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Carbon Dioxide in the Aortic Arch: Coronary Effects and Implications in a Swine Study

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Abstract

Purpose: CO_2 angiography is considered dangerous in the aortic arch where bubbles may cause critical cerebral and cardiac ischemia. We investigated CO_2 distribution, physiologic effects in the heart, methods of detection and treatments.
Methods: Eight pigs had CO_2 and iodinated contrast arch angiograms in supine and both lateral decubitus positions. An electrocardiogram, physiologic data and cardiac ultrasound were obtained. Therapies included precordial thumps and rolls to lateral decubitus positions.
Results: Supine high descending aorta CO_2 injections floated retrograde up the arch during diastole and preferentially filled the right coronary artery (RCA): mean score 3.5 (of 4), innominate artery 2.4, left coronary artery 1.2; $n = 17$; $p = 0.0001$. Aortic root injections preferentially filled the RCA when the animal was supine, left coronary in the right decubitus position, and showed a diffuse pattern in the left decubitus position. Right decubitus rolls filled both coronaries causing several lethal arrhythmias. Precordial thumps successfully cleared CO_2. Ultrasound is a sensitive detector of myocardial CO_2.
Conclusion: Arch distribution of CO_2 primarily involves the RCA. Diagnostic ultrasound detects cardiac CO_2 well. Precordial thumps are an effective treatment.

Key words: Carbon dioxide—Angiography—Complications—Aortic arch—Coronary arteries

Carbon dioxide (CO_2) angiography is a widely accepted technique of alternative vascular imaging for use in patients with renal compromise or iodine allergies [1–7]. Though isolated reports suggest major complications including death can be related to the use of CO_2 as an angiographic agent, most studies report excellent acceptance and only moderate discomfort, with actual complications being uncommon [8–12]. However, use in the arterial tree has been restricted to infradiaphragmatic locations due to suspected cerebral toxicity [13–17], and direct left coronary injections of CO_2 have been shown to cause cardiac ischemia in swine [18]. The mechanism for possible death has remained obscure, with most concern focused on intracerebral embolization.

CO_2 is a very soluble physiologic substance and is found in all tissues as a product of metabolism. Clearly, diagnostic amounts of CO_2 are usually safe in the venous system and in the arterial system below the diaphragm. It is also widely used to distend the abdominal cavity and other cavities for laparoscopic procedures. When used properly, complications are rare.

However, "vapor lock" has been reported in many locations including the pulmonary artery, the inferior mesenteric artery and other vessels. This complication is based on the buoyancy of the gas, which produces obstructing bubbles in vessels that proceed upwards and then turn back downwards in an inverted "U" configuration. Vapor lock occurs when the propulsive force of the blood is inadequate to displace the buoyant bubble, which then occludes blood flow until the gas dissolves into solution. The high solubility of CO_2, many times that of oxygen and nitrogen, usually limits vapor lock from CO_2 to only a few minutes. Nevertheless, vapor lock in the pulmonary artery can cause clinically important right-sided cardiac obstruction, and vapor lock in the inferior mesenteric or other visceral vessels can cause bowel ischemia that is often manifest as immediate abdominal cramping. These acute situations usually respond well to rolling into a decubitus position, which allows the buoyant bubble to progress through the vessel. The left decubitus position is

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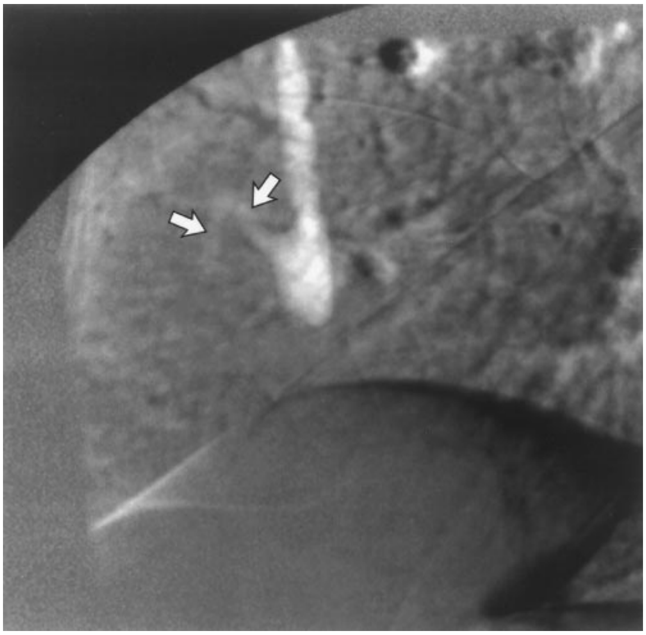


Fig. 1. A magnified digital subtraction angiography frame from an infradiaphragmatic aortic CO_2 injection in a human shows CO_2 that refluxed from the descending aorta and floated up into the RCA (arrows) due to partial aortic obstruction caused by aortic dissection. The CO_2 caused bradycardia, a hypotensive episode and, on the third injection which is pictured, asystole. This responded to voluntary coughing on command with complete recovery. Central nervous system symptoms were absent.

chosen for pulmonary artery vapor lock and either right or left is appropriate for abdominal ischemia.

