Comparison Between Intra-Arterial Carbon Dioxide and Iodinated Contrast Agent Injections in Patients With Lower-Limb Peripheral Arterial Diseases and Mild-to-Moderate Renal Dysfunction: A Randomized Controlled Trial

Omid Shafe, MD[1]; Ehsan Samiee, MD[1]; Jamal Moosavi, MD[1]; Bahram Mohebbi, MD[1]; Amir A. Fakhrabadi, MD[1,2]; Hooman Bakhshandeh, MD, PhD[2,3]; Batoul Naghavi, MD, MPH[1,2]; Reza Tahivili[1]; Saeed Cheraghi[1]; Parham Sadeghipour, MD[1,2]

Abstract

Background. This randomized, controlled trial was designed to compare the rate of postangiographic contrast-induced nephropathy (CIN) between the intra-arterial injections of carbon dioxide (CO_2) and the iodinated contrast agent (ICA). The study population was chosen to investigate the direct toxicity of the ICA while eliminating the role of catheter manipulation and the resultant microembolization as a confounding cause of CIN. **Methods.** Candidates for lower-limb endovascular procedures with a baseline glomerular filtration rate exceeding 30 mL/min/1.73 m^2 were randomized into CO_2 and ICA angiography groups. The primary endpoint of this study was the occurrence of CIN, defined as an elevation in baseline serum creatinine exceeding 25% or 0.5 mg/dL within 72 hours after the procedure. **Results.** The study population comprised 110 patients: 57 in the ICA group and 53 in the CO_2 group. The incidence of CIN was significant in the ICA group compared with the CO_2 group (13 [22.8%] vs 4 [7.5%], respectively; *P*=.03). Our multivariate regression analysis determined ICA volume to be a significant predictor of CIN. **Conclusion.** In the present study, which was performed on patients undergoing lower-limb endovascular procedures with mild-to-moderate renal dysfunction, CO_2 angiography decreased CIN incidence. The ICA volume was an important predictor of CIN in the absence of microembolization.

J CRIT LIMB ISCHEM 2021;1(3):E104-E109. Epub 2021 August 9.

Key words: carbon dioxide angiography, contrast-induced nephropathy, digital subtraction angiography, peripheral arterial disease

Contrast-induced nephropathy (CIN) is a postprocedural rise in creatinine of >25% above the baseline.[1] CIN is a well-recognized complication of diagnostic angiography or percutaneous and coronary interventions, and it can increase not only morbidity and mortality rates but also healthcare costs.[1,2] The prevalence of CIN is reported to range between 1% and 45% according to comorbidities in various populations and different definitions in studies.[3] CIN is among the most common etiologies of hospital-acquired renal insufficiency,[4] with high in-hospital and 12-month direct healthcare costs.[5] Indeed, CIN increases in-hospital mortality (odds ratio, 5.5), with 1-year mortality rising among patients whether they require dialysis or not (45.2% and 35.4%, respectively).[6]

CIN usually occurs within 24 to 72 hours after the administration of the iodinated contrast agent (ICA).[7] Conditions such as chronic kidney disease, diabetes, congestive heart failure, anemia, increased age, cirrhosis, non-steroidal anti-inflammatory drug or diuretic consumption, proteinuria, dehydration, peripheral artery disease, and hypertension could increase the risk of CIN.[8,9]

The plausible mechanisms of CIN include the direct toxicity of the ICA on nephrons and catheter manipulations in the arterial system upstream from the renal arteries, causing microembolic showers into the renal arteries.[8-13] The cited etiologies are bolstered by reports of higher rates of CIN in patients who undergo intra-arterial ICA injection or angiography via femoral access, in which the risk of CIN increases due to catheter manipulation.[12,14] Theoretically, carbon dioxide (CO_2) does not cause renal toxicity directly; hence, the increasing popularity of CO_2 use as an alternative to the ICA in diagnostic and endovascular procedures in both venous and arterial systems below the diaphragm.[15,16] In the present study, we sought to compare intra-arterial CO_2 and ICA injections in terms of their effects on the incidence of CIN in patients undergoing infrainguinal endovascular procedures.

