

# World Journal of *Cardiology*

*World J Cardiol* 2017 September 26; 9(9): 715-772



**MINIREVIEWS**

- 715 Use of carbon dioxide as an intravascular contrast agent: A review of current literature  
*Ali F, Mangi MA, Rehman H, Kaluski E*
- 723 Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis  
*Gopalakrishnan P, Zaidi R, Sardar MR*
- 731 Obesity paradox in patients undergoing coronary intervention: A review  
*Patel N, Elsaid O, Shenoy A, Sharma A, McFarlane SI*
- 737 Brugada type 1 electrocardiogram: Should we treat the electrocardiogram or the patient?  
*Delise P, Allocca G, Sitta N*

**ORIGINAL ARTICLE****Retrospective Cohort Study**

- 742 Clinical and anatomic predictors of need for repeat atrial fibrillation ablation  
*Desai Y, Levy MR, Iravanian S, Clermont EC, Kelli HM, Eisner RL, El-Chami MF, Leon AR, Delurgio DB, Merchant FM*

**Retrospective Study**

- 749 Utility and correlation of known anticoagulation parameters in the management of pediatric ventricular assist devices  
*Bhatia AK, Yabrodi M, Carroll M, Bunting S, Kanter K, Maher KO, Deshpande SR*

**Observational Study**

- 757 Geometric comparison of the mitral and tricuspid valve annulus: Insights from three dimensional transesophageal echocardiography  
*Makaryus AN, Ismail H, Makaryus JN, Fan D*

**SYSTEMATIC REVIEWS**

- 761 Safety, efficiency and cost effectiveness of Bivalirudin: A systematic review  
*Mehrzaad M, Tuktamyshov R, Mehrzaad R*

**ABOUT COVER**

Editorial Board Member of *World Journal of Cardiology*, Paul Erne, Professor, Department of Cardiology, University Hospital, Zurich CH-8091, Switzerland

**AIM AND SCOPE**

*World Journal of Cardiology* (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJC* covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJC*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

**INDEXING/ABSTRACTING**

*World Journal of Cardiology* is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

**FLYLEAF**

**I-IV** Editorial Board

**EDITORS FOR THIS ISSUE**

**Responsible Assistant Editor:** *Xiang Li*  
**Responsible Electronic Editor:** *Ya-Jing Lu*  
**Proofing Editor-in-Chief:** *Lian-Sheng Ma*

**Responsible Science Editor:** *Jin-Xin Kong*  
**Proofing Editorial Office Director:** *Jin-Lai Wang*

**NAME OF JOURNAL**  
*World Journal of Cardiology*

**ISSN**  
 ISSN 1949-8462 (online)

**LAUNCH DATE**  
 December 31, 2009

**FREQUENCY**  
 Monthly

**EDITORS-IN-CHIEF**  
**Jian-Jun Li, MD, PhD, Professor**, Center for Coronary Artery Disease, Fu Wai Cardiovascular Hospital, Chinese Academy of Medical Science, Beijing 100037, China

**Giuseppe De Luca, PhD**, Assistant Professor, Department of Cardiology, Piedmont University, Novara 28100, Italy

**Nathan D Wong, FACC, FAHA, PhD, Director, Professor**, Heart Disease Prevention Program, Division of Cardiology, Department of Medicine, University of California, Irvine, CA 92629, United States

sity of California, Irvine, CA 92629, United States

**EDITORIAL BOARD MEMBERS**  
 All editorial board members resources online at <http://www.wjgnet.com/1949-8462/editorialboard.htm>

**EDITORIAL OFFICE**  
 Xiu-Xia Song, Director  
*World Journal of Cardiology*  
 Baishideng Publishing Group Inc  
 7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
 Telephone: +1-925-2238242  
 Fax: +1-925-2238243  
 E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
 Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLISHER**  
 Baishideng Publishing Group Inc  
 7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
 Telephone: +1-925-2238242  
 Fax: +1-925-2238243  
 E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
 Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLICATION DATE**  
 September 26, 2017

**COPYRIGHT**  
 © 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

**SPECIAL STATEMENT**  
 All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

**INSTRUCTIONS TO AUTHORS**  
<http://www.wjgnet.com/bpg/gerinfo/204>

**ONLINE SUBMISSION**  
<http://www.f6publishing.com>

## Use of carbon dioxide as an intravascular contrast agent: A review of current literature

Fahad Ali, Muhammad Asif Mangi, Hiba Rehman, Edo Kaluski

Fahad Ali, Division of Cardiology, Department of Medicine and Lehigh Valley Hospital, Allentown, PA 18105, United States

Muhammad Asif Mangi, Hiba Rehman, Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Jacksonville, FL 32224, United States

Edo Kaluski, Division of Cardiology, Department of Medicine, Guthrie Robert Packer Hospital and Guthrie Health Services, Sayre, PA 18840, United States

**Author contributions:** All authors contributed to the manuscript equally; all authors read and approved the final manuscript.

**Conflict-of-interest statement:** None of the authors have any conflicts of interest relative to this publication.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to:** Fahad Ali, MD, Division of Cardiology, Department of Medicine and Lehigh Valley Hospital, P.O. Box 689, Allentown, PA 18105, United States. [drfahadalis@yahoo.com](mailto:drfahadalis@yahoo.com)  
Telephone: +1-570-8673025

Received: January 11, 2016

Peer-review started: January 14, 2016

First decision: March 7, 2016

Revised: October 9, 2016

Accepted: October 22, 2016

Article in press: October 24, 2016

Published online: September 26, 2017

### Abstract

Use of X-ray contrast allows us to differentiate between two or more adjacent structures on radiographic studies. The X-ray contrast agent can be the one with increase X-ray absorption, like iodine and a barium X-ray contrast agent or the one with decrease X-ray absorption like air and carbon dioxide contrast agent. Each contrast agent possesses different risks and benefits in various ways. Carbon dioxide as an intravascular contrast agent can be used as an alternative intravascular contrast agent and has superior results in some cases. In patients with renal dysfunction or iodinated contrast allergy, the use of Iodinated Contrast Agent poses the risk of considerable morbidity. Similarly, use of Gadolinium is discouraged in subject with severe renal dysfunction. Use of carbon dioxide (CO<sub>2</sub>) as an intravascular contrast, offers an alternative in such patients for certain procedures, as it is not nephrotoxic and it does not incite allergic reactions. It is inexpensive, readily available and due to its unique physical properties, it can be used to image a wide variety of vascular beds and chambers. The aim of this paper is to systemically review the current literature to describe the indications, contraindications, adverse effects, instruments, precautions, latest methodologies and data supporting for the use of CO<sub>2</sub> as a contrast agent.