A human patient of ours (Fig. 1) showed a vapor lock in the right coronary artery following an injection of 40 cm^3 of CO_2 in the abdominal aorta. Due to a combination of decreased cardiac output and partial aortic obstruction from an aortic dissection, reflux of the CO_2 occurred into the arch and filled the right coronary artery causing vapor lock. The symptoms from three CO_2 injections were life-threatening in this patient and included hypotension, bradycardia, and asystole typical of the Bezold-Jarisch reflex frequently seen in right coronary artery (RCA) ischemia. Since the RCA supplies the sino-atrial and atrioventricular nodes, cardiac rate and rhythm are commonly disrupted with ischemia here. Acute myocardial infarction due to RCA ischemia often presents with hypotension and bradycardia. In this patient the vapor lock and reflex responded well to coughing on command, which led to an uneventful recovery.

Our animal study was designed to test the hypothesis that buoyant CO_2 would preferentially enter the most nondependent branch of the aortic arch. It mapped the distribution of intra-aortic CO_2 when injected into the ascending aorta or the descending portion of the arch. Effects of buoyancy and blood flow in standard angiographic positions, i.e., supine and both decubitus positions, were investigated along with practical ways to disperse the bubbles.

Since buoyancy and blood flow characteristics may lead to specific patterns of bubble distribution, specific patterns of signs, symptoms and specific ischemic events may result. Specific evaluation of coronary involvement with ultrasound [19] was obtained since ischemia of the RCA, the most anterior branch of the ascending aorta, was seen in our human patient.

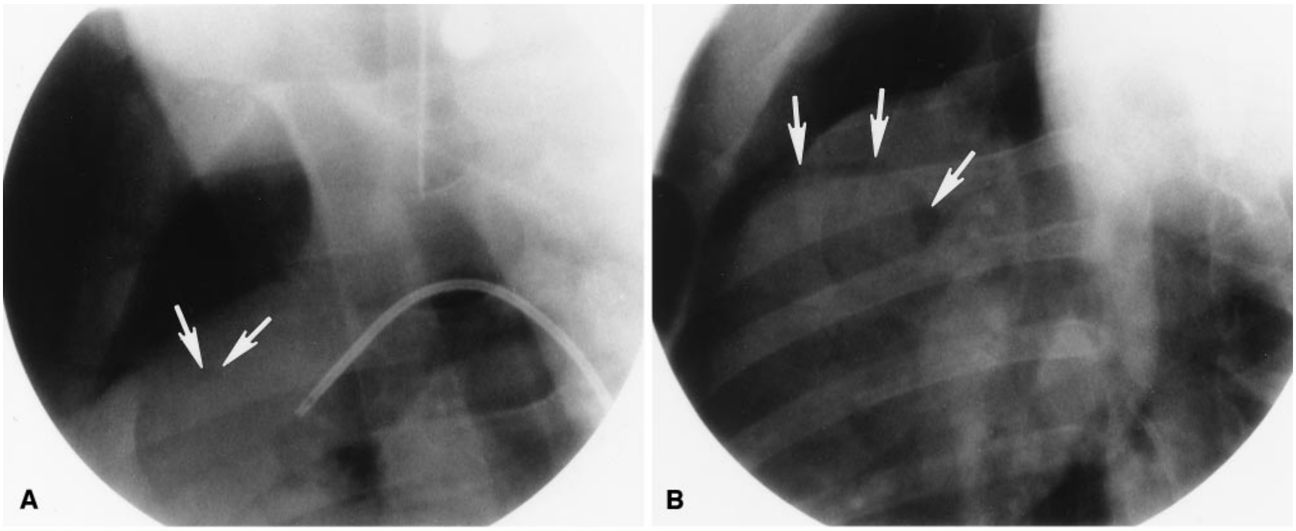
Materials and Methods

Studies were performed in eight pigs of either sex ranging in size from 30 to 34 kg, in compliance with the guidelines of the institutional review board and animal care committees of our institution and in keeping with the principles of *The Guide for the Care and Use of Laboratory Animals* [20]. The animals were anesthetized with intravenous pentobarbital sodium 28 mg/kg with supplemental doses to effect, intubated, and placed in a supine position on the special procedures table.

