Renal Effects of CO_2 and Iodinated Contrast Media in Patients Undergoing Renovascular Intervention: A Prospective, Randomized Study

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PURPOSE: CO_2 gas has been proposed for use instead of iodinated contrast media in angiographic examinations in patients at risk of developing renal failure from contrast media. The influence of intraarterial injection of CO_2 with small added amounts of ioxaglate (200 mgI/mL) or ioxaglate alone on renal function in patients with suspected renal artery stenosis was studied in a prospective, randomized study.

MATERIALS AND METHODS: One hundred twenty-three patients underwent renovascular intervention (n = 83) and/or renal angiography (n = 40) for suspected renal artery stenosis. Patients with a serum creatinine concentration less than 200 μmol/L (n = 82) were randomized prospectively to receive CO_2 with small added amounts of ioxaglate (n = 37) or only ioxaglate (n = 45). Patients with serum creatinine levels greater than 200 μmol/L (n = 41) were not randomized and initially received CO_2. Serum creatinine concentrations were measured within 1 day before and 1 day, 2 days, and 2–3 weeks after the procedure.

RESULTS: The amount of injected CO_2 did not relate to an increase in serum creatinine level. In the randomized groups, and also when the whole patient sample was considered, the amount of injected iodine was significantly correlated (P = .011) with an increase in serum creatinine level and a decrease in estimated creatinine clearance after 2 days. Among the randomized patients, one in the CO_2 group and three in the ioxaglate group had a more than 25% increase in serum creatinine level within the first 2 days after the intervention.

CONCLUSION: The risk of impairment of renal function is lower after injection of CO_2 with small amounts of added ioxaglate compared with injection of a larger amount of ioxaglate alone. The larger the amount of administered iodinated contrast medium, the greater the risk of development of renal failure.

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Abbreviations: CrCl = creatinine clearance, PTRA = percutaneous transluminal renal angioplasty

THE third leading cause of acute renal failure in hospitalized patients is radiographic contrast medium–induced nephropathy (1). The reported incidence of contrast medium–induced nephropathy varies from zero (2,3) to 50% (4). This variation is probably a result of differences in study design, definition of renal failure, and populations studied. The number of patients in need of radiologic interventions is increasing and the interventions are often carried out in patients with a high risk of developing contrast medium–induced nephropathy, particularly those with preexisting renal insufficiency and diabetes mellitus. The exact mechanism for the increased risk of developing nephropathy in patients with reduced renal function is not fully understood, but medullary hypoxia has been proposed among numerous other mechanisms. The increased use of endovascular procedures has increased the demand for less-nephrotoxic techniques and contrast media. It has been