**Key words:** Iodinated; Carbon dioxide; Contrast; Vascular; Gadolinium

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** In patients with renal dysfunction or iodinated contrast allergy, use of iodinated contrast agent poses the risk of considerable morbidity. Similarly, use of gadolinium is discouraged in subject with severe renal dysfunction. Use of carbon dioxide (CO<sub>2</sub>) as an intravascular contrast offers an alternative in such patients for certain procedures, as it is not nephrotoxic and it does not incite

allergic reactions. It is inexpensive, readily available and due to its unique physical properties it can be used to image a wide variety of vascular beds and chambers. This article describes the indications, contraindications, adverse effects, instruments, precautions, latest methodologies and data supporting for the use of CO<sub>2</sub> as a contrast agent.

Ali F, Mangi MA, Rehman H, Kaluski E. Use of carbon dioxide as an intravascular contrast agent: A review of current literature. *World J Cardiol* 2017; 9(9): 715-722 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i9/715.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i9.715>

## INTRODUCTION

In medical parlance, contrast is a mean which allows us to differentiate between two or more adjacent elements on a radiographic study. There are essentially two prototypes of X-ray contrast agents: (1) Positive agents (which increase X-ray absorption: Iodine or barium based); and (2) negative agents [decrease X-ray absorption: Air, carbon dioxide (CO<sub>2</sub>)]<sup>[1]</sup>. In animal experiments (1940s) and later in human studies (1950s), CO<sub>2</sub> enabled investigators to delineate both right and left heart structures. With the introduction of digital subtraction angiography (DSA) in 1980s, the image quality improved significantly<sup>[1]</sup>. Conditions where use of iodinated contrast agent (ICA) are precluded such as impaired kidney functions, dye allergy, CO<sub>2</sub> may be used as an alternate contrast agent with comparable results and in some cases superior results<sup>[2-4]</sup>.

### Physical properties

Understanding of physical properties of CO<sub>2</sub> is central for its use. Administration of CO<sub>2</sub> needs extreme care. It is a colorless, odorless and significantly compressible gas. CO<sub>2</sub> has low molecular weight as compared to ICA, is less viscous than blood and ICA and due to this property it can be used to image small collateral vessels. It displaces the blood in the vessels and acts as a negative contrast agent. This property creates a significant gradient between the radiographic density of the vessel wall and the lumen. DSA technique uses this difference in the densities to provide a contrast image. CO<sub>2</sub> is more soluble than oxygen (O<sub>2</sub>) and dissolves in the blood within 2-3 min after injection. When mixed with water it creates carbonic acid (H<sub>2</sub>CO<sub>3</sub>) which dissociates into bicarbonate (HCO<sub>3</sub><sup>-</sup>) and hydrogen (H<sup>+</sup>) ions carried by blood flow to the lungs. Reverse reaction happens in the lungs where the breakdown product of H<sub>2</sub>CO<sub>3</sub>, CO<sub>2</sub> is then exhaled. These chemical reactions are facilitated by enzymes called carbonic anhydrases.

During its use, monitoring of vital signs is required. Capnography if available would be useful in monitoring the ventilation.

### Administration

There are 3 commonly used methods of administering CO<sub>2</sub>. Preferred method is *via* automated injectors (automated CO<sub>2</sub> mmanders). Hand held syringes have been used in the past but are not commonly used now due to increased risk of complications such as air contamination and explosive over dosage<sup>[5,6]</sup>.

**Automated CO<sub>2</sub> mmanders:** Have the utility of being handy, portable, safe and easy to use but their high cost (approximately 3000 USD)<sup>[7]</sup> make them an unpopular choice.

**The modified plastic bag system with O-ring:** Is a preferred method by some experts. Kit packs consisting of bag, tube and valves are available commercially (custom waste management kit by Merit Medical, South Jordan, UT; or Angio-Dynamics Queensbury, NY)<sup>[8,9]</sup>. The usual source of CO<sub>2</sub> is an Aluminum or steel cylinder of medical grade CO<sub>2</sub> which is about 99.99% pure, fitted in a series circuit with a valve, a gauge, a regulator, a diaphragm and an antibacterial filter. A 1500 mL plastic bag with a single port connected with a low pressure tube and a 2-way stopcock at the distal end of the tube is then connected to the CO<sub>2</sub> cylinder. It is then filled and manually purged at least 3 times. The filled bag is then connected at its 2-way stopcock end with an O-ring connector which on the other end is connected with the delivery syringe (20-60 mL). There is a 1-way valve between the O-ring and the syringe. The syringe is then connected with another 1-way valve and then with a 100 cm connecting tube. The distal end of this tube has one more 1-way valve which is then connected with a 3-way valve. This 3-way valve can then be connected with the angiographic catheter. On the other port an additional syringe for back-bleeding or eliminating the air from the system can be attached (Figure 1). To fill the delivery syringe the plunger is simply retracted. The 1-way valves will allow the CO<sub>2</sub> in the plastic bag to move into the syringe. The plunger can then be advanced at the desired rate and amount. The 1-way valves will allow the gas to move towards the 3-way valve which can then be adjusted depending on the ports required to be used. The angiographic catheter is at times filled with blood which can be cleared by using the additional syringe attached at the 3-way valve. Forceful boluses of 3-5 mL CO<sub>2</sub> can be used to clear the catheter from any remaining fluid. The catheter can then be flushed with 1-3 mL of CO<sub>2</sub> every 2-3 min. All the connections of the circuit need to be air tight to avoid any air aspiration or embolism. The plastic bag should be filled enough to remain flaccid as tightly filled bag may pose risk of overdose due to gas compression<sup>[9]</sup>.

