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INVESTIGATIVE RADIOLOGY
Volume 29, Supplement 2, S45–S46

Carbon Dioxide as an Angiographic Contrast Agent

A Prospective Randomized Trial

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Bettmann MA, D'Agostino R, Juravsky LI, Jeffery RF, Tottle A, Goudey CP. Carbon dioxide as an angiographic contrast agent: a prospective randomized trial. Invest Radiol 1994;29: S45–S46.

KEY WORDS. **Carbon dioxide; angiography; contrast agents.**

CONTRAST AGENTS ARE integral to performing angiographic procedures, but they pose substantial problems in terms of unwanted effects, such as adverse reactions, and cost considerations. An alternative contrast agent that has been considered for many years but has never been systematically investigated is carbon dioxide (CO_2). To begin an assessment of the possible role of carbon dioxide for angiography, the authors performed a prospective randomized trial comparing CO_2 to a nonionic contrast agent in patients undergoing angiography for the evaluation of symptomatic peripheral vascular disease.

Patients and Methods

Twenty-one patients at two centers were randomized to receive either CO_2 or dilute ioversol for abdominal aortography and peripheral angiography. Eleven patients received ioversol and 10 received CO_2. All patients had successful completion of examinations. All patients were evaluated using digital subtraction angiography. The parameters evaluated in all patients were blood chemistry studies and complete blood counts at baseline, immediately after the procedure, and 24 hours after the procedure; occurrence of procedural and contrast-related adverse events; and vital signs and blood gases at baseline, after each injection, and after the procedure. Also evaluated were the quality and adequacy of the images and patient comfort during contrast injection.

Results

In the 10 patients receiving CO_2, the total volume administered ranged from 460 to 1447 mL. On a scale of 0 to 4 for discomfort (0 = none; 4 = severe), the mean discomfort rating was 1.1, or mild. No adverse events were encountered. Images were judged diagnostically adequate and consistent with clinical and noninvasive findings in all 10 patients. With ioversol, the 11 patients received a range of 28 to 141 mL of total contrast (diluted 2:1 with normal saline for imaging purposes). The average discomfort rating was 0.4 (none to mild). One adverse reaction was encountered, a vagal episode, which was thought to be related to the procedure and to patient anxiety, rather than to the contrast agent per se.

As with CO_2, images were diagnostically adequate and clinically consistent in all patients.

With regard to measured parameters, there was no clinically significant alteration in the results of any of the blood chemistry studies or the complete blood count in any of the patients in either group. With regard to the blood gases, the values were evaluated by individual injection, individual patient, pooled individual injections, and pooled injections overall. The baseline values for the blood gases were within normal limits and were no different for the two groups. The pooled values for both groups showed no significant change, with final values of pH of 7.40, an oxygen saturation of 95 ± 2, partial pressure of carbon dioxide of 38 ± 5, and bicarbonate level of 23 ± 3 for both groups. Overall,

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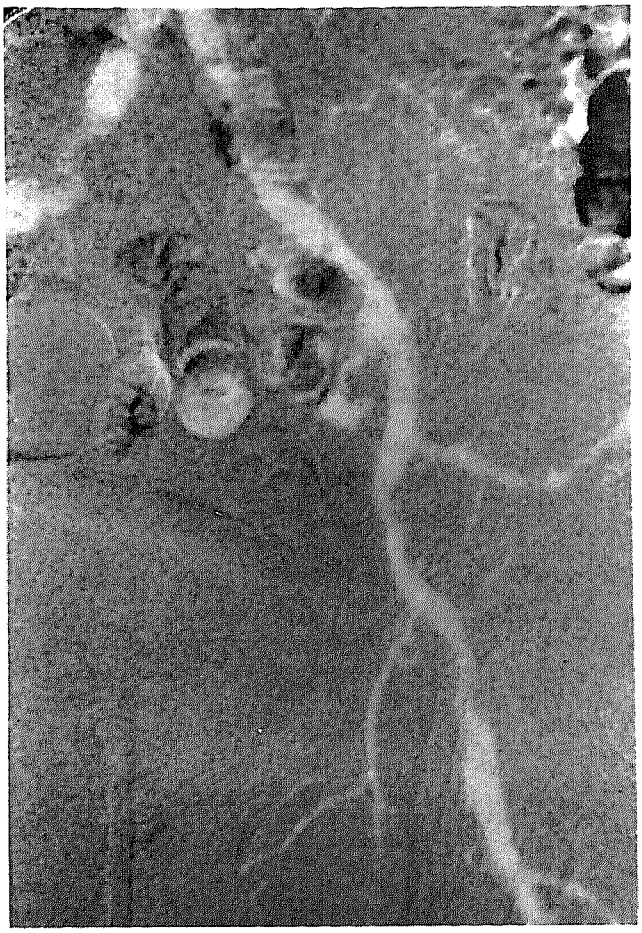