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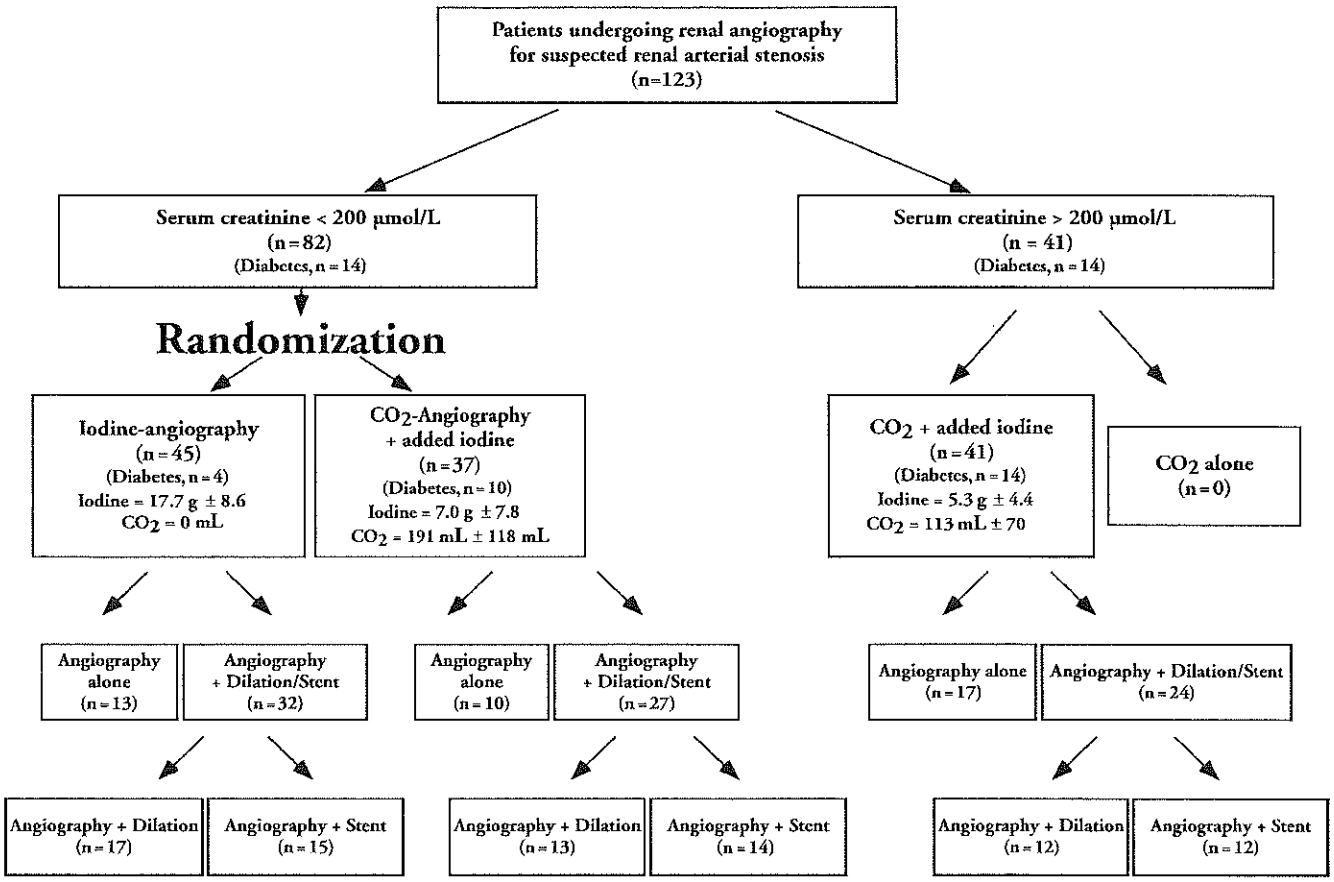

Figure 1. Schematic illustration of disposition of patients in the study.

suggested that, by reducing the amount of iodinated contrast medium, the risk of nephropathy will be lowered (5). CO_2 gas has been used for several decades as negative contrast medium in angiography (6). Improvements in CO_2-enhanced digital subtraction angiography have resulted in acceptable arteriograms, but with considerably less attenuation differences compared with iodinated contrast media (7–10). It has been reported in several studies that CO_2 angiography does not affect renal function (9,11). However, we are aware of no prospective, randomized study in which the effects on renal function of CO_2 gas supplemented with small amounts of iodinated contrast medium have been compared with those of iodinated contrast medium alone.

The purpose of our study was to compare the effects on renal function of an intraarterial injection of the iodinated low-osmolarity contrast agent ioxaglate with that of CO_2 supplemented with a small amount of iodinated contrast medium.

MATERIALS AND METHODS

Patient Group

All patients referred to our hospital for renal angiography investigation for suspected renal artery stenosis during the period of March 1999 to February 2001 were studied (**Fig 1**).

Procedures

Patients with serum creatinine levels greater than 200 μmol/L (n = 41) were excluded from the randomization because of the known high risk for developing renal failure after injection of large amounts of contrast medium in patients with severely reduced renal function (4,12,13). All these patients initially received CO_2 to reduce the amount of injected contrast medium. Patients with serum creatinine levels lower than 200 μmol/L (n = 82; 45 men, 37 women; mean age, 67 years; age range, 36–86 years) were randomized prospectively to receive CO_2 supplemented with small amounts of ioxaglate (ionic dimer, osmolality 600 mOsm/kg H_2O, 200 mg I/mL; n = 37) or ioxaglate alone (n = 45; **Table 1**). The randomization was performed immediately before the procedure by drawing a lot. The protocol was approved by the university research ethics committee. Informed consent was obtained from all patients.