**Underwater seal:** This is a relatively simple, inexpensive and easier method but there may be a slight risk of air contamination and or inadvertent explosive

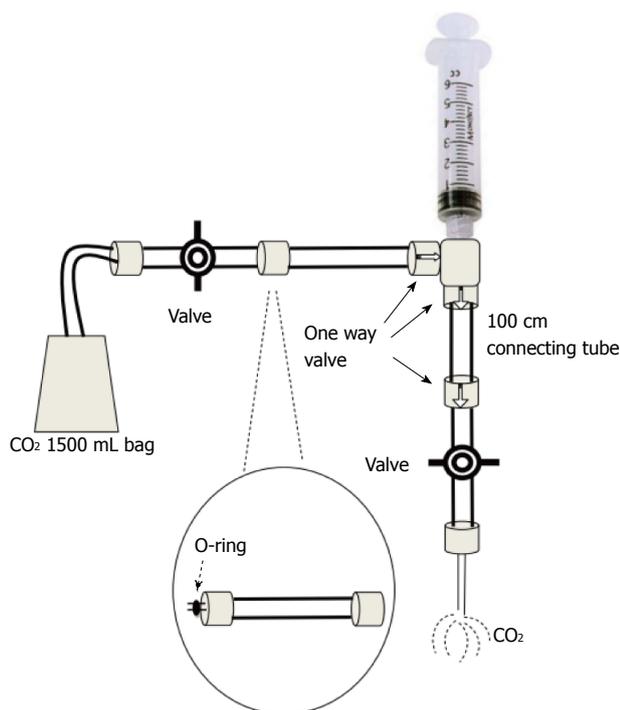


Figure 1 The modified plastic bag system with O-ring.

administration of CO<sub>2</sub> into the patient<sup>[10]</sup>. In this system, the CO<sub>2</sub> source is connected to a regulator, a particle filter and a 3-way tap by connecting tubes. One end of 3-way valve has a sliding 2-way valve connected to a 60 cc syringe. The other end of 3-way valve has a tube serving as a simple under water seal by having the other end of the tube dipped in a bowl of saline. When the CO<sub>2</sub> source is turned on and the 3-way valve is on to the syringe, the syringe will get filled without pulling the plunger, by the positive pressure of the CO<sub>2</sub> coming from the source. Once the syringe is filled the 2-way valve is turned off and 3-way valve is turned to the under-water seal. Bubbles of CO<sub>2</sub> would be seen in the bowl of saline coming out of the tube's end. The CO<sub>2</sub> source is then turned off and the 3-way valve is then turned on to the syringe and the water seal. The CO<sub>2</sub> can then be purged through the water seal. This process of filling and purging can be repeated at least 3 times to make sure that there is only CO<sub>2</sub> and no air in the tubing and syringe system. Then the filled syringe along with a 2-way valve turned off, can then be disconnected and attached to the angiography catheter. Right before it is connected to the angiography catheter, the 2-way valve is turned on to release the positive pressure in the syringe to come down to atmospheric pressure. This will avoid explosive administration and or over dosing of pressurized CO<sub>2</sub> in the syringe but at the same time this may create a very small risk of air contamination. Only fully filled syringes should be used while using this method as half-filled syringes when opened to atmospheric pressure will certainly lead to higher risk of air contamination. The innovators of this system also described their experience of 5 years in

over 250 patients and no directly related complications were noticed<sup>[10]</sup>.

### Dosage

Typically 30-40 mL of CO<sub>2</sub> is injected for abdominal aortography or IVC visualization. Twenty to thirty milliliter is used for lower extremity vessels and other aortic branches like celiac, superior mesenteric or renal arteries. The left renal artery which is more posteriorly located can be filled even with 10 mL if injected with patient lying on the right side. Injections can be repeated at approximately 3 min intervals. Thirty to fifty milliliter may be used for runoff studies by injecting at low rate of 10 mL/s.

### Potential uses of CO<sub>2</sub>-based angiography (Figure 2)

The diagnostic accuracy is acceptable in comparison to contemporary ICA and in some conditions such as TIPS, CO<sub>2</sub> is even rendered superior to the ICA.

**Aortic aneurysm repairs:** CO<sub>2</sub> has been used in endovascular repairs of aortic aneurysms<sup>[11-14]</sup>. A recent prospective study of 72 patients with abdominal aortic aneurysm (AAA) endovascular repair demonstrated that CO<sub>2</sub> has overall sensitivity of 84% and specificity of 72% as compared to ICA as the standard criterion for detection of endoleaks and in patients who are at risk of nephrotoxicity from ICA, CO<sub>2</sub> can be used as an acceptable alternative to ICA<sup>[15]</sup>. Another study describes the outcomes of CO<sub>2</sub>-guided procedures are similar to those which are ICA-guided<sup>[14]</sup>. Additional benefit of CO<sub>2</sub> use in endovascular repair of AAA is that an accessory catheter which is otherwise required for ICA may not be required for CO<sub>2</sub> injection as it can be administered through the endograft sheath or femoral access sheath<sup>[13]</sup>.

**Aortography:** CO<sub>2</sub> may be used for aortography and for runoff studies in most patients<sup>[16]</sup>. If needed supplemental ICA imaging may be used in order to obtain additional information. To get the retrograde aortogram, CO<sub>2</sub> may be injected retrograde through the femoral artery by percutaneous catheterization with a 4-Fr end-hold catheter (Cobra-shaped or shepherd hook catheter) or catheters with side-holes (Omni-flush, pigtail, Racquet, multipurpose). Contra-lateral superficial femoral arterial views can also be taken through the same port by moving the catheter into the contralateral superficial femoral artery. For antegrade views micro-catheters of 3-Fr may be used for popliteal, tibial and peroneal arteries. Use of intra-arterial nitroglycerine and or leg elevation may be done for better visualization of smaller vessels such as tibial and plantar branches.

**Renal artery angiography (Figure 3):** CO<sub>2</sub> can be used in the assessment of renal artery stenosis, aneurysms, AV (arterio-venous) malformations, AV fistulas, renal artery stenting, invading tumors in renal

