patients in the US (11), and other positive data come from Asian colleagues (12). Even homemade delivery systems have been proposed, but fur-
ther details concerning their safety and efficacy are required (13). Finally, alternative imaging approaches relying only on ultrasound have also been proposed (14), with Kusuyama and colleagues and Kawasaki et al. both recommending the combination of intravascular ultrasound and CO2 to maximize imaging yield and avoid nephrotoxic contrast (15-16).

Notwithstanding the above mentioned evidence, CO2 is not devoid of safety issues. Supra-diaphragmatic injections are absolutely contraindicated in proximal vessels, given the risk of cerebral or coronary ischemia, even if shunt or distal upper limb procedures appear safe.

In addition, CO2 may cause discomfort when excessive or repeated injections are administered, and other complications, such as gas trapping and ischemia, must be borne in mind.

Indeed, at least 2-3 minutes should pass between two repeated series of CO2 boluses each building up to 100 mL. Nonetheless, these limits are difficult to overcome, as the operator typically takes time to review the images and plan the best management strategy between injections.

This work has all the limitations typical of retrospective single center registries, including the small sample size, lack of control group, and reliance on surrogate clinical outcomes (17).

In addition, all procedures were performed by a very experienced operator, thus these findings may not apply as well to less skilled colleagues (e.g. trainees).

Notably, given the few patients included and the varying patterns in the types of procedures over time, the play of chance cannot be disregarded as explanation for our results. Learning curves for CO2 angiography could obviously differ substantially between trainees and experienced operators, and accordingly our findings can be extrapolated mainly to operators who are already proficient in diagnostic and interventional procedures with iodinated contrast media. Finally, as other automated injectors for CO2 already exist, further studies from other centers with different expertise and patient populations will be required to verify the present findings.

CONCLUSION

Carbon dioxide-based angiography using an automated injection system appears feasible in patients undergoing infra-diaphragmatic diagnostic or interventional procedures. This technology may appear particularly promising for transcatheter renal sympathetic denervation and lower limb procedures.

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