Before the procedure, each patient received hydration with 300–500 mL of physiologic saline solution. Arterial access was achieved through the common femoral artery. All patients initially received an injection of CO_2 (as described by Hawkins et al [7,11]) or ioxaglate in the aorta to detect the renal arteries with use of a 4-F catheter with extra side holes (Sos Omni; Angiodynamics, Glens Falls, NY). For se-

Table 1
Data on Patients Undergoing Renal Angiography for Suspected Renal Artery Stenosis ($N = 123$)

	Prospective Randomized Groups		Nonrandomized Group*
	Iodine	CO_2	
Baseline serum creatinine (μmol/L)	<200	<200	>200
No. of patients	45	37	41
Age (y)	63 ± 11	67 ± 8	71 ± 8
Weight (kg)	74 ± 12	73 ± 10	67 ± 13
Diabetes	4*	10*	14
Ischemic heart disease	13	11	15
Hypertension	40	33	37
Stroke	8	7	6
Aortic disease (aneurysm)	3	5	6
Smoking	8	13	10
Iodine (g)	17.7 ± 8.6 (0.8–50.0)	7.0 ± 7.8 (0–36)	5.3 ± 4.4 (0–20)
Iodinated contrast medium (mL)	88.4 ± 42.9 (4–250)	35.1 ± 6.4 (0–180)	26.4 ± 22.2 (0–100)
CO_2 (mL)	0	191 ± 118 (40–600)	113 ± 70 (50–300)
Angiography alone	13	10	17
Angiography and dilation	17	13	12
Angiography and dilation and stent	15	14	12
Serum creatinine level (in μmol/L)†			
1 day before	120 ± 37 (1.36 ± 0.42)	128 ± 38 (1.45 ± 0.43)	297 ± 83 (3.36 ± 0.94)
1 day after	119 ± 36 (1.35 ± 0.41)	126 ± 39 (1.43 ± 0.44)	275 ± 86 (3.11 ± 0.97)
2 days after	122 ± 49 (1.28 ± 0.42)	139 ± 45 (1.57 ± 0.51)	288 ± 97 (3.26 ± 1.10)
2–3 weeks after	124 ± 43 (1.40 ± 0.49)	133 ± 48 (1.50 ± 0.54)	271 ± 94 (3.07 ± 1.06)
Creatinine clearance (mL/min)			
1 day before	59 ± 29	54 ± 22	20 ± 8
1 day after	57 ± 26	54 ± 22	21 ± 9
2 days after	56 ± 23	45 ± 17	20 ± 8
2–3 weeks after	59 ± 29	52 ± 20	21 ± 7
Serum creatinine increase >25% within 2–3 weeks after intervention	5	2	5
Serum creatinine increase >25% within 1 week after intervention	3	1	3
Need for dialysis	1	0	1
Hypotension during intervention	0	1	1
Nausea	1*	8*	5
Vomiting	0	1	4
CRP 1 day before (mg/L)	7 ± 16	7 ± 17	22 ± 33
Hemoglobin A1c 1 day before (%)	5.2 ± 1.4	5.2 ± 1.4	6.5 ± 1.9
S-glucose 1 day before (mmol/L)	6.1 ± 2.0	7.3 ± 2.7	8.7 ± 5.6
Hemoglobin 1 day before (g/L)	137 ± 12	140 ± 16	118 ± 15
S-urea 1 day before (mmol/L)	9.7 ± 6.1	8.9 ± 3.9	22 ± 6.3

* Significant difference ($P < .05$).
† Values in parentheses are mg/dL.
Note.—Values presented as means ± SD and ranges are given within parentheses. CRP = C-peptide protein.