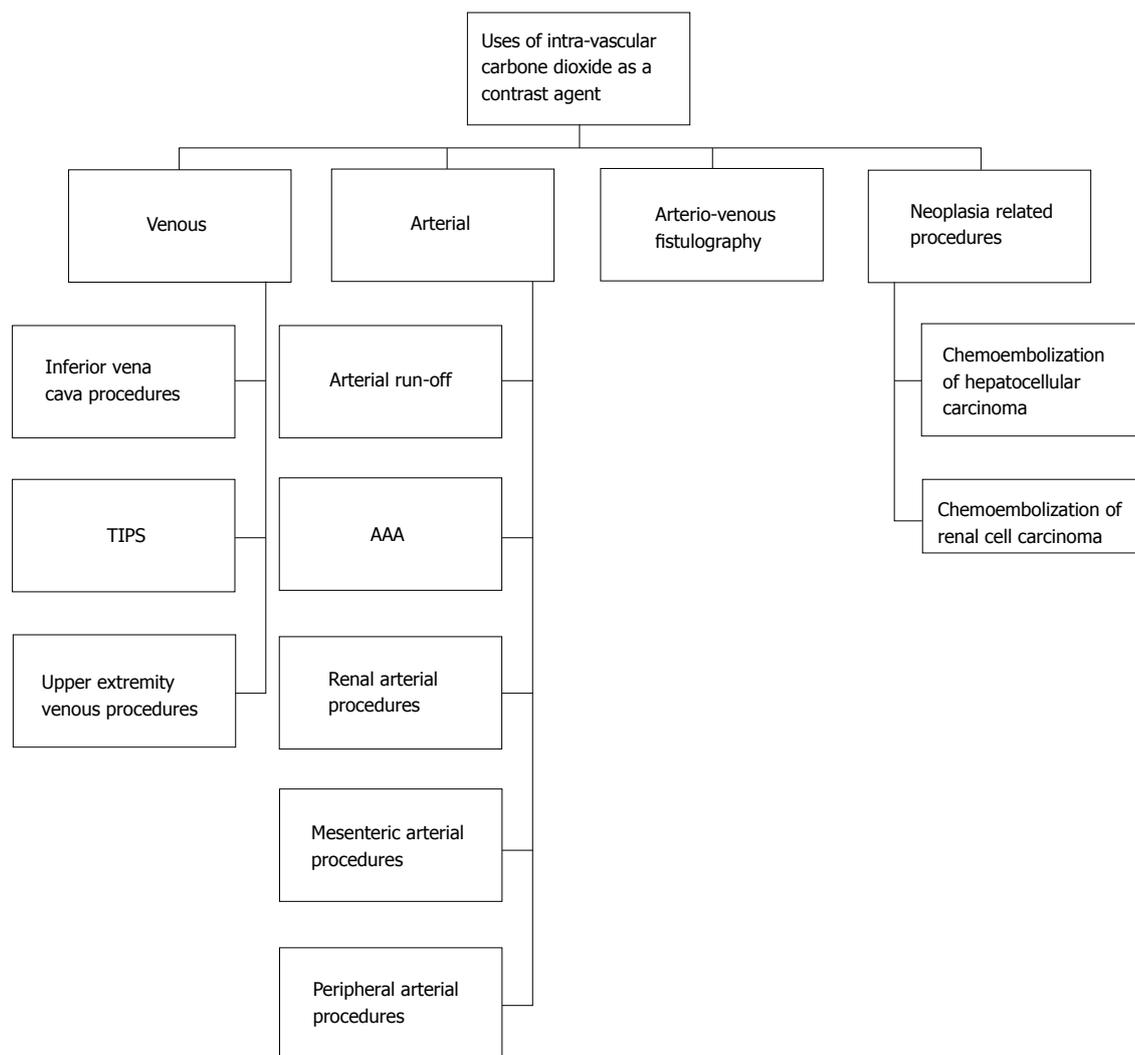


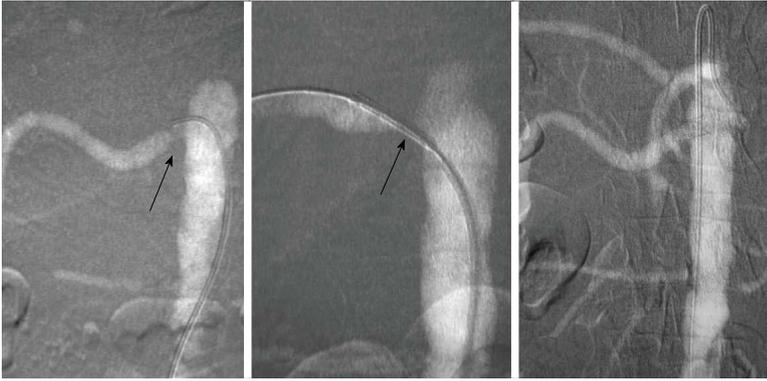
Figure 2 Potential uses of carbon dioxide angiography. AAA: Abdominal aortic aneurysm.

veins or arteries, renal cell carcinomas, evaluation of transplanted kidney vascular stenosis and for its angioplasty and/or stenting, anastomotic stenosis, diffuse arterial disease related to chronic rejection and AV fistulas after renal transplant biopsy (in which case it may be superior to ICA)<sup>[17,18]</sup>. In such cases CO<sub>2</sub> may be used as initial imaging modality to get an overview and then small dose ICA may be used for confirmation of the findings<sup>[11]</sup>. CO<sub>2</sub> does not adequately fill the distal portion of renal artery very well in a supine patient, as it is located posterior to the aorta. In this situation, the patient may be turned on the side to bring the renal arteries superior with respect to the aorta. Recent studies have also demonstrated the use of CO<sub>2</sub> in combination with intravascular ultrasound for successful vascular stenting. In a study of 18 patients, 27 successful renal artery stenting procedures were done using CO<sub>2</sub> and intravascular ultrasound with good outcomes<sup>[19,20]</sup>.

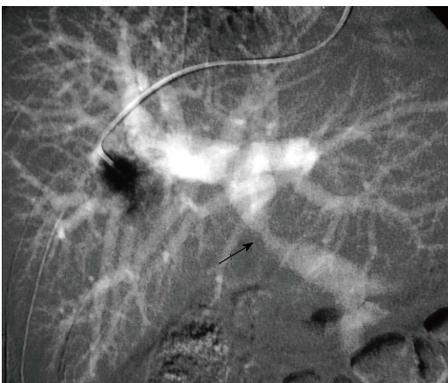
**Inferior venae cava imaging:** CO<sub>2</sub> can be used for the placement of inferior venae cava (IVC) filters, IVC venous

anomalies and thrombus visualization, recanalization of occlusion and estimation of IVC diameters (accuracy of about 97%). In a study of 50 patients, CO<sub>2</sub> was used for IVC filter placement at the bedside in ICU setting. Only 2 of these patients required additional ICA for better visualization. The study concluded with positive results and favored the use of CO<sub>2</sub> as first line contrast agent in ICU patients requiring IVC filter<sup>[21]</sup>.

**Portal vein imaging (portography):** A very important utility of CO<sub>2</sub> is in the delineation of the portal vein anatomy (wedged hepatic venography) during TIPS procedure (Figure 4). CO<sub>2</sub> is found to be superior to ICA for this use and can be used as first line contrast agent for portography<sup>[22]</sup>. The reason is buoyancy and low viscosity of CO<sub>2</sub> making it travelling through the sinusoids easily and deeply. In liver transplants, anastomosis can also be visualized using CO<sub>2</sub>. In a study of 16 patients, the utility of CO<sub>2</sub> was compared with ICA for balloon-occluded retrograde trans-venous venography (BRTV) and obliteration (BRTO) for gastric varices and it was found that varices were visualized



**Figure 3** A carbon dioxide renal arteriogram showing renal artery orifice stenosis with subsequent stent placement and resolution of the stenosis with good flow. The carbon dioxide contrast is injected through the sheath. Adapted with permission from Dr. Kyung Cho.