Percutaneous access was obtained in both femoral arteries and one femoral vein with placement of vascular sheaths in each. A CO_2 plastic bag delivery system (Angiodynamics, Queensbury, NY) [2, 3] was used in the standard manner with rapid manual injections. The catheter was cleared of fluid with gentle CO_2 injection low in the aorta before advancing to the first injections in the arch. Following any iodinated contrast injections in the arch, there was clearing of fluid from the catheter with gentle CO_2 injection followed by 4 min delays to allow the gas to dissipate. Angiographic catheters (5 and 6 Fr multipurpose coronary catheters with side holes near the tip) were used to selectively inject CO_2 and iodinated contrast agents high in the descending aorta and in the ascending aorta in all pigs. Injections in the ascending and descending aorta were also made in both lateral decubitus views. Injected volumes increased from 2 cm^3 through 5 cm^3, 10 cm^3, 20 cm^3, and, in some pigs, up to 30 cm^3 of CO_2, and from 2 cm^3 to 10 cm^3 of iodinated contrast in the ascending aorta. A similar series started with 5 cm^3 in the high descending aorta. Delays between runs were normally 4 min, but this was lengthened occasionally when ultrasound showed persistent abnormal myocardial echogenicity or when other factors delayed progress through the protocol. Each pig received two or more rolls to decubitus positions immediately following ascending aorta injections of CO_2. A total of eight precordial thump maneuvers were performed in recumbent and lateral decubitus views following large injections of 15–25 cm^3 of CO_2 in the ascending aorta.

One-third of the arch runs were imaged on transthoracic ultrasound, and two-thirds were recorded on cine film. A clinical ultrasound machine using a 1.7 MHz harmonic transducer (HDI 3000 ATL; Bothell, WA) was used to obtain parasternal short axis images of the left and right ventricle at the mid-papillary muscle, and images were recorded on video tape in color with full audio. Visualization was continued until myocardial echogenicity returned to normal several minutes after injection. Continuous electrocardiography (EKG), pulse rate and arterial pressure (arterial line) recordings were also made. The animals were killed at the end of the procedure and neurologic sequelae were not assessed.

The cine images were evaluated for relative volume of gas filling or iodinated contrast filling in each of the major branches of the arch and the arch itself. A 0 to 4 scale was used with 0 indicating no visible bubbles or iodinated contrast, 1 indicating scattered bubbles or faint contrast, 2 indicating approximately one-



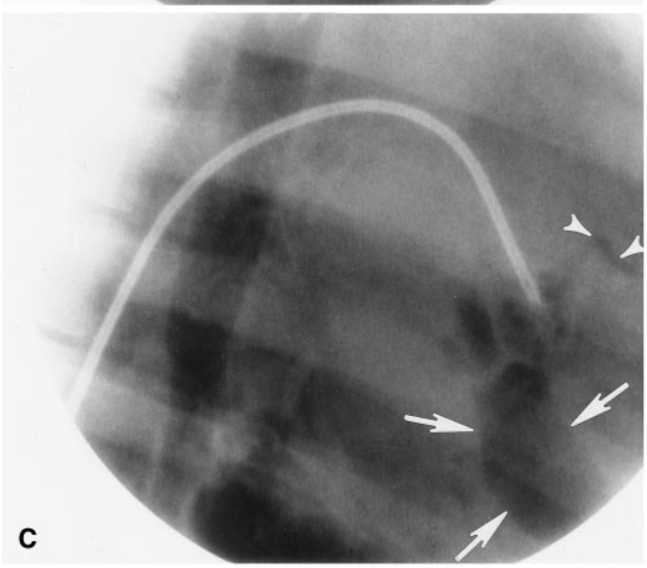


Fig. 2. A–C. Cine frames following arterial CO_2 injections demonstrate degrees of RCA and left ventricular filling. The definition ranges from grade 0 (no vascular filling) to grade 4 (complete filling). **A** Grade 1, scattered bubbles. Note the small bubble (arrows) moving promptly through the RCA following a 2 cm^3 injection of CO_2 into the ascending aorta with the pig in a supine position. It was clearly visible during cine viewing but is difficult to appreciate on a single frame. **B** Grade 4, complete gaseous filling. The proximal 5 cm of the RCA is filled (arrows). Little movement was seen here for several cardiac cycles, but laminar flow can also be present with complete filling and no vapor lock. Ten cubic centimeters of CO_2 were injected in the high descending aorta in the supine position. **C** Grade 3 left ventricular filling. Just over one-half of the left ventricle appears filled (arrows) by reflux from a 15 cm^3 CO_2 injection in the ascending aorta in the left decubitus position. Note some filling of the RCA (arrowheads) and CO_2 outlining the leaflets of the valve.

half of the column was filled, 3 indicating more than one-half of the vessel was filled, and 4 indicating an essentially full vessel with annular flow of gas (Fig. 2). The duration was scored as the number of complete cardiac cycles in which the contrast agent was visible on cine runs. On ultrasound runs, the duration was recorded in seconds and minutes of observation.