Methods

Study design. The present study is a single-center, open-label, parallel, randomized controlled trial. The participants were randomly assigned to 2 contrast-type groups: CO_2 and the ICA. Randomization was performed with a web-based system via the simple random sampling method and allocation sequence concealment. All the patients provided written informed consent, and the study protocol complied with the Declaration of Helsinki. The study was approved by the ethics committee of Rajaie Cardiovascular Medical and Research Center (Ethic ID: IR.RHC.REC.1398.055), and it was registered in the Iranian Registry of Clinical Trials (IRCT 20191107045359N1).

Study population. All candidates for peripheral lower-limb angiography older than 18 years of age and with a baseline glomerular filtration rate (GFR) of >30 mL/min/1.73 m² based on the Modification of Diet in Renal Disease (MDRD) equation were considered eligible for recruitment in the study. The exclusion criteria were a history of contrast exposure in the preceding 30 days, heart or kidney transplantation, proteinuria, or cirrhosis; chronic hemodialysis fluctuations in serum creatinine levels exceeding 15% in the preceding 2 days; the presence of intracardiac shunts; and the need for catheterization higher than the renal arteries including antegrade upper limb access (radial or brachial arteries). For the prevention of confounding effects, patients allocated to the CO_2 group who might need the administration of >20 mL of the ICA based on the results of a previous study[17] were also excluded from this study.

Study interventions. According to the contrast medium selected for the procedure, the study patients were randomized into a CO_2 group and an ICA group. A low-osmolar ICA diluted at a minimum 1:3 ratio was used for the current study. Automated injection (Angiodroid SRL) was employed for CO_2 angiography. The preprocedural work-up included thorough clinical examination, complete blood count, and baseline biochemical examination (the levels of blood urea nitrogen, serum creatinine, blood glucose, sodium, and potassium, as well as the prothrombin time). A unified protocol was drawn upon for hydration in both groups. Both groups were hydrated based on the left ventricular ejection fraction (LVEF) in the period starting 12 hours before and 6 hours after the procedure. Intravenous saline (0.9%) was administered at a rate of 1 mL/kg/h to patients with LVEFs >30% and at a rate of 0.5 mL/kg/h to those with LVEFs ≤30%. All procedures were performed below the renal arteries via lower-limb access sites, including retrograde common femoral access with the conversion potential to crossover access for angiography or endovascular management on the contralateral limbs, antegrade femoral access, retrograde pedal access, and popliteal access. For the prevention of microembolic showers in the renal arteries during the crossover technique, special measures were taken to maintain catheters and sheets below the renal arteries. Both ICA and CO_2 angiography procedures were performed under mild sedation. Blood urea nitrogen and serum creatinine were measured 72 hours after the procedure.

Study endpoints. The primary endpoint of this study was the occurrence of CIN, defined as a rise in baseline serum creatinine exceeding 25% or 0.5 mg/dL within 72 hours after the procedure. The secondary endpoint was death or the need for kidney replacement therapy during a 1-month follow-up period. Limb or abdominal pain due to CO_2 injection was also recorded.

Statistical analysis. The fitness of interval variables to normal distribution was assessed via the 1-sample Kolmogorov–Smirnov test. The data were described as mean ± standard deviation for continuous variables and as frequencies (percentages) for nominal variables. Comparisons between the 2 study groups were performed using the independent sample t-test for interval variables and the Pearson Chi-square or Fisher's exact test for categorical variables. A multivariate analysis was applied through a binary logistic regression model to investigate the adjusted association between CIN and the intra-arterial injection of CO_2 or the ICA. A *P*-value of <.05 was considered statistically significant. The statistical analyses were performed with IBM SPSS Statistics, version 22, for Windows (IBM, Inc).

Results

The study population comprised 110 patients who were randomly divided into the ICA group (n = 57) and the CO_2 group (n = 53). The participants' demographic, clinical, and procedural characteristics are summarized in **Table 1**. Except for baseline creatinine, which was significantly higher in the CO_2 group (1.46 ± 0.45 mg/dL vs 1.13 ± 0.28 mg/dL; *P*<.01), and also the baseline GFR, which was significantly lower in the CO_2 group (60.86 ± 22.01 mL/min/1.73 m² vs 74.7 ± 23.62 mL/min/1.73 m²; *P*<.01), the other variables were not significantly

TABLE 1. Comparison of the participants' characteristics between the 2 study groups.