**Figure 4** Carbon dioxide wedged hepatic protogram showing portal vein stenosis (arrow). Adapted with permission from Dr. Kyung Cho.

better with CO<sub>2</sub> than with ICA and even in cases where ICA could not reach the varices, CO<sub>2</sub> successfully delineated these varices (in 7 out of 16 patients), leading to successful obliteration of the varices<sup>[23]</sup>. According to some estimates, success rate of portal vein visualization with CO<sub>2</sub> wedged hepatic venography is approximately 90%. A diagnostic catheter of 5-Fr can be used for wedged hepatic venography. Using the femoral or jugular vein approach, catheter can be advanced into a peripheral hepatic vein for wedging. It is also being used for multi-detector CT cholangiopancreatography. In a study of 73 patients, the feasibility of CO<sub>2</sub> enhanced CT cholangiopancreatography was assessed and found to be very useful for interventional procedures<sup>[24]</sup>.

**Splenoportography:** Can also be done by using CO<sub>2</sub> in selected patients<sup>[25]</sup> such as a patient in which portal vein imaging study for patency is inconclusive<sup>[26]</sup>. Twenty-two to twenty-five gauge needle can be used to inject CO<sub>2</sub> into the parenchyma of spleen. This is useful in pediatric patients as it obviates the catheterization of femoral artery for arterial portography. Endoscopic ultrasound guided direct portal venography with CO<sub>2</sub> by using a small FNA needle has also been used in animal studies with favorable results<sup>[27]</sup>.

**Tumor embolization procedures:** CO<sub>2</sub> can be used

for the following oncological embolization procedures: Embolization of renal cell carcinoma and its metastatic lesions in the bone, hepatocellular carcinoma<sup>[28,29]</sup>, radiofrequency ablation and transcatheter arterial chemo-embolization of hepatocellular carcinoma (by using intra-arterial CO<sub>2</sub> for enhancement for ultrasonography guidance)<sup>[30]</sup>, uterine artery embolization in uterine leiomyoma<sup>[31]</sup>. These procedures can be optimized by using super-selective angiographic techniques with help of micro-catheters of 3 Fr.

**Upper extremity venography:** Can be performed using the CO<sub>2</sub><sup>[32]</sup>. It can be useful for AV-fistula formation<sup>[33]</sup>, insertions of trans-venous pacer wires<sup>[34]</sup>, central venous catheters and for the delineation of any atypical vascular anatomy. The preferable site of injection is antecubital vein and a 21 gauge catheter may be used. In a series of 146 AV fistulography procedures using CO<sub>2</sub> as the first line contrast agent, 141 cases required AV fistula intervention and in 115 of these cases intervention was performed successfully using CO<sub>2</sub> alone. Rest of the cases required ICA for various reasons in addition to CO<sub>2</sub> for intervention<sup>[35]</sup>. For AV fistula assessment, one needs to be careful of not letting CO<sub>2</sub> reflux into arterial system due to potential risk of neurologic sequelae including infarction. Also there is a potential of overestimation of fistula stenosis.

**Gastrointestinal bleeding:** Due to increased compressibility and low viscosity it may be useful in detecting the site of occult bleeding or ongoing blood loss such as the gastrointestinal tract, with higher sensitivity than ICA. CO<sub>2</sub> can also be used in selected angiographies for chronic mesenteric ischemia<sup>[36]</sup>.

**Contrast ultrasonography:** CO<sub>2</sub> can be used to enhance sonography by employing CO<sub>2</sub> microbubbles. In a study where conventional sonography was compared with CO<sub>2</sub> micro-bubble enhanced sonography; the former detected only 6 tumors however with CO<sub>2</sub>-microbubble enhanced sonography 14 tumors were detected and then treated successfully with radiofrequency ablation

**Table 1 Summary of the characteristics of carbon dioxide and against iodinated contrast agents**

Characteristics	Carbon dioxide	Iodinated contrast agents
Overall sensitivity	Less	Higher
Overall specificity	Less	Higher
Nephrotoxicity	No	Yes
Allergenic	No	Yes
Cost	Low	High
Ease of administration	Cumbersome	Easier
Limitations	Visibility and air contamination	Dose related toxicity and allergy
Delivery <i>via</i> small caliber catheters	Possible	Difficult
Radiation exposure	Increased if digital subtraction angiography used	Standard
Dose	Rate related toxicity	Volume related nephrotoxicity
Contraindications	Pulmonary-systemic communications; not for use in heart, brain or spinal vasculature	Allergy, nephrotoxicity
Hepatotoxicity	Rare	Rare
Quality of image	Good	Better
Procedure duration	Increased	Standard

using CO<sub>2</sub>-microbubbles enhanced sonography<sup>[37]</sup>.

## LIMITATIONS

Overall CO<sub>2</sub> is a relatively safe agent<sup>[38]</sup>. In a study of 800 subjects, only one complication of transient colonic ischemia was reported. In another study of 1200 subjects only 7 subjects developed some kind complication. Livedo reticularis, bowel ischemia and renal dysfunction have been described after in 1 patient with CREST syndrome<sup>[38]</sup> (Table 1).

The adverse effects are primarily either dose related or buoyancy related. Majority of the adverse effects are due to "vapor-lock phenomenon" which result when large amounts of CO<sub>2</sub> are injected or a small amount is injected too frequently with very short intervals causing trapping of CO<sub>2</sub> gas column in the vessel and consequently obstructing the vessel. This may lead to ischemia of the tissues. Cases with transient mesenteric ischemia and ischemic colitis secondary to "vapor lock phenomenon" have been described in the literature. Similar mechanism may potentially precipitate right sided heart failure. Sometimes CO<sub>2</sub> bubbles may accumulate in an aortic aneurysm and may cause blood flow obstruction, leading to tissue ischemia. Even a transient occlusion of inferior mesenteric artery may result in mesenteric ischemia. Typically, this happens with the use of excessive dose of CO<sub>2</sub>. Similarly a vapor lock may happen in the pulmonary artery and this may lead to significant hypotension. Air contamination may also cause vapor-lock phenomenon that is typically worse and more persistent. Usually CO<sub>2</sub> bubbles in the pulmonary artery dissolve within 30 s. If they persist beyond 30 s then either air contamination or CO<sub>2</sub> over-dosage should be suspected and the tubing system should be checked for any air leak. For hypotension secondary to vapor lock phenomenon, patient should be placed in Trendelenburg position or lateral decubitus positions. Aspirating the air using a catheter from the pulmonary artery should also be considered.