The scores for each portion of the aorta and each aortic branch were compared statistically using the Mann–Whitney rank sum test and a two-tailed Student's *t*-test. Statistical significance was assumed at the $p < 0.05$ level.

Results

High descending aorta CO_2 injections (Figs. 3, 4) in supine position followed a retrograde course during diastole along the inferior half of the arch to the ascending aorta and preferentially filled the right coronary (RCA): mean volume score RCA 3.5, arch 2.8, innominate artery (IA) 2.4, left subclavian artery (LSA) 0.8, left coronary artery (LCA) 1.2; $n = 17$; $p = 0.0001$ (RCA vs others). With descending thoracic aorta injections, CO_2 did not reflux above the level of the arch during systole ($n = 8$), even when large volumes were used. Reflux occurred only during diastole. Then even small volumes (<5 cm^3) progressed upward rapidly over the arch.

Aortic root injections (Fig. 5): (1) preferentially filled the RCA when the pig was supine (RCA 4.0, arch 1.1, IA 1.9, LSA 0, LCA 1.5; $n = 20$; $p = 0.0001$, RCA vs others), (2) preferentially filled the LCA in the right decubitus position (RCA 1.9, arch 2.6, IA 1.7, LSA 0.5, LCA 3.7; $n = 36$; $p = 0.0001$, LCA vs others), and (3) produced a diffuse pattern sparing the LCA in the left decubitus position (RCA 2.6, arch 2.6, IA 2.3, LSA 0, LCA 0.1; $n = 37$; $p = 0.0001$, LCA vs others). During diastole, almost all flow entered the nondependent coronary artery. At systole, wider distribution into other vessels occurred as the large bubble in the aortic root was suddenly dispersed. In the right decubitus position, cine showed some flow of bubbles from the ascending aorta along the inferior margin of the arch to the descending aorta. This spared the IA, except when very large volumes were present. Aortic valvular reflux occurred in 77% of CO_2 injections

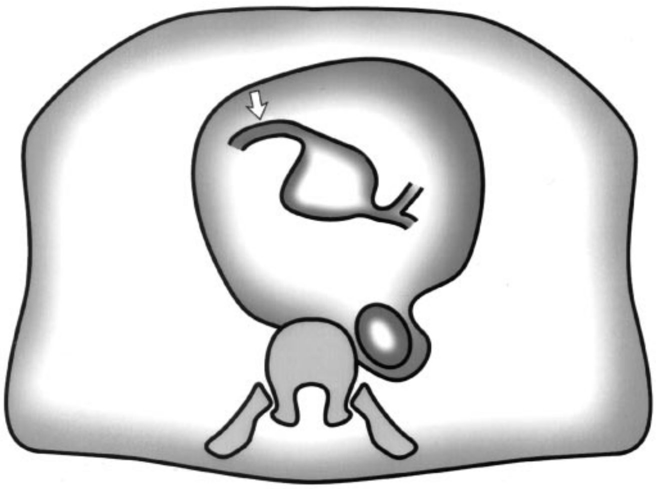


Fig. 3. A transverse diagram of the mediastinum at the aortic root level in the supine position shows the anterior location of the RCA and posterior location of the LCA. The proximal RCA loops anteriorly and then posteriorly in its first several centimeters forming an inverted "U" which favors vapor lock formation (arrow). Swine and human anatomy are similar at the coronary level, though there are differences in the carotid branching patterns.

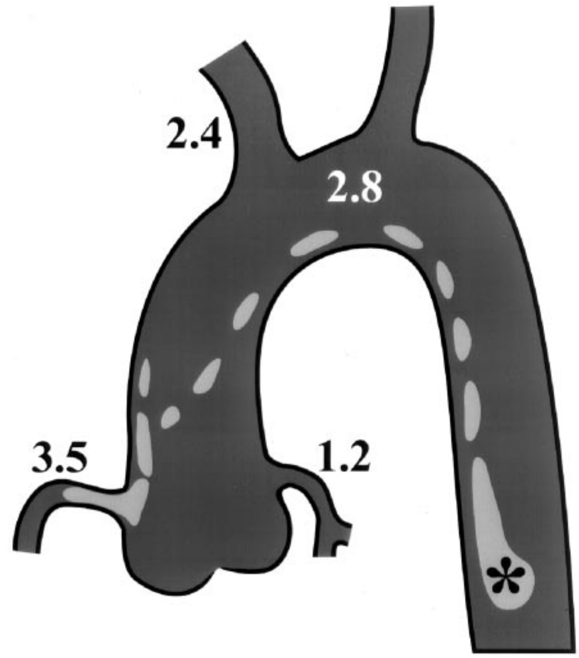


Fig. 4. CO_2 reflux flow patterns from the descending aortic arch injections (*) in swine. This anatomy closely resembles the human except that both common carotid arteries originate from the innominate artery. Supine studies show predominate filling of the RCA (3.5 mean volume score of a possible 4.0) with relative sparing of the LCA. The upward route of the bubbles follows the inferior margin of the arch to the ascending aorta and then to the RCA during periods of low flow. Systole disperses the bubbles, primarily to the RCA and innominate artery.

which reached the valvular level, compared with 4% of iodine injections ($n = 125$, $p = 0.0001$).