lective renal artery injections, a 4-F catheter (Shephard Hook; Cordis, Miami, FL) was used. Angiograms were obtained with a 40-cm image intensifier and digital subtraction systems (Siemens Medical Systems, Iselin, NJ). The CO_2 injection in the aorta was performed with a syringe filled with 40–50 mL of CO_2 and usually repeated 2–3 times with a time interval of at least 5 minutes between injections. CO_2 angiograms were initially performed in the anteroposterior position. Additional CO_2 angiograms were obtained with the side of the patient ipsilateral to the renal artery being studied elevated on a 45° wedge cushion. Pressure gradients were measured in all patients to establish the hemodynamic significance of the stenosis. A systolic pressure gradient of 15 mm Hg or more was considered a significant stenosis and treated initially with percutaneous transluminal

renal angioplasty (PTRA). If the pressure gradient was still significant after PTRA, a stent was inserted followed by a pressure gradient measurement. The serum creatinine concentration was measured the day before and 1 and 2 days and 2–3 weeks after the procedure. During the first week after the intervention, additional blood samples of serum creatinine were taken in patients who had increased serum creatinine levels on day 1 or 2 after the procedure.

Calculation of Creatinine Clearance

The baseline creatinine clearance (CrCl) was calculated with use of the Cockroft-Gault formula (14) based on the serum creatinine concentration as follows:

$CrCl_{Female} = [(140 - age) \times weight]/[serum\ creatinine]$

$CrCl_{Male} = 1.2 \times CrCl_{Female}$

(To convert serum creatinine from mg/dL to μmol/L multiply by 88.4)

Study Endpoints and Definitions

The participant criteria in the study included patients referred for renal angiography investigation for suspected renal artery stenosis during the period of March 1999 to February 2001. The exclusion criteria were age younger than 15 years, complications, and requirement of acute operation or reintervention. In the randomized part of the study, patients with baseline serum creatinine levels greater than 200 μmol/L were excluded. Study endpoints were serum creatinine level and CrCl 1 day, 2 days, and 2–3 weeks after the intervention. Contrast medium–induced nephropathy was defined as an increase in serum creatinine of more than 25% during the first week after the intervention if there was no other explanation for renal failure (15).

Statistical Analysis

The repeated-measures data for serum creatinine and CrCl at days 1 and 2 and at 2–3 weeks were analyzed with use of mixed models as described by Littell et al (16). As opposed to repeated measures analysis of variance, this approach allows measurements within individual over time to correlate freely. The baseline CrCl or serum creatinine level was used as a covariate. The within-individual covariance matrix was left free in all analyses.

Two different analyses of the data were performed. In the first analysis, based on the intent-to-treat principle (17), data were modeled as a function of treatment, time, baseline value, and interactions between these variables.

Because most patients, including those in the CO_2 group, actually received some form of iodine injection, a second analysis, based on the treatment-received principle, was also made. In this analysis, assignment to the iodine or CO_2 group was not used. Instead, serum creatinine and CrCl were modeled as a function of baseline value (serum creatinine and CrCl level before the procedure), time, amount of iodine administered, and interactions between these variables. This analysis is valid if it can be assumed that the way the ioxaglate or CO_2 is administrated is unrelated to the outcome. Values are presented as means ± SD. A P value <.05 was accepted as significant in all analyses.

RESULTS

A total of 137 patients were referred for investigation. Ten patients were excluded from the study from June 1, 2000, to August 15, 2000, because of absence of the research nurse during this period. Children younger than the age of 15 years were excluded (n = 1). Two patients required an emergency operation after the angiography and were excluded from the study. In one case, occlusion of the vessel occurred during the procedure, and in the second case, the inserted stent slipped away and had to be removed surgically. There were no postoperative complications. One patient was excluded because the vessel ruptured; in this case, angiography was repeated the following day with insertion of a covered stent.

In 83 of the 123 patients who underwent renal angiography, a significant hemodynamic stenosis (gradient >15 mm Hg) was found in the renal artery (**Table 1**). In 42 of these 83 patients, only PTRA was successfully performed, whereas 41 patients were treated with stent placement. A total of 193 renal arteries were examined with pressure measurements. The pressure gradient in the vessels with a significant stenosis (n = 87) was 85 mm Hg ± 59, and the corresponding gradient in the vessels without a stenosis (n = 106) was 6 mm Hg ± 12. A total of 28 diabetic patients (14 in the randomized groups and 14 in the group with initial serum creatinine level >200 μmol/L) were studied. Significant stenosis was found in 17 of the 28 patients with diabetes mellitus. In the randomized groups, nine of the 14 diabetic patients had a significant stenosis.

