Carbon Dioxide Angiography: Effect of Injection Parameters on Bolus Configuration

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PURPOSE: Predict the intravascular distribution of carbon dioxide during angiography.

MATERIALS AND METHODS: Mathematical modeling was used to predict the flow pattern of CO2 in a pulsatile system as a function of the CO2 flow rate. Findings were validated in an in vitro pulsatile circuit.

RESULTS: The annular flow pattern with filling of nearly the entire lumen with CO2 is the most desirable, followed by intermittent bubble flow (provided individual bubbles are large). Stratiﬁed ﬂow relates to a continuous floating CO2 bubble. Conﬁguration of the CO2 bolus depends on vessel properties, ﬂuid velocity, ﬂow rates, mean intraluminal pressure, pressure amplitude, pulse rate, and vessel diameter. In vessels with less than 10-mm inner diameter, annular ﬂow can be achieved relatively easily with injection rates above 20–30 mL/sec. Higher rates are not expected to produce superior results. When imaging a 2-cm artery, the best that can be realized clinically is intermittent ﬂow with large bubbles. Bubbles size increases with increasing CO2 flow rate. In aneurysms, only stratiﬁed ﬂow can be achieved with reasonable injection rates. Periodicity of the ﬂow patterns is determined by the pulsatile circuit and can produce indentations in the CO2 bolus, which can be mistaken for stenoses.

CONCLUSIONS: Flow regime maps can be used to optimize bolus configuration during CO2 angiography.

VASCULAR imaging has traditionally relied on aqueous solutions of radiopaque contrast media. These solutions, however, have osmolar, chemotoxic, and anaphylactic risks. Substitution of carbon dioxide as contrast medium has signiﬁcant potential to avoid these recognized limitations. Despite the increasing use of CO2 as vascular contrast medium, optimal injection parameters have not been deﬁned. Because of the inherent difference of gases and liquids, the broad experience that has been accumulated with aqueous contrast media solutions cannot be transferred to use of CO2. The best diagnostic yield is to be expected when the CO2 column ﬁlls the entire vascular lumen. Floating or disrupted bubbles are less desirable. Most angiographers, however, are not familiar with the physical foundations of CO2 distribution in liquids, and remain uncertain about predicting the flow patterns of CO2 in relation to injection parameters. Distribution of gases in steadily ﬂowing liquids (such as oil in pipelines or vapor in nuclear reactor conduits) has been extensively evaluated by hydraulic engineers. Unfortunately, this knowledge has not found translation into the clinical arena. Lack of interdisciplinary cross-fertilization delayed develop-
Stratified Flow

Interruption Flow

Dispersed Bubble Flow

Annular Flow

Periodic Intermittent Flow

Periodic Wavy Stratified Flow

Figure 1. Flow patterns of gases in liquids. From an imaging perspective, the annular flow pattern with filling of nearly the entire lumen with CO₂ is the most desirable flow regime, followed by intermittent bubble flow (provided individual bubbles are large). Stratified flow relates to a continuous floating CO₂ bubble. Dispersed bubble flow is useless for conventional imaging. The bottom two drawings show variations only encountered under conditions of pulsatile flow: the intermittent flow pattern assumes a periodic nature with relatively equally sized individual bubbles. The stratified flow pattern exhibits waves with a periodicity determined by the cycle rate (“heart rate”) of the system.

- Definition of Flow Patterns

When CO₂ is introduced into a pulsatile circuit, one of following flow patterns can result: annular flow, wavy stratified flow, intermittent flow, and dispersed bubble flow (Fig 1). Annular flow is the most desirable for imaging: most of the lumen is filled with CO₂, and only a small film of blood remains at the vessel’s inner contour. Stratified flow relates to a continuous floating CO₂ bubble, and only nondependent portions of the vasculature are amenable to radiographic depiction. Dispersed bubble flow represents a myriad of tiny bubbles; it is useless for arteriography but may have applications for ultrasonic imaging. In intermittent bubble flow, distinct bubbles fill most of the vessel’s circumference and are separated by trains of liquid and small bubbles. Intermittent flow can be used for radiographic imaging when the individual bubbles are large and fill long vascular segments, in particular when stacking programs in digital arteriographic units permit electronic summation of the CO₂ filled spaces.