Characteristics	Iodine Contrast (n = 57)	Carbon Dioxide (n = 53)	*P*-Value
Female patients	11 (19.3%)	13 (24.5%)	.83
Age (years)	63.28 ± 11.74	62.50 ± 8.44	.69
Body mass index (kg/m²)	29.21 ± 2.29	29.86 ± 2.03	.10
Diabetes mellitus	23 (40.4%)	27 (50.7%)	.34
Dyslipidemia	15 (26.3%)	16 (30.2%)	.68
Cigarette smoking	36 (63.2%)	37 (69.8%)	.56
Ejection fraction (≤30%)	3 (5.3%)	1 (1.9%)	.62
Baseline glomerular filtration rate (mL/min)	74.7 ± 23.62	60.86 ± 22.01	<.01
Baseline creatinine (mg/dL)	1.13 ± 0.28	1.46 ± 0.45	<.01
Complaint at admission			.42
Claudication	41 (71.92%)	40 (75.47%)	
Critical limb ischemia	16 (28.08%)	13 (14.53%)	

Data presented as mean ± standard deviation or counts (percentages).

different between the 2 study groups. Diagnostic-only angiography was performed in 32 patients (29.0%) and diagnostic and endovascular procedures were performed in 78 patients (70.0%). Aortoiliac, femoropopliteal, and infrapopliteal endovascular procedures were performed in 15 (13.6%), 31 (28.1%), and 32 (29.0%) of the remaining population, respectively. All of the procedures were successful, without any major vascular or allergic contrast-medium related complications. In the CO_2 group, 12 patients (22.64%) experienced mild self-limiting lower-limb pain. The mean volume of the iodinated contrast medium was 11.35 ± 6.09 mL in the CO_2 group and 93.15± 43.01 mL in the ICA group.

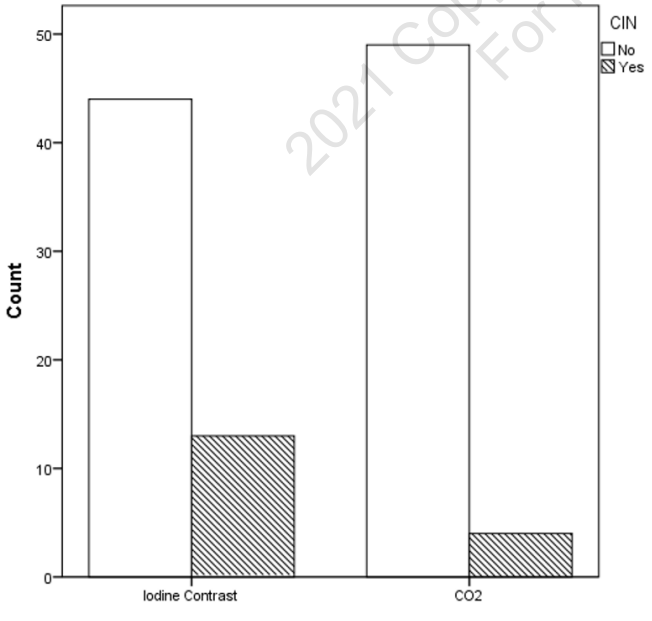

FIGURE 1. The bar chart depicts a comparison of the incidence of contrast-induced nephropathy (CIN) between the iodine contrast agent (ICA) group and the carbon dioxide (CO_2) group.

The incidence of CIN, as the primary endpoint, was higher in the ICA group than in the CO_2 group (13 [22.8%] vs 4 [7.5%]; *P*=.03) (**Figure 1**). The differences in terms of GFR and creatinine between the groups are summarized in **Table 2**. None of the patients in the 2 groups required hemodialysis. The incidence of CIN was correlated with a higher contrast volume. The mean ICA dose in patients without CIN was 44.54 ± 41.14 mL vs 100.88 ± 65.34 mL in those who developed CIN (*P*<.01). There were no deaths or need for renal replacement therapy during the 1-month follow-up, as the secondary endpoint.

The multivariate logistic regression model, after adjustments for the baseline creatinine level and other factors, showed that whereas no significant associations existed between CO_2 treatment and CIN incidence, there was a weak positive association between the volume of the iodinated contrast medium and CIN. The association between age and CIN, albeit non-significant, was considerable (**Figure 2**).

