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Correspondence

Re: CO_2 microbubble contrast enhancement in x-ray angiography

Sir — Kariya et al.[1] describe the use of carbon dioxide (CO_2) microbubbles as an angiographic contrast agent. Microbubbles are exciting in the context of ultrasound where they have diagnostic and therapeutic effects related to the physical interactions between the ultrasound waves and the bubbles. There is no such interaction between x-rays and bubbles, so the crucial question to ask is does this technique have the potential to increase the clinical utility of CO_2 angiography in its current form or in any future iteration? Leaving aside questions of safety, the answer with the technique described is a resounding no for many reasons.

First, the evidence shows that this technique is inferior to both conventional iodinated contrast enhancement and CO_2 bolus angiography. This is no surprise: CO_2 has always been a less effective angiographic contrast agent than iodinated contrast agents except in a few specific circumstances.[2] Angiographic techniques rely on changes in x-ray attenuation caused by the contrast agent. In conventional CO_2 angiography, the gas bolus displaces blood and fills the vessel lumen decreasing its attenuation compared to soft tissue. Iodinated contrast media mix with the blood increasing its attenuation, the degree of enhancement depending on the iodine concentration (contrast strength and rate of delivery). Microbubbles mix with the blood in the same way as iodinated contrast. The degree by which they will lower the attenuation depends on the fraction of the lumen occupied by gas bubbles (the CO_2 void volume). As the void volume is typically low, the effect on attenuation is diminished and confined to a CO_2 gas bolus. The authors make the confusing statement that "physiological saline is the main contrast medium component in CO_2 microbubble contrast enhancement". A more useful analogy is that the saline carrier reduces the contrast effect by diluting the CO_2 microbubbles, just as it would dilute conventional contrast media.

Second, non-invasive techniques have massively reduced the need for diagnostic angiography; this has left CO_2 angiography with a niche role in contemporary practice.[2] It is used to advantage in some interventions, and a small number of patients in whom conventional contrast medium is contraindicated. It is unlikely that an inferior contrast agent will be helpful in these circumstances.

Third, the current system uses a 20 F catheter with a stainless steel shaft. This would be impractical in all but a tiny number of cases. In addition, it completely negates one of the key advantages of CO_2 over conventional contrast media, which can be injected through conventional catheters due to its low viscosity.

Fourth, microbubbles have a short half-life in solution.[3]Those used in ultrasound require some form of shell to stabilize them. If there is to be a future for microbubbles to be used for conventional angiography, they will need to remain in a stable state for long enough for imaging to be performed. The physical properties of bubbles in solution are complex; they may grow or shrink depending on surface tension and saturation of the solution. If the gas bubbles dissolve rapidly, there will be no contrast effect. Conversely, if the bubbles coalesce, they will start to float; scrutiny of Fig 2 suggests that a gas–liquid interface is developing within a few centimetres of the bubble generator.

Is there any future in angiography using CO_2 microbubbles? If the microbubbles were stable and the void volume could be increased, the technique would be intriguing. In particular, it would be interesting to know whether microbubble techniques would make CO_2 angiography safe above the diaphragm. An additional area where conventional CO_2 angiography provides relatively poor imaging is in small vessels distal to the site of injection, such as the tibial arteries, often due to significant bolus fragmentation and increased patient discomfort from CO_2 injection. The use of microbubbles would become a more interesting prospect if they could be shown to improve on these limitations.

Unfortunately, the technique as described appears inferior to conventional CO_2 angiography in every respect and seems to have limitations that are unlikely to be overcome.

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Re: CO_2 microbubble contrast enhancement in x-ray angiography. A reply

Sir — We thank Dr Patel for his interest in our article.[1] The study compares CO_2 microbubble contrast enhancement, conventional CO_2 contrast enhancement, and iodinated contrast medium enhancement. The reasons for this comparison were twofold: first, to quantitatively examine the angiographic performance of CO_2 microbubble contrast enhancement; and second, to determine the reference standard for aortic angiography with existing angiographic techniques. It was necessary to verify both that the angiographic contrast created by CO_2 microbubble contrast enhancement was low and that the acquired image was a shadow of the aorta to the iliac artery by comparing it with the reference-standard angiogram. The study was not intended to show the superiority of CO_2 microbubble contrast enhancement over existing angiographic techniques. As shown in the results, CO_2 microbubble contrast enhancement using our current device and angiographic equipment will not immediately replace iodinated contrast enhancement in the clinical setting.

The microbubble generator in our system uses a metallic shaft and a 20 F diameter generator component; therefore, both modification of the shaft to a soft dual lumen tube and reduction of the diameter of the generator are necessary. It is possible to reduce the size of the generator component due to its simple structure; however, we were unable to provide this in the study.[2]

The ultimate goal of the study was to use the cavitation effect of CO_2 microbubbles. Cavitation effects have been experimentally applied to various studies, including those that involve high-intensity focused ultrasound, microvessel rupture, thrombolysis, and the introduction of drugs and genes into cells.[3–7] Ultrasound contrast agents were used as microbubbles in those particular studies. Microbubbles of ultrasound contrast agent are stabilized using shell substances, and the target site can be reached even if administered from peripheral veins. However, the quantity of bubbles is extremely low, which results in a weak cavitation effect. The study resolved this issue. The microbubble generator used was presumed to uniformly and continually produce large quantities of microbubbles in arteries that supply nutrition to the target sites. This suggests that microbubbles can reach the target site without using microbubble-stabilizing shells.

Although the study was limited to confirming the feasibility of angiography by CO_2 microbubble contrast enhancement, we also claim that it proved the existence of a large quantity of microbubbles in blood vessels to the point of promoting radiolucency.

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