None of the groups showed a statistically significant change in mean serum creatinine level 1 day, 2 days, or 2–3 weeks after the intervention compared with the value before the intervention (**Fig 2**). The amount of injected CO_2 did not relate to an increase in serum creatinine or estimated CrCl. In the intent-to-treat analysis, which was based on the randomization of patients, there were no significant differences in mean serum creatinine and CrCl levels between the CO_2 and iodine groups at day 1 or 2 or 2–3 weeks after the procedure. One day and 2–3 weeks after the intervention, there was no statistical relationship between the amount of iodine injected and the change in CrCl and serum creatinine level. However, on day 2, the serum creatinine and CrCl showed a statistically significant (P = .011) change with increasing iodine doses in patients with baseline serum creatinine levels less than 200 μmol/L (ie, randomized patients). This was also true when the whole patient sample was considered (randomized patients and patients with serum creatinine level >200 μmol/L).

An increase in serum creatinine of more than 25% after the intervention was seen in 12 of 123 patients (10%; five patients with baseline serum creatinine level >200 μmol/L; two in the CO_2 group and five in the iodinated contrast medium group with baseline serum creatinine level <200 μmol/L; **Tables 1,2**). Of these 12 patients, seven had an increase in serum creatinine during the first 2 days after the intervention and are therefore considered to have experienced contrast medium–induced nephropathy. As a result of the relatively fast decrease in renal function after the intervention, two patients were considered to be in need of

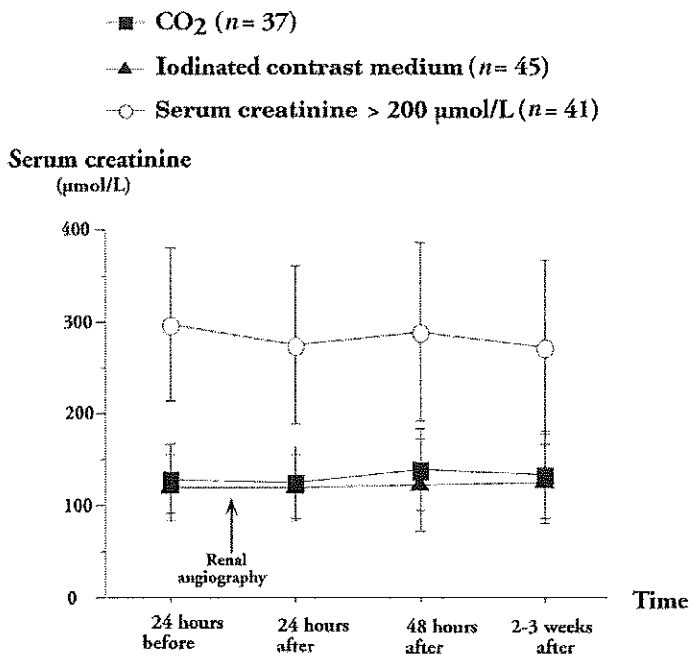

Figure 2. Effects of renal angiography on mean serum creatinine levels. Bars indicate SD.

dialysis, both of whom had diabetes mellitus. One of these patients, who had a duration of diabetes mellitus of 58 years, was randomized to receive iodinated contrast medium. The patient had a baseline serum creatinine level of 188 μmol/L, CrCl of 29 mL/min, and received 19 g iodine. A stenosis was found and treated technically successfully with PTRA. The serum creatinine level increased to 236 μmol/L 2 days after the intervention and the patient was considered in need of dialysis. The other patient who required dialysis had a baseline serum creatinine level of 369 μmol/L, CrCl of 18 mL/min, and received 100 mL CO_2 and 6 g iodine. A stenosis was found and treated technically successfully with PTRA. The serum creatinine level increased to 404 μmol/L 2 days after intervention. Six days after intervention, the serum creatinine level had increased to 477 μmol/L and the patient was considered to be in need of dialysis. This patient had a duration of diabetes of 2 years.