Duration scores closely paralleled volume measurements. Mean duration of grade 3 and 4 bubbles in the RCA was 6.85 cardiac cycles ($n = 41$). The corresponding value in the left ventricle for grade 2 and 3 bubbles (the two highest categories observed) was 7.15 cardiac cycles ($n = 27$, $p = 0.85$). In supine position without left ventricular reflux and filling ($n = 7$), mean RCA duration was 3.45 cardiac cycles. With left ventricular reflux and replenishment of the RCA filling as the left ventricle emptied on subsequent systoles, RCA duration was 7.34 cycles ($n = 35$, $p = 0.022$). Fifteen of 35 duration values with LV reflux and one of seven without reflux were limited by the cine acquisition time limit, which ranged from 8 to 22 sec.

Two precordial thumps reduced CO_2 volume by two levels in both the ventricle and the arteries within two cardiac cycles in four of five cases on cine. RCA flow immediately resumed. In three cases ultrasound showed that the bubbles quickly dispersed with thumps, except for very small ventricular residuals which could still be identified at 3–4 min. Ultrasound quantification of ventricular bubbles was not thought reliable due to the partial imaging of the ventricle.

Lethal arrhythmias occurred three times, but only with large volumes of CO_2 and when both RCA and LCA were filled with CO_2 immediately after rolling the pig into the right decubitus position. Each followed a 20–25 cm^3 CO_2 injection in the ascending aorta in the supine position with large volume left ventricular reflux and prolonged RCA filling. This was then followed by LCA filling as the right decubitus position was assumed. These lethal rhythms occurred in three of eight runs. Two of the three events were successfully defibrillated. The third led to premature death.

Transthoracic cardiac ultrasound was a sensitive method of CO_2 detection and initially showed increased echogenicity in the RCA distribution (posterior wall and septum) with very small doses. As little as 2 cm^3 was easily detected when injected in the ascending aorta (Fig. 6). Hypokinesis appeared in the affected area with moderate volumes (100% of those of >5 cm^3) or prolonged vapor lock. Aortic valvular reflux was readily visible on ultrasound. Left ventricle bubbles replenished the ascending aortic bubble and RCA bubbles during systole and prolonged abnormal myocardial echogenicity in the RCA distribution when recumbent. Washout of the increased echogenicity increased from 2 min without ventricular replenishment to more than 4 min with ventricular replenishment of the aortic bubbles. Right decubitus positioning added similar late LCA distribution involvement.

Vital sign changes with small drops in pulse rate and blood pressure were reliably seen, but were of mild proportions in these animals. Only with constant intra-arterial recording did pressure measurements become useful, since the changes were quite small. Only with prolonged ischemia of