Discussion

To investigate the potential role of different confounding factors vis-à-vis CIN after invasive angiography, given the paucity of randomized controlled trials on the pathophysiology of CIN and the role of potential confounding factors such as catheter manipulation, we designed the present randomized controlled trial and assessed the effects of CO_2 in comparison with ICA in patients with mild-to-moderate renal impairment

Table 2. Creatinine and glomerular filtration rate alterations during the first 72 hours post procedure.

	Iodine Contrast	Carbon Dioxide	*P*-Value
Absolute creatinine change	0.0561	-0.1094	<.01
Perceptual/relative change (%)	7.5292	-6.5700	<.001
Absolute glomerular filtration rate change	-5.3018	4.6170	<.001
Perceptual/relative glomerular filtration rate change (%)	-3.5592	9.3129	<.001

undergoing lower-limb peripheral angiography. Our inclusion criteria ensured the presence of the fewest confounding factors. For instance, the study population consisted of patients with non-severe chronic kidney disease to lessen the role of renal dysfunction. Additionally, lower-limb angiography/angioplasty was chosen to omit the role of catheter manipulation higher than the renal arteries and the resultant distal embolization. Our results revealed a lower rate of CIN in the CO_2 group than in the ICA group (13 [22.8%] vs 4 [7.5%], respectively; *P*=.03). Importantly, the volume of the contrast medium compared with baseline GFR was an important predictor of CIN, even in a setting where the potential roles of catheter manipulation and microembolization were eliminated.[18] Although weak, this effect persisted after the multivariate analysis.

CIN is a generally uncommon but potentially devastating complication with significant morbidity and mortality.[19] In a previous study, CIN increased in-hospital mortality on average by 5.5-fold, with the rise persisting during a long-term follow-up.[4] Despite a significant rise in mortality in patients requiring dialysis, the impact of CIN on the population without the need for renal replacement therapy is also considerable. A previous investigation reported the occurrence of this rise in the mortality rate regardless of baseline creatinine.[20] Research has shown that the incidence of CIN varies according to patients'