Due to its buoyancy the visualization of a dependent

(inferior or caudal positioned) vessels may be sub-optimal (such as visualization of renal arteries in supine position). This problem can be circumvented by putting the patient in lateral decubitus position. CO<sub>2</sub> may get trapped in organs which are non-dependant and cause decreased blood flow or ischemia such as in transplanted kidneys or mesenteric vessels. If we place the patient in lateral decubitus position, the CO<sub>2</sub> may remain trapped in right atrium instead of moving into pulmonary arteries. Changing the body position may help clearance in these situations. Similarly using low volumes of CO<sub>2</sub> with adequate time intervals may help avoiding these adverse effects. Although 100 mL is the recommended maximum volume for arterial use and 50 mL for venous use, by using above mentioned precautions, larger total volume may be used. Vessels which are more anterior such as superior mesenteric artery (SMA), CO<sub>2</sub> is useful in their evaluation, particularly for proximal mesenteric stenosis. For more distal assessment ICA probably provides superior imaging.

Due to its dissolution in blood soon after injection vessels with slower flow may not have adequate visualization and this may lead to overestimation of stenosis. Similarly due to the expansive nature of CO<sub>2</sub> and elasticity of vessels, CO<sub>2</sub> may lead to overestimation of the vessel diameter. This may cause errors in estimation of balloon or stent size during intervention procedures.

The use of CO<sub>2</sub> for cerebral, spinal and or cardiac procedures should be avoided as there is a potential risk of ischemia to vital organs<sup>[39]</sup>. In animal models neurotoxicity has been reported after cerebral use. For the same reasons, before the use of CO<sub>2</sub> presence of atrial or ventricular septal defects or pulmonary arterio-venous malformation should be ruled out to avoid the risk of paradoxical embolism to CNS and or coronary embolization. CO<sub>2</sub> may also aggravate or worsen pulmonary arterial pressure therefore the use of this agent should be avoided in pulmonary hypertension. There are some relative contraindications for the use of CO<sub>2</sub> for upper extremity which are similar for other uses

as well and these are the presence of cardiac septal defects, pulmonary AV malformations, pulmonary hypertension and severe emphysema. In a series of 146 arteriovenous fistulography procedures, in 3 cases when manual injection of CO<sub>2</sub> into the brachial artery was performed, a reflux of the gas into the thoracic aorta occurred precipitating transient loss of consciousness<sup>[35]</sup>.

Typically, CO<sub>2</sub> angiography does not cause any significant changes in the serum osmolality or blood gas values<sup>[40]</sup> unless excessive quantities of CO<sub>2</sub> are used or significant derangements of pulmonary function happen. Caution is required in cases where pulmonary functions are compromised such as in chronic obstructive pulmonary disease, as clearance of CO<sub>2</sub> may be decreased. Doses of CO<sub>2</sub> for diagnostic purposes are typically between 20–40 cc and it has no effect on vital signs. Any change in vital signs should prompt the considerations for air contamination or air trapping.

Peristaltic and breathing movements sometime may decrease the image quality of mesenteric CO<sub>2</sub> angiography. This problem may be avoided by selective or superselective CO<sub>2</sub> injection into the mesenteric arterial branch, getting additional mask images or using intravenous glucagon to suppress the peristalsis. While using CO<sub>2</sub>, sedation should be avoided or minimized as any of the side effects of CO<sub>2</sub> overdosing or air contamination may be missed in the presence of heavy sedation. During the procedure patients vital signs (pulse-oxymetry, blood pressure, heart rate, respiratory rate, ECG, and if possible capnography) need to be monitored closely. Any change in these parameters should raise the suspicion of CO<sub>2</sub> over dosage or air contamination.

The utility of CO<sub>2</sub> as contrast agent for CT angiography for abdominal aorta and peripheral vessels is also currently being evaluated<sup>[41,42]</sup>. In an animal study the use of CO<sub>2</sub> micro-bubbles mixed in saline was compared with conventional CO<sub>2</sub> gas and ICA and demonstrated that vessels can be depicted using X-ray angiography and CO<sub>2</sub> micro-bubbles as enhancement<sup>[43]</sup>. CO<sub>2</sub> bubbles sometimes may provide better visualization than plain CO<sub>2</sub> gas with additional benefit of low dose requirement<sup>[44]</sup>.

## CONCLUSION

CO<sub>2</sub> is useful in cases where ICA cannot be used due to allergy or impaired kidney functions. CO<sub>2</sub> may be superior to ICA in certain procedures such as in TIPS.

## REFERENCES

- 1 **Hawkins IF**, Caridi JG. Carbon dioxide (CO<sub>2</sub>) digital subtraction angiography: 26-year experience at the University of Florida. *Eur Radiol* 1998; **8**: 391-402 [PMID: 9510571]
- 2 **Shipovskii VN**, Kurbanov RV, Saakian AM, Marov KB. Carbonyl angiography: a new type of opacification in angiographic practice—first clinical experience. *Angiol Sosud Khir* 2010; **16**: 73-79 [PMID: 21389948]
- 3 **Hawkins IF**, Cho KJ, Caridi JG. Carbon dioxide in angiography to reduce the risk of contrast-induced nephropathy. *Radiol Clin North*