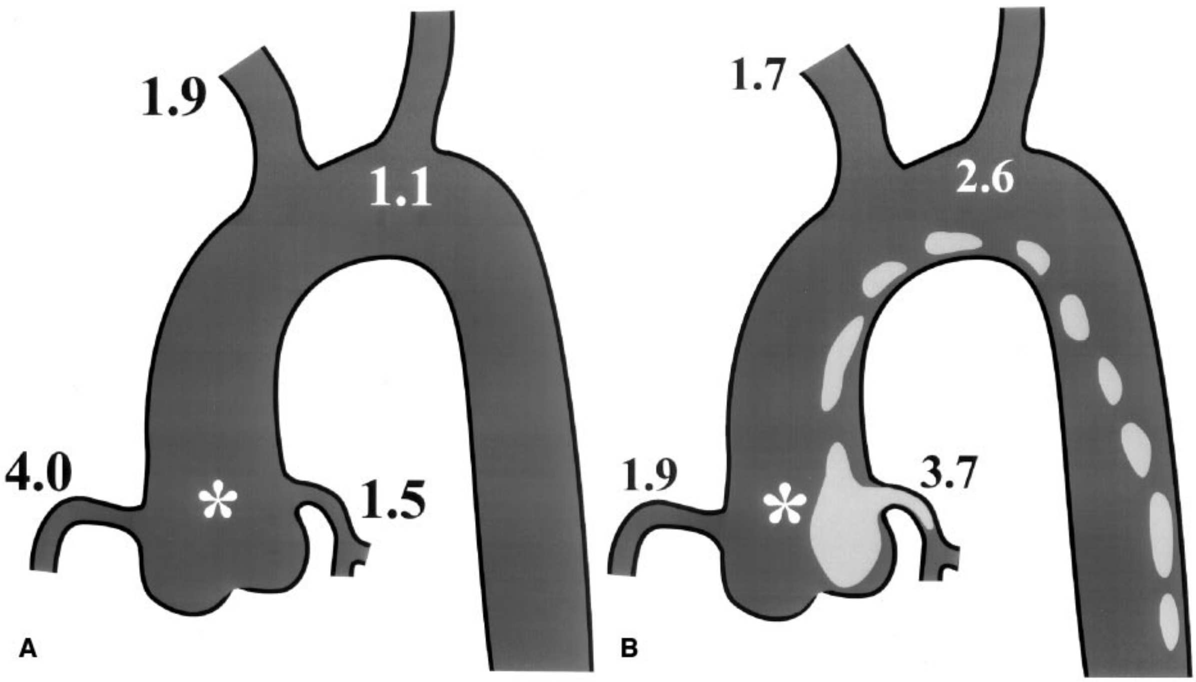


Fig. 5. A, B. CO_2 flow patterns from aortic root injections (*) in swine. **A** Recumbent distribution fills the RCA and spares the LCA. **B** Right decubitus distribution fills the LCA and spares the RCA. Small bubbles track up the inferior margin of the aortic arch to the descending aorta, bypassing the innominate artery.

both right and left coronary distributions did the classic changes of ischemia become apparent on EKG and in depressed vital signs which were clinically obvious. The EKG findings of T wave inversion, ST segment depression or elevation, and eventually Q waves and arrhythmias were only seen very late in the most severe ischemic events. Cutaneous changes in the form of a patchy, mottled appearance to the nondependent portion of the skin occurred late in the series of runs in five of the pigs.

Discussion

CO_2 angiography using digital subtraction angiography is an important and well-accepted alternative angiographic technique in cases of renal compromise and iodine allergy. The applications are steadily increasing [1–7]. Recently side effects and complications, including possible death, have been more fully explained and reported [8–12]. Cerebral and cardiac causes have been suspected, with the majority of concern for intracerebral embolization. The exact mechanism for possible death has remained obscure. RCA ischemia can explain this in some acute cases. Indeed, it may be the primary risk, as was seen in our human example.

Careful attention to details of use, including safe gas handling techniques such as the plastic bag delivery system [2, 3] and use of small volumes in very selective delivery sites, make this a useful and safe technique. Explosive delivery can lead to uncontrolled spread of the CO_2 and widespread reflux, and must be avoided. Use above the diaphragm is presumably contraindicated. Though some animal studies have been performed there with mixed results [13–16], the use of CO_2 which accidentally reached the aortic arch has been associated with major complications including seizures and loss of consciousness [17]. The danger here is high, and even higher if air (which is much less soluble) happens to be mixed with the CO_2. Air will cause more severe ischemia and occasionally death [21].

Buoyancy effects on gas distribution overpower simple flow volume effects. Flow effects should favor filling of the large innominate artery or descending aorta. In the supine aortic arch, predominant bubble flow is into the nondependent RCA. In the right decubitus position the RCA was less filled with buoyant CO_2, while the nondependent LCA was routinely well filled. In all positions the IA showed less filling than the nondependent coronary artery. This pattern of preferential flow into the most nondependent aortic arch branch is quite reproducible.

In addition, the RCA not only has a proximal inverted U-shaped configuration, which favors vapor lock, but also provides blood to the sino-atrial and atrioventricular nodes controlling heart rate. With ischemic changes here, bradycardia and hypotension of the Bezold-Jarisch pattern could be expected. This developed consistently in the swine model, though not to the severe degree seen in the previous human case.

Rolls into lateral decubitus positions and precordial thumps following CO_2 injection into the ascending aorta were compared as rescue maneuvers in the swine model. Rolls into left lateral decubitus position did not change the