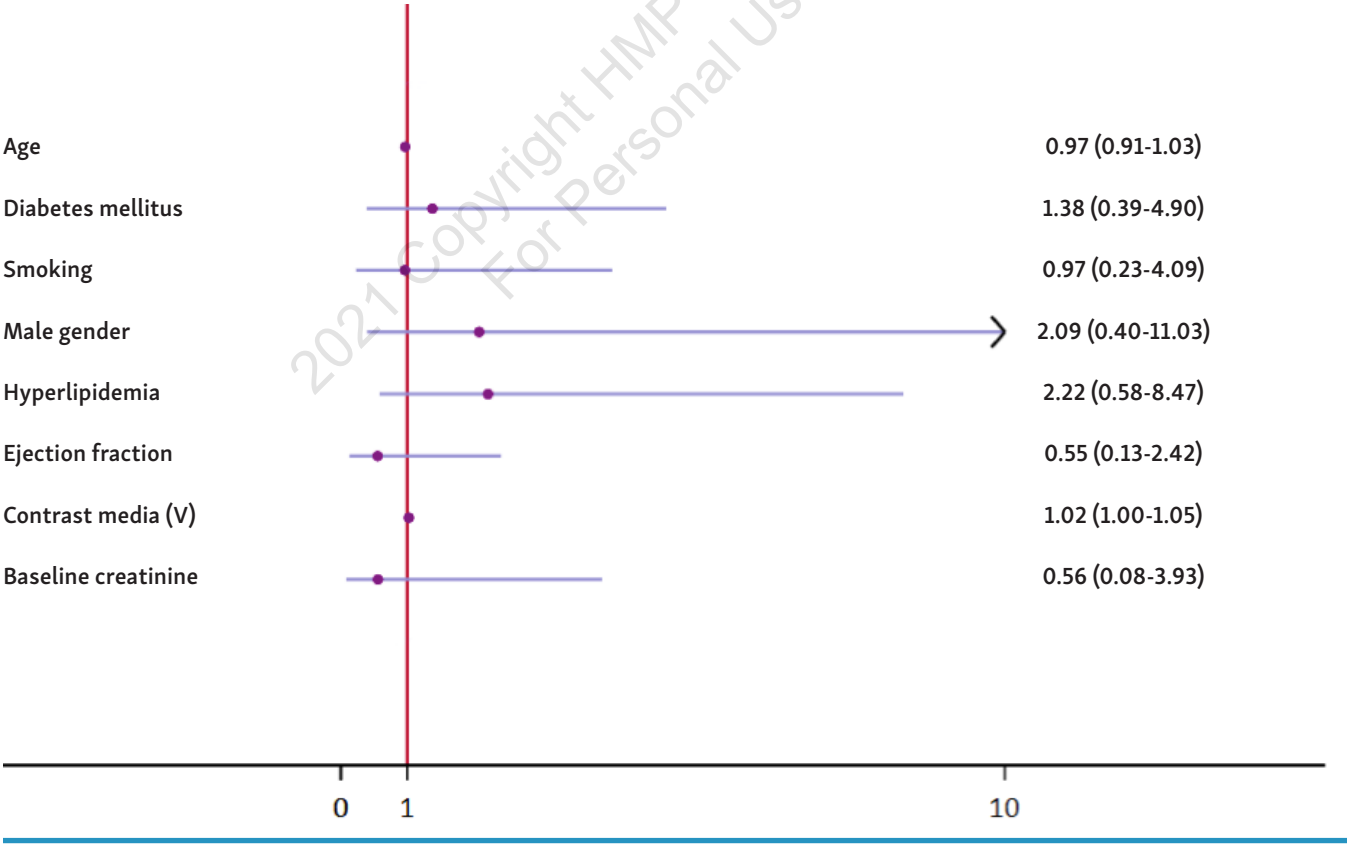

FIGURE 2. The image presents the results of the multivariate logistic regression model for adjusted associations between the study variables and the incidence of contrast-induced nephropathy. Data presented as odds ratio (95% confidence interval).

comorbidities and procedural settings,[3] but it persists as one of the most common etiologies of acquired in-hospital acute renal failure.[4] The average in-hospital and 1-year cost of CIN was reported to have increased by $10,345 and $11,812, respectively, which underscores the economic burden of the complication.[5] The results of a prior study showed that in patients complicated by CIN, compared with an uncomplicated population, hospital stay was lengthened irrespective of previous renal function (6.8 ± 7.1 days vs 2.3 ± 2.5 days in patients with previous kidney disease and 3.6 ± 5.1 days vs 1.8 ± 2.4 days in patients without kidney disease).[6] Patients suffering from peripheral artery disease and comorbidities, such as chronic kidney disease, diabetes mellitus, hypertension, and heart failure, as well as older age, are at a higher risk of CIN.[21,22] The roles of preventive measures such as hydration,[23] adjunctive therapies (eg, statin, N-acetylcysteine, and sodium bicarbonate),[24] and sophisticated methods like left ventricular end-diastolic pressure-guided hydration[25] are still controversial. The current medical armamentarium lacks a definitive treatment for this complication and the suggested preventive measures are controversial; hence, the significance of having a clear pathophysiological picture of CIN. The pathophysiology of CIN encompasses various factors, such as direct cytotoxic effects and the related acute sustained vasoconstriction, unstable hemodynamics, autocrine and paracrine factors, hypoxia, and direct tubular endothelial injury with reactive oxygen species.[26,27] Catheter manipulation and the ensuing microembolic showers through the kidney circulation are also deemed a potential cause of CIN.[12,14] Notably, chronic kidney disease (estimated GFR <60 mL/min/1.73 m^2) is regarded as an important predictor of CIN.[12,26]

There is a dearth of data in the existing literature on the mechanism of increased CIN incidence after intra-arterial ICA injection, especially in studies with a robust setting (ie, randomized controlled trials). Furthermore, due heed should be paid to microembolic showers on the distal vascular bed (including the renal arteries) following the manipulation of the descending aorta during catheterization. Therefore, we sought to assess the effects of the intra-arterial injection of the ICA in comparison with CO_2 on renal function and CIN incidence after endovascular procedures carried out below the origin of the renal arteries on the lower-limb vascular system. The benefits of CO_2 over ICA as the contrast medium for arteriography have been demonstrated in previous studies.[18,27,28] Nonetheless, the use and benefits of CO_2 as the routine contrast medium for peripheral and aortic arteriography constitute a new emerging topic.[24] No randomized studies have hitherto evaluated the effects of ICA compared with CO_2 on lower-limb angiographic procedures. Liss et al examined the role of CO_2 angiography in comparison with conventional angiography in patients who underwent renovascular intervention. Patients with a serum creatinine concentration of <200 mol/L (n = 82) were randomized prospectively to receive CO_2 with small added amounts of ioxaglaten (n = 37) or only ioxaglate (n = 45). The authors concluded that the amount of ICA significantly correlated with a higher risk of CIN (P=.01) and reported that the risk of CIN was higher among patients with a baseline GFR of <40 mL/min.[29] We showed a significantly higher rate of CIN in patients allocated to the ICA group vs the CO_2 group (13 [22.8%] vs 4 [7.5%], respectively; P=03).