- Am* 2009; **47**: 813-825, v-vi [PMID: 19744596 DOI: 10.1016/j.rcl.2009.07.002]
- 4 **Chanis G**. [Carbon dioxide angiography: technique and indications]. *Rev Med Panama* 2002; **27**: 18-25 [PMID: 16737194]
- 5 **Corazza I**, Rossi PL, Feliciani G, Pisani L, Zannoli S, Zannoli R. Mechanical aspects of CO<sub>2</sub> angiography. *Phys Med* 2013; **29**: 33-38 [PMID: 22138139 DOI: 10.1016/j.ejmp.2011.11.003]
- 6 **Kawasaki D**, Fujii K, Fukunaga M, Masutani M, Nakata A, Masuyama T. Safety and efficacy of endovascular therapy with a simple homemade carbon dioxide delivery system in patients with iliofemoral artery diseases. *Circ J* 2012; **76**: 1722-1728 [PMID: 22504126]
- 7 **AngioAdvancements**. Products. [accessed 2015 Mar 21]. Available from: URL: <http://www.angioadvancements.com/Products.html>
- 8 **Funaki B**. Carbon dioxide angiography. *Semin Intervent Radiol* 2008; **25**: 65-70 [PMID: 21326495 DOI: 10.1055/s-2008-1052308]
- 9 **Hawkins IF**, Caridi JG, Klioze SD, Mladinich CR. Modified plastic bag system with O-ring fitting connection for carbon dioxide angiography. *AJR Am J Roentgenol* 2001; **176**: 229-232 [PMID: 11133571 DOI: 10.2214/ajr.176.1.1760229]
- 10 **Cronin P**, Patel JV, Kessel DO, Robertson I, McPherson SJ. Carbon dioxide angiography: a simple and safe system of delivery. *Clin Radiol* 2005; **60**: 123-125 [PMID: 15642303 DOI: 10.1016/j.crad.2004.05.005]
- 11 **Knipp BS**, Escobar GA, English S, Upchurch GR, Criado E. Endovascular repair of ruptured aortic aneurysms using carbon dioxide contrast angiography. *Ann Vasc Surg* 2010; **24**: 845-850 [PMID: 20831984 DOI: 10.1016/j.avsg.2010.05.013]
- 12 **Lee AD**, Hall RG. An evaluation of the use of carbon dioxide angiography in endovascular aortic aneurysm repair. *Vasc Endovascular Surg* 2010; **44**: 341-344 [PMID: 20308167 DOI: 10.1177/1538574410364252]
- 13 **Criado E**, Kabbani L, Cho K. Catheter-less angiography for endovascular aortic aneurysm repair: a new application of carbon dioxide as a contrast agent. *J Vasc Surg* 2008; **48**: 527-534 [PMID: 18632243 DOI: 10.1016/j.jvs.2008.04.061]
- 14 **Chao A**, Major K, Kumar SR, Patel K, Trujillo I, Hood DB, Rowe VL, Weaver FA. Carbon dioxide digital subtraction angiography-assisted endovascular aortic aneurysm repair in the azotemic patient. *J Vasc Surg* 2007; **45**: 451-458 [PMID: 17254739 DOI: 10.1016/j.jvs.2006.11.017]
- 15 **Huang SG**, Woo K, Moos JM, Han S, Lew WK, Chao A, Hamilton A, Ochoa C, Hood DB, Rowe VL, Weaver FA. A prospective study of carbon dioxide digital subtraction versus standard contrast arteriography in the detection of endoleaks in endovascular abdominal aortic aneurysm repairs. *Ann Vasc Surg* 2013; **27**: 38-44 [PMID: 23257072 DOI: 10.1016/j.avsg.2012.10.001]
- 16 **Ho CF**, Chern MS, Wu MH, Wu HM, Lin WC, Chang CY, Chen MC, Chou TY. Carbon dioxide angiography in lower limbs: a prospective comparative study with selective iodinated contrast angiography. *Kaohsiung J Med Sci* 2003; **19**: 599-607 [PMID: 14719557 DOI: 10.1016/S1607-551X(09)70513-3]
- 17 **Cheng PM**, Van Allan RJ. Superior sensitivity of angiographic detection of arteriovenous fistula after biopsy in a renal allograft with CO<sub>2</sub> compared with iodinated contrast medium. *J Vasc Interv Radiol* 2006; **17**: 1963-1966 [PMID: 17185694 DOI: 10.1097/01.RVI.0000252569.30036.F3]
- 18 **Pérez L**, Lecannelier E, Fernández A, Parra J, Aburto G, Robles I. [Renal angioplasty with stent using CO<sub>2</sub> as contrast medium: report of one case]. *Rev Med Chil* 2007; **135**: 365-369 [PMID: 17505583]
- 19 **Kawasaki D**, Fujii K, Fukunaga M, Fukuda N, Masuyama T, Ohkubo N, Kato M. Safety and efficacy of carbon dioxide and intravascular ultrasound-guided stenting for renal artery stenosis in patients with chronic renal insufficiency. *Angiology* 2015; **66**: 231-236 [PMID: 24604913 DOI: 10.1177/0003319714524297]
- 20 **Kusuyama T**, Iida H, Mitsui H. Intravascular ultrasound complements the diagnostic capability of carbon dioxide digital subtraction angiography for patients with allergies to iodinated contrast medium. *Catheter Cardiovasc Interv* 2012; **80**: E82-E86 [PMID: 22887964 DOI: 10.1002/ccd.24577]