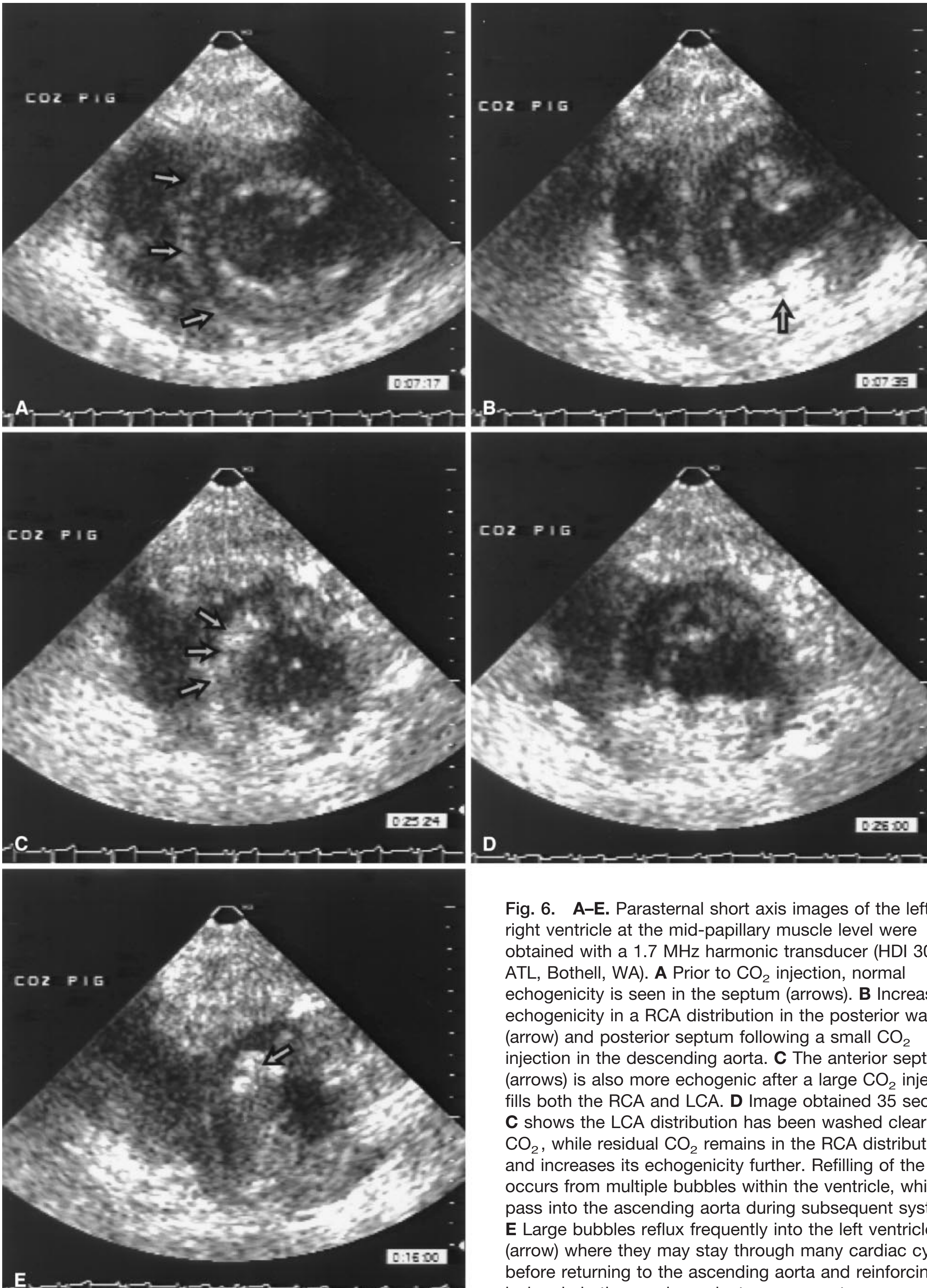


Fig. 6. A–E. Parasternal short axis images of the left and right ventricle at the mid-papillary muscle level were obtained with a 1.7 MHz harmonic transducer (HDI 3000; ATL, Bothell, WA). **A** Prior to CO_2 injection, normal echogenicity is seen in the septum (arrows). **B** Increased echogenicity in a RCA distribution in the posterior wall (arrow) and posterior septum following a small CO_2 injection in the descending aorta. **C** The anterior septum (arrows) is also more echogenic after a large CO_2 injection fills both the RCA and LCA. **D** Image obtained 35 sec after **C** shows the LCA distribution has been washed clear of CO_2, while residual CO_2 remains in the RCA distribution and increases its echogenicity further. Refilling of the RCA occurs from multiple bubbles within the ventricle, which pass into the ascending aorta during subsequent systoles. **E** Large bubbles reflux frequently into the left ventricle (arrow) where they may stay through many cardiac cycles before returning to the ascending aorta and reinforcing the ischemia in the nondependent coronary artery.

distribution of the CO_2 in the ascending aorta and RCA a great deal. While the left decubitus roll is therapeutic for pulmonary artery obstruction with gas, it provided little advantage here. Filling of the RCA was slightly decreased due to its anterior location in the ascending aorta (Fig. 3), and the buoyant gas showed slightly increased filling of the IA instead. This might increase detrimental cerebral effects. This did protect the LCA from CO_2 filling quite effectively, however. The very dependent LCA was only rarely filled with gas with the left side down and only occasionally filled when the animal was supine.