In the current study, 7.5% of the patients assigned to CO_2 angiography were complicated by CIN, which is in accordance with the results of previous investigations, although the exact etiology of this observation has yet to be elucidated. Among the authors reporting a similar finding, Moos et al[30] reported a 0.5 mg/dL increase in the serum creatinine level and Fujihara et al[17] reported an incidence rate of 5.1% for CIN.

The recent advent of automated CO_2 injectors and improved image processing with the resulting better image quality have somewhat assuaged previous concerns regarding the probable incidence of CO_2 injection complications, such as explosive gas delivery and gas embolization.[26,31] In our study, except for mild self-limiting lower-limb and hypogastric pain, no CO_2-related complications occurred.

Study limitations. The results of the current investigation should be interpreted in light of the following limitations. First, the complete difference both in equipment for CO_2 and ICA injection and in imaging protocols concerning digital subtraction angiography precluded a blinded design. Second, despite our random assignment of the study population to CO_2 or ICA groups, the baseline creatinine level was higher in the CO_2 group. However, the final rate of CIN was significantly lower in the mentioned group, and importantly, baseline creatinine was not a significant predictor of the risk of CIN in our multivariate analysis. Third, we did not compare x-ray exposure time between our 2 study groups. Finally, our results would have been bolstered had we evaluated the long-term impact of CIN on patient survival and the related economic burden.

Conclusion

Patients with critical limb ischemia develop various comorbidities, which are likely to be increased by renal function aggravation. According to the results of the present study, CO_2 angiography was associated with a lower risk of CIN than ICA angiography in a patient cohort with mild-to-moderate renal dysfunction undergoing endovascular procedures. The ICA volume was still an important predictor of CIN in our patients with the lowest risk of microembolization due to catheter manipulation. Consequently, contrast-free angiography, even in patients with less severe forms of renal dysfunction, could be potentially beneficial, although larger investigations are required to confirm this strategy.