As demonstrated in **Figure 3**, in the randomized groups, three of the four patients who developed an increase in serum creatinine of more than 25% within 2 days after the intervention had an estimated baseline CrCl of less than 40 mL/min. When the patients with baseline serum creatinine levels greater than 200 μmol/L were also considered, six of the seven patients with an increase of more than 25% in serum creatinine level had an estimated baseline CrCl of less than 40 mL/min. These six patients received an average of 18 g iodine (range, 6–50 g). The only patient with a baseline CrCl greater than 40 mL/min who had an increase in serum creatinine of more than 25% was randomized to the iodine group and received 50 g of iodine and stent implantation. The serum creatinine level increased to 135 μmol/L on the second day and was back to normal 2–3 weeks after the intervention (**Table 2**).

Thirteen of 78 patients who received CO_2 reported nausea, compared with one of the 45 patients injected with iodinated contrast medium only. Five patients who received CO_2 vomited, compared with none of those given only iodinated contrast medium. Two of the 123 patients developed hypotension, both of whom received CO_2 and iodine.

DISCUSSION

The present study focused on the effect on renal function after administration of CO_2 compared with low-osmolar iodinated contrast medium. When comparing the group of patients with a baseline serum creatinine level of less than 200 μmol/L who received iodinated contrast medium alone with the group who primarily received CO_2 with small amounts of iodinated contrast medium added, no significant difference in the influence of contrast medium on renal function was found. However, the results show that the larger amount of injected iodine contrast medium, the higher the risk of developing contrast medium–induced nephropathy. In addition, patients at the highest risk for developing contrast medium–induced nephropathy were patients with a CrCl less than 40 mL/min before intervention (4). Surprisingly small amounts of injected iodine (<10 g) resulted in reduced renal function in these patients. The possibility of embolization during intervention as an explanation for a reduced renal function can not be ruled out in some patients. Two days after the intervention, serum creatinine showed a significant change (P = .011) with increasing amounts of iodinated contrast medium. This finding is in line with the clinical observation that the serum creatinine levels increase 2 days after the intervention and usually return to baseline values after 7–10 days (18).

The results of the present study confirm previous investigations (4,12) by showing that the amount of iodine is of importance for the development of contrast medium–induced nephropathy in patients with compromised renal function. In our study, six of the seven patients who showed an increase of more than 25% in serum creatinine during the first week after the intervention had a baseline CrCl of less than 40 mL/min (**Fig 3**). Although the number of patients was reasonably high, we were not able to show a significant difference in renal function between the CO_2 group and the group of patients who received iodinated contrast medium. However, no power calculation was performed before the investigation, and the failure to show a correlation can be a result of the number of patients.

With modern digital subtraction angiographic equipment, CO_2 is an alternative to iodinated contrast medium for obtaining a vascular image, but injection of CO_2 causes signifi-

Table 2
Description of Patients with an Increase in Serum Creatinine Greater than 25% after Intervention

Pt. No.	Time of Serum Creatinine Change (wk)	Baseline Serum Creatinine (μmol/L)	Group	Intervention	Diabetes	Baseline Creatinine Clearance (mL/min)	Creatinine Change 1 day before Maximum Change (in μmol/L)*	Injected Iodine (g)	Contrast Medium Volume (mL)	CO_2 (mL)
1	1	<200	Iodine	Angio/PTA	Yes	29	188–236 (2.13–2.67)†	19	95	–
2	1	<200	Iodine	Angio/PTA/stent	No	81	94–135 (1.06–1.53)	50	250	–
3	1	<200	Iodine	Angio/PTA/stent	No	33	175–218 (1.98–2.47)	24	120	–
4	1	<200	–	Angio/PTA/stent	No	38	158–294 (1.79–3.33)	8	40	50
5	1	>200	CO_2	Angio/PTA/stent	No	33	228–293 (2.58–3.31)	7	35	200
6	1	>200	CO_2	Angio/PTA/stent	No	26	218–287 (2.47–3.25)	10	50	200
7	1	>200	CO_2	Angio/PTA	Yes	18	369–477 (4.17–5.40)†	6	30	100
8	2–3	<200	CO_2	Angio	No	103	82–105 (0.93–1.19)	1	5	110
9	2–3	<200	Iodine	Angio/PTA/stent	No	35	196–248 (2.22–2.81)	10	50	–
10	2–3	<200	Iodine	Angio/PTA/stent	No	27	182–233 (2.06–2.64)	15	75	–
11	2–3	>200	CO_2	Angio/PTA	No	15	220–304 (2.49–3.44)	6	30	200
12	2–3	>200	CO_2	Angio/PTA	No	18	262–376 (2.96–4.23)	1.4	7	50