The right lateral decubitus position shifted CO_2 filling to the LCA, with a marked decrease in CO_2 filling of the RCA (Fig. 5). A quick roll to this position worsened the ischemic effect on the pig's heart, which had tolerated right coronary ischemia fairly well up to that point. Only with both left and right coronary ischemia did the pigs develop any fatal arrhythmias. Three times this occurred after rolls into the right decubitus position when left coronary ischemia was suddenly added to pre-existing right coronary ischemia. Two of the three animals responded well to being returned to a supine position, thumps, and defibrillation. Lambert et al.'s study [18] of CO_2 injections into the LCA of supine pigs did not result in fibrillation. This is consistent with our results. The LCA probably emptied rapidly in the supine position used in that study. In our study, right decubitus runs with prolonged filling of the LCA did not result in fibrillation. Though vapor lock did sometimes occur in the LCA, fibrillation required simultaneous RCA and LCA ischemia.

Earlier indications for the precordial thump for ventricular tachycardia or ventricular fibrillation have been discounted recently [22–25]. However, here the precordial thumps were quite effective, decreasing the bubble score by two or more levels in two cardiac cycles in almost all cases. This immediately restored flow to the affected vessels. In addition, it helped speed emptying the left ventricle of bubbles. These bubbles prolonged ischemia in the most nondependent branches of the ascending aorta, typically the RCA when the pig was supine, but the LCA when the animal was in the right decubitus position. This reservoir of CO_2 commonly doubled the period of ischemia, as seen with ultrasound, from about 2 min to 4 min or more.

Detection of CO_2 in the arch and its branches is not easy. Patients' symptoms, EKG findings, and vital sign findings are usually late in a series of ischemic events. Fluoroscopy is a very poor method of detection as it is insensitive to small amounts of air or CO_2 in small vessels with rapid flow, such as the coronary arteries. It is more useful in larger vessels, such as the main pulmonary artery, where obstructing bubbles are easily identified and there is less organ motion.

Subtraction techniques are much more sensitive. In a clinical situation, it seems wise to position the image intensifier well above the diaphragm on the first digital subtraction angiography (DSA) run to see whether reflux from abdominal aortic injections will be a problem. This is particularly applicable in cases where the distal aorta is obstructed or compromised or when cardiac output is poor. A very slow cardiac rate could also justify this technique since reflux occurs only during diastole and bubbles are quickly propelled downstream during systole. DSA is the best of the radiographic imaging techniques, but was not available for comparison in this animal laboratory.

Cine angiography could also show small bubbles, but requires developing and delay. It is of little use in a clinical situation outside the experimental laboratory. Video recording of fluoroscopy is quickly available and replay is helpful with small bubbles.

Vital sign changes in these animals were minimal until severe and prolonged ischemia was present. Only with constant intra-arterial recording did hemodynamic pressures become useful, since the changes were quite small. Traditional blood pressures changed little and changes were too brief to use as a screening procedure. This change related to RCA ischemia might be more dramatic in humans with compromised coronary collateral vessels, but was rarely an obvious finding in the animal study. It does not seem a useful sign for a clinical setting.

The most promising detection technique is transthoracic ultrasound. It is sensitive and cheap, but does require skill and some preparation in having the ultrasound machine available during CO_2 angiography. In this animal study, volumes as small as 2 cm^3 in the ascending aorta were readily detected by the appearance of intense echogenicity in the myocardial distribution of the RCA. The sudden increased echogenicity in the septum posteriorly and in the posterior wall of the heart was quite typical. This could also be used to follow clearing of the CO_2. Long after cine angiography had shown resolution of the bubble in the first few centimeters of the right coronary artery, ultrasound continued to show increased echogenicity and hypokinesis in the affected walls of the ventricles. Transesophageal ultrasound may also be readily available for this role in some clinical situations.

Limitations of this study include the absence of the most sensitive radiographic imaging technique, DSA, in the animal laboratory. Cine angiography almost certainly missed some gas DSA would have detected. Neurologic and cerebral perfusion changes were not assessed in this nonsurvival study, though the IA, which supplies both common carotids in swine, was reliably imaged and scored.

In summary, when CO_2 reaches the aortic arch in a supine pig, it will primarily involve the RCA and reflux into the left ventricle. Other branches of the arch are also involved but are relatively spared, especially when volumes are low. Ischemic changes in the heart initially may include hypokinesis, bradycardia and hypotension and may progress to fatal arrhythmias. A high position on the first DSA run of all cases is recommended to detect this problem, and cardiac ultrasound is also a sensitive method of detection. Cine angiography, fluoroscopy, vital signs and EKG changes are less helpful. Decubitus positions are not useful in treatment of acute RCA vapor lock and may result in a worse outcome compared with simply maintaining a supine position and performing two precordial thumps. These are an effective method for clearing the bubbles from critical sites. The single human experience suggests that coughing may be a good equivalent in the cooperative patient. In addition to proven cardiac sequelae, CO_2 does reach other branches of the arch not fully studied here and will have detrimental effects in those organs. This makes it important that CO_2 never be used in the area.

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