- Predictions of Flow Patterns with Flow Regime Maps

Knowing which flow pattern is favored under which conditions aids the angiographer to adjust expectations and injection parameters for CO₂ thus avoiding unnecessary intravascular pressure surges and diagnostic pitfalls. Engineers use “flow regime maps” to predict patterns of gas distributions in flowing liquids. We adapted these relatively complex flow regime maps into a simpler presentation that used CO₂ flow rate the independent variable (Fig 2). On these flow regime maps, dashed lines (“transitions”) separate regions in which different flow patterns are expected: flow in the region below the P-transition line is stratified; flow in the region above the P-transition line and left to the A transition (vertical dashed line) is intermittent, and flow in the region above the P-transition line and right to the A-transition line is annular. The flow regime indicator line (FRI) solid line is constructed as a function of the CO₂ flow rate. It depicts the flow pattern that can be realized as a function of the CO₂ flow rate under specific experimental conditions including vessel diameter, fluid properties, flow rate, blood velocity, heart rate, pulse pressure amplitude (1-3).

Flow regime maps can be used in two ways: First, to know which flow pattern to expect for a given CO₂ flow rate, find the intersection of the CO₂ flow rate value (x axis) and the FRI line and note in which flow pattern region it falls. For example, at a flow rate of 100 mL CO₂/sec the FRI falls in the annular flow region on Figure 2a, the intermittent flow region on Figure 2b, and the stratified flow region in Figure 2c. Second, to know at which CO₂ flow rate a particular flow pattern is produced follow the FRI until it enters that particular flow region and read the corresponding x value.

Please note that the x axis is on a logarithmic scale and that clinically unrealistic high values have

MATERIALS AND METHODS

- Overview

This study attempts to utilize mathematical modeling for clinical applications. In an attempt to provide understanding for the clinician while preserving transparency of the methodology Materials and Methods will be in the following simplified summary and in a more technical Appendix.
Figure 2. Flow regime maps for different physiological conditions. Dashed lines ("Transitions") separate regions in which different flow patterns are expected: flow in the region below the P-transition line is stratified, flow in the region above the P-transition line and left to the A transition (vertical dashed line) is intermittent, and flow in the region above the P-transition line and right to the A-transition line is annular. The FRI (solid line) is a function of the CO₂ flow rate under specific experimental conditions including vessel diameter, fluid properties, flow rate, blood velocity, heart rate, and pulse pressure amplitude. Its relative location to the regions of flow patterns indicates which flow pattern is expected for a given CO₂ flow rate. (a) Artery with 0.5-cm ID, blood flow rate of 2 mL/sec, blood pressure 120/80 mm Hg at sea level, and heart rate of 60 beats per minute. (b) Artery with 2-cm ID, blood flow rate of 29 mL/sec, blood pressure 120/80 mm Hg at sea level, and heart rate of 60 beats per minute. (c) Aneurysm with 5-cm ID, blood flow rate of 20 mL/sec, blood pressure 120/80 mm Hg at sea level, and heart rate of 60 beats per minute.
been included in the calculations.
This was necessary to document that certain flow regimes can be achieved only under unrealistic conditions. Such knowledge can help the angiographer to adapt practice and avoid expectation of the clinically impossible.

Whether flow is dispersed or not depends on a calculated T parameter (parallel to the x axis) and a T transition. Both lines were omitted from the flow regime map presented for the sake of simplicity, as this flow pattern is typically not encountered under physiological flow conditions.

Analytical flow regime maps were constructed for vessel diameters ranging from 0.5 to 5 cm, and blood flow rates between 1 and 20 mL/sec.

- Experimental Assessment of Flow Regimes

\textbf{CO}_2 \textbf{Injector}—A prototype gas delivery device has been developed to provide for controlled delivery of a nominal amount of gas at a prescribed pressure. Gas was pressurized in a reservoir and delivered through a mass flow meter. Flow rates varied linearly: 10 mL/sec at a pressurization of 100 mm Hg and 34 mL/sec at 500 mm Hg at atmospheric intraluminal pressure. Flow rates were calibrated with a 5-F endhole catheter to facilitate measurement of bubble volume (Cook, Bloomington, IN).