* Values in parentheses are in mg/dL.
† Dialysis
Note.—Angio = angiography.

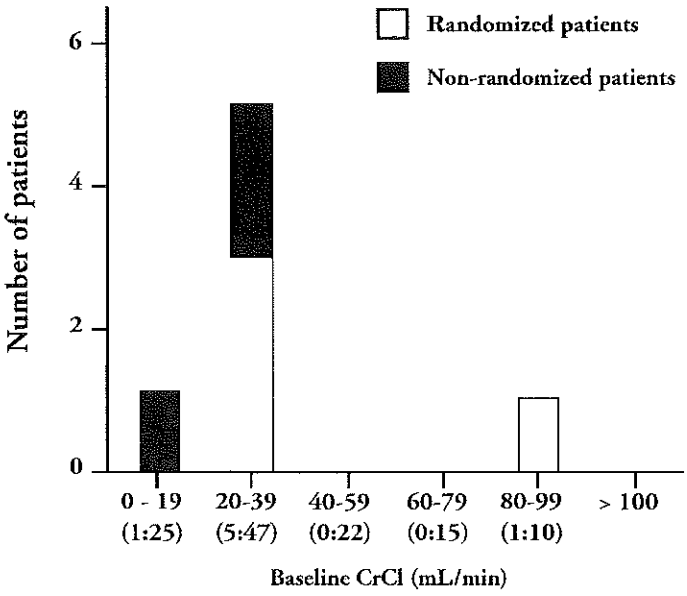

Figure 3. Number of patients with an increase in serum creatinine of more than 25% during the first week after the intervention, compared with the baseline CrCl. The figures in brackets are number of patients with an increase in serum creatinine of more than 25% in the interval and the total number of patients in the interval.

cantly less attenuation differences compared with regular iodinated contrast medium. In renal interventions, the amount of iodinated contrast medium can be considerably reduced with combined use of pressure gradient measurements and CO_2 injections. A drawback with the present study is that it was not possible to totally exclude the use of iodinated contrast medium in the randomized CO_2 group. CO_2 alone was not sufficient to visualize the small and narrow vessels, and in patients in whom the investigation had a therapeutic aim, it was of major importance that PTRA and stent placement could be performed optimally. Small amounts of iodinated contrast medium were therefore added. Addition of iodinated contrast medium to obtain adequate visualization has been reported in previous studies (19–22).

The equiattenuating concentration (ie, concentration to achieve similar contrast effects) and dose of iodinated contrast medium compared with CO_2 is approximately 30 mgI/mL (23). Despite this, previous studies comparing the risk of developing contrast medium–induced nephropathy after iodinated contrast medium and CO_2 angiography have used the ordinary concentration of iodinated contrast medium (200–300 mgI/mL). It would be more logical to compare the risk after administration of equiattenuating concentrations. To achieve the same attenuation as with CO_2, the normal iodinated contrast medium (200 mgI/mL) could be diluted at approximately a 1:7 ratio to 32 mgI/mL. Recently, gadolinium-based contrast agents have also been used in patients to avoid contrast medium–induced nephropathy (24–27). The image quality with gadolinium contrast agents is consistently inferior to that of regular iodinated contrast medium, but is better than CO_2 image quality. Adverse effects on renal function (28) and acute renal failure have also been reported after injection of gadolinium (23,29). Besides the lower nephrotoxic effects of CO_2, other advantages of CO_2 gas are that it can be used in patients who are allergic to iodinated contrast medium and is inexpensive. Aspelin et al (15) recently reported that the nonionic dimer iodixanol showed significantly less incidence of contrast medium–induced nephropathy compared with nonionic iohexol. The reason for this advantage for the nonionic high-viscosity dimer iodixanol is not clear; however, the isoosmolarity of the compound may be of importance.