Fig. 1. Carbon dioxide angiogram of the pelvis demonstrating severe atherosclerotic changes of both common iliac arteries and of the left external iliac artery. Images obtained with carbon dioxide are more positron-dependent than those obtained with iodinated contrast, so unilateral pelvic or lower extremity imaging may lead to improved visualization.

there was a trend for increased oxygen saturation in the ioversol group, with no trend toward a change in the CO_2 group.

Five patients in the CO_2 group and three in the ioversol group had variations in blood gas values of greater than 30% at one or more time points. In the CO_2 group, three patients had an increase in oxygen saturation, and in two patients there was a transient increase in CO_2. In the ioversol group, one patient had an increase in oxygen saturation, one an increase in bicarbonate, and one a decrease in oxygen and increase in CO_2.

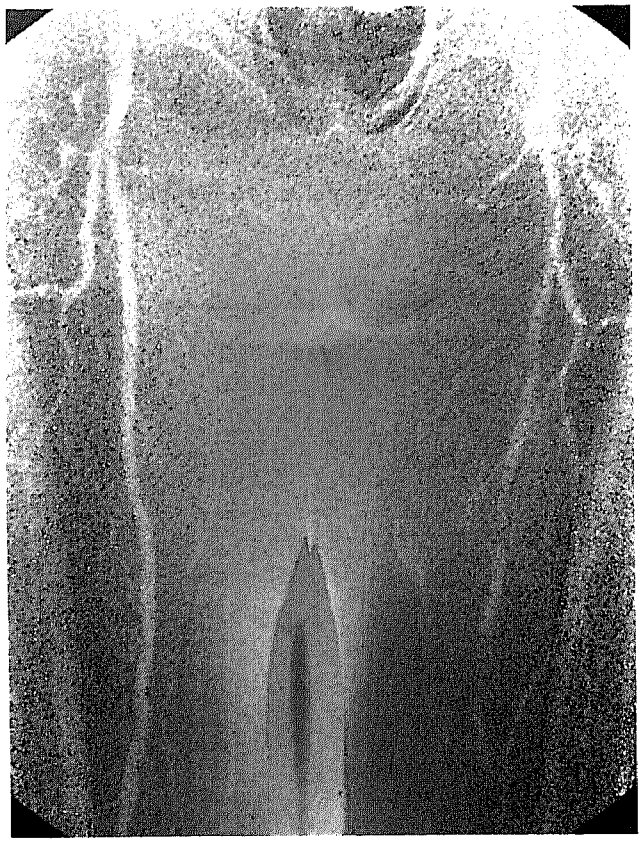

Fig. 2. Bilateral thigh angiography with carbon dioxide demonstrates moderate diffuse disease bilaterally, with tight mid-left superficial femoral artery stenosis that slows flow compared with the right. Injection was made at the aortic bifurcation.

Conclusion

This randomized prospective study suggests that CO_2 is diagnostically adequate and safe for peripheral angiography. In comparison with a standard iodinated contrast agent, CO_2 causes no statistically significant alteration in results of blood chemistry studies, complete blood counts, or blood gas studies. Although prior experience has shown CO_2 to be safe when used in small amounts and in occasional patients, this is the first systematic, randomized evaluation to compare CO_2 with standard iodinated contrast agents. It also is the first to assess the effect of CO_2 and iodinated contrast agents on blood gases. The lack of significant changes in blood gas results in both groups is reassuring. Additional evaluation of CO_2 in terms of its role for diagnosis and its role in certain patient groups (eg, those with renal failure or with a prior contrast reaction) is warranted.

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Discussion 3

Dr. Adams to Dr. Poirier: In the cerebral arteriographic study of iodixanol and iohexol, was the incidence of nausea, and particularly of vomiting, considered clinically significant?

Dr. Poirier: Statistically, this was not considered one of the things that was significantly different between the two groups.

Dr. Hamm to Drs. Wolf and Hanna: You reported your results on CT [computed tomography] lymphography of the axillary and popliteal lymph nodes; these are the lymph nodes of the first filter. What about the lymph nodes of the second and third filter (for example, the inguinal or paraaortic lymph nodes)? From a clinical point of view, these are much more important. What about the time-response enhancement of these lymph nodes and the enhancement pattern of these, was it homogeneous or inhomogeneous? Did you prove that your lymph node enhancement is an intracellular contrast enhancement, or is it only an unspecific extracellular contrast enhancement?