References

1. Liss P, Persson P, Hansell P, Lagerqvist B. Renal failure in 57,925 patients undergoing coronary procedures using iso-osmolar or low-osmolar contrast media. *Kidney Int.* 2006;70:1811-1817.
2. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation.* 2002;105:2259-2264.
3. Taylor AJ, Hotchkiss D, Morse RW, McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. *Chest.* 1998;114:1570-1574.
4. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis*. 2002;39:930-936.
5. Subramanian S, Tumlin J, Bapat B, Zyczynski T. Economic burden of contrast-induced nephropathy: implications for prevention strategies. *J Med Econ.* 2007;10:119-134.
6. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol*. 2000;36:1542-1548.
7. McCullough PA, Soman SS. Contrast-induced nephropathy. *Crit Care Clin*. 2005;21:261-280.
8. Wong PCY, Li Z, Guo J, Zhang A. Pathophysiology of contrast-induced nephropathy. *Int J Cardiol.* 2012;158:186-192.
9. Heinrich MC, Kuhlmann MK, Grgic A, Heckmann M, Kramann B, Uder M. Cytotoxic effects of ionic high-osmolar, nonionic monomeric, and nonionic iso-osmolar dimeric iodinated contrast media on renal tubular cells *in vitro*. *Radiology*. 2005;235:843-849.
10. Hardiek K, Katholi RE, Ramkumar V, Deitrick C. Proximal tubule cell response to radiographic contrast media. *Am J Physiol Renal Physiol.* 2001;280:F61-F70.
11. Peer A, Averbukh Z, Berman S, Modai D, Averbukh M, Weissgarten J. Contrast media augmented apoptosis of cultured renal mesangial, tubular, epithelial, endothelial, and hepatic cells. *Invest Radiol.* 2003;38:177-182.
12. Wichmann JL, Katzberg RW, Litwin SE, et al. Contrast-induced nephropathy. *Circulation.* 2015;132:1931-1936.
13. Quintavalle C, Brenca M, De Micco F, et al. *In vivo* and in vitro assessment of pathways involved in contrast media-induced renal cells apoptosis. *Cell Death Dis.* 2011;2:e155.
14. Keeley E, Grines CL. Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1,000 cases. *J Am Coll Cardiol.* 1998;32:1861-1865.
15. Ghumman SS, Weinerman J, Khan A, et al. Contrast induced-acute kidney injury following peripheral angiography with carbon dioxide versus iodinated contrast media: a meta-analysis and systematic review of current literature. *Catheter Cardiovasc Interv*. 2017;90:437-448.
16. de Almeida Mendes C, de Arruda Martins A, Teivelis MP, et al. Carbon dioxide is a cost-effective contrast medium to guide revascularization of TASC A and TASC B femoropopliteal occlusive disease. *Ann Vasc Surg.* 2014;28:1473-1478.
17. Fujihara M, Kawasaki D, Shintani Y, et al. Endovascular therapy by CO_2 angiography to prevent contrast-induced nephropathy in patients with chronic kidney disease: a prospective multicenter trial of CO_2 angiography registry. *Catheter Cardiovasc Interv*. 2015;85:870-877.
18. Diamantopoulos A, Patrone L, Santonocito S, et al. Carbon dioxide angiography during peripheral angioplasty procedures significantly reduces the risk of contrast-induced nephropathy in patients with chronic kidney disease. *CVIR Endovasc*. 2020;3:1-7.
19. Basu A, Talavera F, Lederer E, et al. Contrast-induced nephropathy. 2014. Available at https://emedicine.medscape.com/article/246751-overview. Accessed on August 9, 2021.
20. Dangas G, Iakovou I, Nikolsky E, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol.* 2005;95:13-19.
21. Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. *J Am Soc Nephrol.* 2000;11:177-182.
22. Gleeson TG, Bulugahapitiya S. Contrast-induced nephropathy. *Am J Roent*. 2004;183:1673-1689.
23. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet.* 2017;389:1312-1322.
24. Bangalore S, Briguori C. Preventive strategies for contrast-induced acute kidney injury: and the winner is.... *Circ Cardiovasc Interv.* 2017;10:e005262.
25. Marashizadeh A, Sanati HR, Sadeghipour P, et al. Left ventricular end-diastolic pressure-guided hydration for the prevention of contrast-induced acute kidney injury in patients with stable ischemic heart disease: the LAKESIDE trial. *Int Urol Nephrol.* 2019;51:1815-1822.
26. Stegemann E, Tegtmeier C, Bimpong-Buta NY, et al. Carbondioxide-aided angiography decreases contrast volume and preserves kidney function in peripheral vascular interventions. *Angiology.* 2016;67:875-881.
27. Moos JM, Ham SW, Han SM, et al. Safety of carbon dioxide digital subtraction angiography. *Arch Surg.* 2011;146:1428-1432.
28. Fujihara M, Kawasaki D, Shintani Y, et al. Endovascular therapy by CO_2 angiography to prevent contrast-induced nephropathy in patients with chronic kidney disease: a prospective multicenter trial of CO_2 angiography registry. *Catheter Cardiovasc Interv.* 2015;85:870-877.
29. Liss P, Eklöf H, Hellberg O, et al. Renal effects of CO_2 and iodinated contrast media in patients undergoing renovascular intervention: a prospective, randomized study. *J Vasc Interv Radiol.* 2005;16:57-65.
30. Moos JM, Ham SW, Han SM, et al. Safety of carbon dioxide digital subtraction angiography. *Arch Surg.* 2011;146:1428-1432.
31. Palena LM, Diaz-Sandoval LJ, Candeo A, Brigato C, Sultato E, Manzi M. Automated carbon dioxide angiography for the evaluation and endovascular treatment of diabetic patients with critical limb ischemia. *J Endovasc Ther.* 2016;23:40-48.

From the [1]Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran; [2]Clinical Trial Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Iran; and [3]Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

Manuscript accepted July 20, 2021.

Address for correspondence: Dr Parham Sadeghipour, Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Vali-Asr Ave, Niyayesh Blvd, Tehran 1996911101, Iran. Email: psadeghipour@hotmail.com