- 21 **Schmelzer TM**, Christmas AB, Jacobs DG, Heniford BT, Sing RF. Imaging of the vena cava in the intensive care unit prior to vena cava filter insertion: carbon dioxide as an alternative to iodinated contrast. *Am Surg* 2008; **74**: 141-145 [PMID: 18306866]
- 22 **Maruyama H**, Okugawa H, Ishibashi H, Takahashi M, Kobayashi S, Yoshizumi H, Yokosuka O. Carbon dioxide-based portography: an alternative to conventional imaging with the use of iodinated contrast medium. *J Gastroenterol Hepatol* 2010; **25**: 1111-1116 [PMID: 20594227 DOI: 10.1111/j.1440-1746.2010.06248.x]
- 23 **Koizumi J**, Hashimoto T, Myojin K, Itou C, Hara T, Sekiguchi T, Ichikawa T, Imai Y, Kagawa T, Nagata N, Watanabe N, Mine T, Nishibe T, Saguchi T, Janne d'Othée B. Carbon dioxide (CO<sub>2</sub>) vs iodinated contrast digital subtraction angiography during balloon-occluded retrograde transvenous obliteration (BRTO) using foam sclerosant for gastric varices. *J Vasc Interv Radiol* 2012; **23**: 1453-1459.e1 [PMID: 23101917 DOI: 10.1016/j.jvir.2012.08.004]
- 24 **Sugimoto M**, Yasuda H, Koda K, Suzuki M, Yamazaki M, Tezuka T, Kosugi C, Higuchi R, Watayo Y, Yagawa Y, Uemura S, Tsuchiya H, Azuma T. Carbon dioxide-enhanced virtual MDCT cholangio-pancreatography. *J Hepatobiliary Pancreat Sci* 2010; **17**: 601-610 [PMID: 19806296 DOI: 10.1007/s00534-009-0201-8]
- 25 **Yu SC**, Cho KJ. Carbon dioxide wedged arterial splenoportography: a new technique--a case report and an experimental study. *Acta Radiol* 2009; **50**: 265-269 [PMID: 19235576 DOI: 10.1080/02841850802712676]
- 26 **Teng GJ**. [Novel use of CO<sub>2</sub> splenoportography: via spleen percutaneous fine needle puncture portography]. *Zhonghua Yixue Zazhi* 2005; **85**: 295-296 [PMID: 15854499]
- 27 **Giday SA**, Ko CW, Clarke JO, Shin EJ, Magno P, Jagannath SB, Buscaglia JM, Kantsevov SV. EUS-guided portal vein carbon dioxide angiography: a pilot study in a porcine model. *Gastrointest Endosc* 2007; **66**: 814-819 [PMID: 17905028 DOI: 10.1016/j.gie.2007.05.056]
- 28 **Wong AA**, Charalel RA, Louie JD, Sze DY. Carbon dioxide contrast enhancement for C-arm CT utility for treatment planning during hepatic embolization procedures. *J Vasc Interv Radiol* 2013; **24**: 975-980 [PMID: 23796085 DOI: 10.1016/j.jvir.2013.03.029]
- 29 **Sonoda A**, Nitta N, Ushio N, Nitta-Seko A, Tomozawa Y, Watanabe S, Ohta S, Takahashi M, Murata K. 320-detector-row computed tomography arteriography using CO<sub>2</sub> gas to detect malignant liver tumors. *Minim Invasive Ther Allied Technol* 2013; **22**: 89-96 [PMID: 22967137 DOI: 10.3109/13645706.2012.704876]
- 30 **Ohmoto K**, Yoshioka N, Tomiyama Y, Shibata N, Kawase T, Yoshida K, Kuboki M, Yamamoto S. Use of intra-arterial carbon-dioxide-enhanced ultrasonography for guidance of radiofrequency ablation and transcatheter arterial chemoembolization in hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2006; **29**: 1111-1113 [PMID: 16933161 DOI: 10.1007/s00270-005-0285-8]
- 31 **Kim HS**, Tsai J, Paxton BE. Safety and utility of uterine artery embolization with CO<sub>2</sub> and a gadolinium-based contrast medium. *J Vasc Interv Radiol* 2007; **18**: 1021-1027 [PMID: 17675621 DOI: 10.1016/j.jvir.2007.03.014]
- 32 **Heye S**, Maleux G, Marchal GJ. Upper-extremity venography: CO<sub>2</sub> versus iodinated contrast material. *Radiology* 2006; **241**: 291-297 [PMID: 16928973 DOI: 10.1148/radiol.2411050714]
- 33 **Heye S**, Fourneau I, Maleux G, Claes K, Kuypers D, Oyen R. Preoperative mapping for haemodialysis access surgery with CO<sub>2</sub> venography of the upper limb. *Eur J Vasc Endovasc Surg* 2010; **39**: 340-345 [PMID: 20080420 DOI: 10.1016/j.ejvs.2009.11.036]
- 34 **Winters SL**, Curwin JH, Sussman JS, Coyne RF, Calhoun SK, Yablonsky TM, Schwartz JR, Quinlan K. Utility and safety of axillo-subclavian venous imaging with carbon dioxide (CO) prior to chronic lead system revisions. *Pacing Clin Electrophysiol* 2010; **33**: 790-794 [PMID: 20132493 DOI: 10.1111/j.1540-8159.2009.02680.x]
- 35 **Kariya S**, Tanigawa N, Kojima H, Komemushi A, Shiraishi T, Kawanaka T, Sawada S. Efficacy of carbon dioxide for diagnosis and intervention in patients with failing hemodialysis access. *Acta Radiol* 2010; **51**: 994-1001 [PMID: 20942731 DOI: 10.3109/02841851.2010.518159]
- 36 **Textor HJ**, Wilhelm K, Strunk H, Schüller H, Schild HH. [The diagnosis of intra-abdominal hemorrhages with CO<sub>2</sub> as the contrast medium]. *Rofo* 1997; **166**: 51-53 [PMID: 9072105 DOI: 10.1055/s-2007-1015377]
- 37 **Miyamoto N**, Hiramatsu K, Tsuchiya K, Sato Y. Carbon dioxide microbubbles-enhanced sonographically guided radiofrequency ablation: treatment of patients with local progression of hepatocellular carcinoma. *Radiat Med* 2008; **26**: 92-97 [PMID: 18301986 DOI: 10.1007/s11604-007-0198-3]
- 38 **Johnson PL**, Neperud J, Arnold J, Thomas J. Livedo reticularis and bowel ischemia after carbon dioxide arteriography in a patient with CREST syndrome. *J Vasc Interv Radiol* 2011; **22**: 395-399 [PMID: 21277800 DOI: 10.1016/j.jvir.2010.11.012]
- 39 **Culp WC**, Porter TR, Culp WC, Vonk BN. Carbon dioxide in the aortic arch: coronary effects and implications in a swine study. *Cardiovasc Intervent Radiol* 2003; **26**: 128-135 [PMID: 12616418 DOI: 10.1007/s00270-002-2623-4]
- 40 **Barrera F**, Durant TM, Lynch PR, Oppenheimer MJ, Stauffer HM, Stewart GH. In vivo visualization of intracardiac structures with gaseous carbon dioxide; cardiovascular-respiratory effects and associated changes in blood chemistry. *Am J Physiol* 1956; **186**: 325-334 [PMID: 13362532]
- 41 **Penzkofer T**, Slebocki K, Grommes J, Bruners P, Isfort PP, Heussen N, Schmitz-Rode T, Kuhl CK, Langer S, Mahnken AH. Carbon dioxide-contrasted computed tomography angiography: high pitch protocols and adapted injection parameters improve imaging quality. *Rofo* 2013; **185**: 128-135 [PMID: 23196833 DOI: 10.1055/s-0032-1325603]
- 42 **Mahnken AH**, Penzkofer T, Grommes J, Isfort P, Bruners P, Langer S, Schmitz-Rode T, Mommertz G. Carbon dioxide-enhanced CT-guided placement of aortic stent-grafts: feasibility in an animal model. *J Endovasc Ther* 2010; **17**: 332-339 [PMID: 20557172 DOI: 10.1583/09-2969R.1]
- 43 **Kariya S**, Komemushi A, Nakatani M, Yoshida R, Sawada S, Tanigawa N. CO<sub>2</sub> microbubble contrast enhancement in x-ray angiography. *Clin Radiol* 2013; **68**: 346-351 [PMID: 22981730 DOI: 10.1016/j.crad.2012.08.011]
- 44 **Okumura Y**, Kakuchi Y, Katano K, Takahashi S. [Visualization of stenosis in vascular access by bubble method under carbon dioxide (CO<sub>2</sub>) angiographic procedures]. *Nihon Hoshasen Gijutsu Gakkai Zasshi* 2010; **66**: 893-900 [PMID: 20953105]

**P- Reviewer:** Landesberg G, Maruyama H **S- Editor:** Kong JX  
**L- Editor:** A **E- Editor:** Lu YJ





Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