Dr. Wolf: I showed slides indicating that the ethyl ester of diatrizoic acid (EEDA) particles at least traveled well from node to node. The abdominal aortic nodes shown were opacified from the injection in the foot. It remains to be seen what the extraction fractions will be and how that can be manipulated. We also used the perflubron to show exactly where the material was located in the cells in the lymph node, and those foamy cells were due to perflubron, which is dissolved in the H and E [hematoxylin and eosin] preparation of the cells. So indeed, the particles are located in the macrophages and do not target the lymphocytes or the extracellular fluid space, which is, in fact, relatively small in the lymph node. We could not account for the quantitative enhancement by the extracellular space. We never see lymphatic vessels unless by accident they are engaged with the 27-gauge needle.

Dr. Hanna: I'll take the second part of the question as far as intracellular versus the extracellular. The emulsion that we studied was fluorescently labeled, and therefore, actually localized. The predominant mechanism was due to extracellular uptake of the emulsion droplets.

Dr. Lasser to Dr. Hamm: Do you have data indicating that they would go only to a first set of nodes and not to the second?

Dr. Hamm: In our experiences with CT lymphography, we see homogeneous enhancement in the first filter and a somewhat inhomogeneous enhancement in the lymph nodes thereafter, and we expect this is a problem for further clinical studies.

Dr. Wolf: I want to clarify what Dr. Hanna talked about in terms of extracellular versus intracellular. I believe that in their methodology, they actually cannulated the lymphatics and saw whether the particles floating in the lymph were free, extracellular, or were transported intracellularly in macrophages. However, at the lymph node, the particles that are arrested and are concentrated in the lymph node are intracellular within macrophages.

Dr. Frija to Dr. Wolf: When nodes were not opacified in tumors, how would you make the distinction between truly tumorous nodes and occlusion of lymph channels?

Dr. Wolf: I think that is going to be an interesting clinical problem. In our particular case, we could harvest the nodes and then stain them to see whether or not their configuration was exactly the same as we had seen on imaging. Since the lymph nodes are fairly well demarcated by fat on the outside, there is really no problem in identifying at least the size of the node. I think Dr. Hanna, in one of her studies of dogs, showed that there was a node that received almost no perflubron and that would be the case where the cancer has obstructed any lymph flow into that node. In this case, something borne in the lymphatics will not target the node.

Dr. Lipton to Dr. Bettmann: What about nitrous oxide? We use it in the pericardium. It is at least soluble, and certainly contrast effective. Is it the anesthetic effect, or is it just that people haven't used it? Would you be willing to comment?

Dr. Bettmann: I think the answer is what you said, and that it is not dispersed on first pass. It does accumulate and does have cumulative effects. There is a serious limitation on the volume that could be used. To my knowledge, it hasn't been used for imaging. Are you aware of anyone trying to use it?

Dr. Lipton: No. We used it in the pericardium at one time. It has been used quite a bit in the early days, but I have not seen a literature reference to its use. It is just a pity that we don't seem to be able to have a gas that is as effective as a liquid contrast agent.

Dr. Spinazzi to Dr. Poirier: Which method did you use to maintain double-blind status?

Dr. Poirier: All the bottles were unlabeled, so that no one knew the contrast identity except for the Sterling Winthrop representatives, and the agent was not known until the results were published, unless there was a serious side effect.

Dr. Spinazzi: The physician injecting the contrast agent didn't recognize the viscosity?

Dr. Poirier: We were using a mechanical injector in most instances.

Dr. Speck to Dr. Poirier: The results do not look very favorable overall in the incidence of side effects. But I wonder why you used the 320 concentration of iodixanol when a 270 concentration is available as well, with a much lower viscosity and far fewer problems. Do you need the high contrast of the 320?

Dr. Poirier: I assume that it was used because it had an iodine concentration closer to iohexol. There was one study that was done in Europe that compared 270 and 320 and found both doses to be efficacious. I assume they picked the higher concentration so it would be closer to iohexol.

Dr. Speck: This should stay for quite a while in the cerebral blood vessels with the higher viscosity of the material. Is there any difference in the quality of the pictures?

Dr. Poirier: We could not tell any difference in the radiographs.