Angiography with CO_2 is not without complications. Spinosa et al (30) reported transient mesenteric ischemia in a 62-year-old woman after CO_2 angiography and dilation of an iliac artery stenosis. They also found that the serum creatinine level increased from 575 μmol/L to 689 μmol/L and did not return to baseline level until 5 days after the intervention. Their explanation was a "vapor lock" of the CO_2 gas (ie, trapping) causing an obstruction. In our study, several patients had nephrosclerosis. In such patients, sudden changes in vessel caliber are often seen, with very narrow parts in distal vessels, which might increase the risk for gas trapping. Another plausible explanation for a decrease in renal function after CO_2 angiography may be embolization of small plaques during the invasive procedure. A fatal incident after CO_2 angiography was reported by Rundback et al (19). In the study by Ehrman et al (31), the use of CO_2 to evaluate arteriovenous fistulas caused "neurologic sequelae" in five patients. Culp et al (32) have reported that injections of CO_2 during diastole in the descending aorta in pigs can pass into the coronary arteries and cause arrhythmias. No arrhythmias were found in our study, and we believe it is unlikely that injections of CO_2 below the diaphragm would result in retrograde filling of the coronary arteries.

Minor complications were more frequent after injection of CO_2 than after iodinated contrast medium. One patient reported nausea after receiving iodinated contrast medium, but 13 reported nausea after the initial CO_2 injection. Five of the patients vomited after CO_2 injection; none did in the iodine group. Although reversible, nausea is a practical disturbance during the investigation. In the study by Beese et al (22), three of 47 patients had severe nausea and abdominal pain after CO_2 injection and 10 patients reported minor symptoms including abdominal, buttock, and foot pain.

In an experimental study in dogs (8), a 12% decrease in renal blood flow was noted immediately after injection of CO_2. The flow returned to normal after 24 hours. In two of nine dogs, who received an amount of CO_2 much higher than would be used in clinical practice, there were histologic findings

of acute tubular necrosis, and vacuolization of the epithelium was seen in one dog. These observations were made in dogs whose kidneys had been positioned vertically.

In our study, randomization resulted in a significantly uneven distribution of diabetic patients between the groups, as there were four diabetic patients in the iodine group and 10 in the CO_2 group. This uneven distribution of diabetic patients conferred an advantage for the group receiving only iodinated contrast medium when interpreting the results.

The explanation for the acute nephropathy after administration of iodinated contrast medium is not clear. Several mechanisms have been suggested. Recent studies (33–38) have focused on the effect of a decrease in oxygen tension in the renal medulla after injection of iodinated contrast medium. Other suggested explanations for contrast medium–induced nephropathy are an increase in intrarenal pressure (39,40); effects on red blood cell aggregation (41,42); increases in calcium (43), adenosine (44,45), and endothelin concentrations (46); and decreased production of nitric oxide (47).

We conclude that, in patients with serum creatinine levels less than 200 μmol/L, CO_2 does not affect the serum creatinine level. Our results show a correlation between the amount of injected iodine and the risk of developing contrast medium–induced nephropathy. In addition, in patients with an estimated CrCl less than 40 mL/min before intervention, the risk of developing contrast medium–induced nephropathy was evident already at low levels of injected iodine. Therefore, we recommend the use of the Cockroft-Gault formula for calculating the CrCl to identify the patients at risk for developing contrast medium–induced nephropathy. In patients with a decrease in renal function, every means should be taken to reduce the amount of injected iodine, such as CO_2 angiography and dilution of the contrast media.

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