Dr. Katzberg to Dr. Bettmann: I know that one of the articles that you referenced was Dr. Lance's article using CO_2 for peripheral vascular disease. Dr. Lance tells me that he is sure that some of the patients showed improvement after CO_2 compared to conventional or any kind of contrast. Did you find any therapeutic affect of CO_2 in these patients?

Dr. Bettmann: No, we did not. I know that Dr. Lance has proposed that a single injection of CO_2 causes substantial vasodilatation and relieves pain in patients with claudication or even rest pain. A concern of the FDA [Food and Drug Administration], interestingly, is whether or not there is vasodilation related to CO_2, and we hope to evaluate that quantitatively in a crossover study that's planned next. But we found no difference and no change in symptomatology in any of these patients. I don't know why there should be, since transit is very rapid. We certainly did not find that, nor did Hawkins, who is studying more than 1,000 patients. It doesn't seem to have a therapeutic effect.

Dr. Katzberg to Dr. Poirier: An interesting thing about the cerebral angiography study was the delayed urticaria, in some cases 24 to 48 hours after the study was performed. Has anybody else seen delayed urticaria with an iodinated contrast agent, or is this totally unrelated to the procedure itself, or was this coincidental?

Dr. Poirier: From a literature review, both ionics and nonionics have a delayed incidence of adverse events, and it is usually a skin reaction within 2 days, but the overall incidence for both ionics and nonionics, I understand, is approximately 5%. In this group, it was 4 of the 99, so it is in that same range; it is just interesting that they were all with the iodixanol group.

Dr. Dawson: There have been a few studies in England. Peter Davis of Nottingham has looked at alleged delayed reactions with ionic and nonionic contrast agents. The problem is that there are no controls. What has not been studied are patients who have gone into the hospital as inpatients or outpatients, not received any contrast, and then gone home and been asked "how do you feel" and "do you have any rashes." I suspect if you ask patients how they feel, they don't feel too good. If you ask them if they have any hangovers from procedures, they probably did. If you ask them if they itch a little or have any rashes, I am sure they all do.

Dr. Sovak: To complete the discussion about the gases, it's not CO_2, it's actually oxygen, which was first used and described in the literature for the purpose which you have mentioned.

Dr. Almen to Dr. Bettmann: You were comparing one negative contrast medium, carbon dioxide, with one positive contrast medium, ioversol. Were you really using them as equally good contrast agents? I was just speculating, should you have used the ioversol at 300 mg iodine/mL to have a similar imaging effect?

Dr. Bettmann: It was dilute ioversol 300 diluted 2 to 1, so it had an iodine content of about 100. So it was a low-iodine concentration. It's a small group of patients, 21 patients, so the accuracy is questionable. In all of the patients, the findings correlated well with the clinical findings and the noninvasive findings. If a stenosis was seen, we saw a pressure gradient; if the stenosis was not seen, we didn't find a pressure gradient. I think your point is very well taken. The images seem to be roughly equivalent in detail between CO_2 and 100 mg iodine/mL. I don't know how much further we

could go with a nonionic and still maintain diagnostic adequacy. I think one of the speculations that comes up is over whether CO_2 will be useful, not only in renal failure, but also in patients with immune-mediated reactions, in which case it's probably not a dose-related or concentration-related phenomenon. In another situation, you are using iodinated contrast at low concentration for peripheral intervention, and the more involved you get in the intervention, I think the more likely you are to use higher iodine concentrations and higher volume. CO_2 in essence obviates that since you can't use a higher concentration, although you can use increased volumes.

Dr. Grabowski to Dr. Bettmann: CO_2 contrast is extremely low in viscosity. Do you have any comment as to whether this might lead to under-representation of some areas of stenosis in peripheral vessels? For example, in having CO_2 pass the stenotic region, is it possible that blood could become trapped just distal to the stenosis as the CO_2 rushes over it because of its low viscosity?

Dr. Bettmann: One of the worries is actually not so much in terms of trapping of the blood and altered images, but in terms of trapping of the CO_2 and the possibility of related anoxia. For example, in abdominal aortic aneurysms, where CO_2 might accumulate as a result of having a lower density than blood, it could accumulate anteriorly due to minimal washout for a long period of time, and then potentially wash out in a very large bolus. Our experience is limited, but I think that is something that has to be examined. The next study planned is a crossover study, rather than a randomized, double-blind study, because it is not possible to do a double-blind between CO_2 and iodinated contrast. We will look at the same areas with both agents in given patients and see if there is qualitatively or quantitatively different information. This is planned in a larger number of patients.