\textbf{Flow Model}—A pulsatile flow circuit was constructed from Tygon tubing (Fischer Scientific, Pittsburgh, PA) connected to a fluid reservoir on a vertically mobile platform. Flow was generated by a positive displacement peristaltic pump (model 7518-10; Cole Palmer Instruments, Chicago, IL). A roller in the pump moves along the surface of a section of the tubing and squeezes out a volume of liquid. The roller imparts a periodic pressure gradient to the liquid, moving it in pulses and determining the systolic/diastolic variation. The intraluminal mean pressure is regulated by adapting the height of a reservoir platform.

\textbf{CO}_2 \textbf{was injected in an antegrade fashion through a straight 5-F angiographic catheter (Cook) inserted through a sidearm of the circuit. Exchangeable vascular modules were used for testing medium and large vessel scenarios. A pressure sensor (Abbott Critical Care Systems, North Chicago, IL) and velocity sensor (T206; Transonic Systems, Ithaca, NY) were fed to the analog input card on a computer (Dell Computer, Round Rock, TX) using LabView software (National Instruments, Austin, TX) modified in the laboratory for experimental use. In experiments assessing the effect of pulsatility on flow regimes, an additional optical density sensor (University of Iowa Electronics Workshop, Iowa City, IA) was clipped onto the tubing and connected to the analog input card of the computer. The optical density sensor served as a bubble detector. In the presence of fluid in the tubing, light is transmitted and registered. In the presence of gas bubbles, light is refracted at the interfaces and the sensor receives less transmission.

The effect of varying injection parameters was assessed at pressures of the \textbf{CO}_2 reservoir from 50 to 500 mm Hg intraluminal mean pressures from 0 and 79 mm Hg, and liquid velocities from 1.7 to 11 mL/sec unless stated otherwise. To avoid initial surges of intravascular pressure and ensure consistent delivery of \textbf{CO}_2, lines and catheters were purged with \textbf{CO}_2 prior to every injection.

For representation of small and medium-sized vessels we chose a test segment of 6.4-mm inner diameter (ID) Tygon tubing. The configuration of the \textbf{CO}_2 bolus was recorded by (a) the optical density sensor ("bubble detector") applied over straight tubing and (b) digital angiography of the tubing cuffed in a spiral. Angiography was done with 50 kV, brasse-filtration, and small focal spot at 6 frames per second on a Polychoson (Philips, Shelton, CT) and recorded on a 1,024 x 1,024 matrix. Numbers and volumes of bubbles were determined on the seventh film frame (1.2 sec) after the first appearance of \textbf{CO}_2 at the catheter tip. In addition, a large vessel module was used. Straight 26 mm ID Tygon tubing was perfused with water at 6.4 mL/sec at 120 rpm and an intraluminal mean pressure of 70 mm Hg, and was injected with 50 mL of \textbf{CO}_2. Imaging was performed on a biplane Neurostar (Siemens Elema, Palatine, IL) at 4 frames per second per plane, 96 kV, aluminum filtration, and a small focal spot for anteroposterior projections, and a microfocal spot for lateral projections. Images were recorded on a 1,024 x 1,024 matrix.
RESULTS

- **Effect of Pulsatility on Flow Patterns of CO₂**

Mathematical analysis of the flow regime maps predicted the intermittent flow regime to assume a periodic pattern in that bubbles would assume an elongated shape and similar size and would be separated by relatively constant interspaces of fluid and occasional small bubbles. Experimentation confirmed the analytical prediction. Figure 3 shows the relationship among intravascular pressure, fluid velocity, and configuration of the CO₂ bolus. The “valleys” of the density profile (elongated bubbles) coincided with the valleys of the intravascular pressure (“diastole”). As the intravascular pressure peaked (“systole”) the density profile also peaked with occasional sharp oscillations indicating fluid with some small bubbles. Fluid velocity and intravascular pressure had the same period but a phase lag between pressure and velocity curves predicted analytically for pulsatile flow (4). Because of the periodicity encountered, intermittent flow was labeled “periodic” intermittent flow on the flow regime maps.

Annular flow exhibited periodic waves with a period equal to that of the roller pump (Fig 4b).

- **Theoretical Predictions of the Flow Regime Maps**

From the variety of flow regime maps that were calculated, three representative examples are shown in Figure 2. Figure 2a was obtained for a 5-mm diameter vessel. The PDH never crosses below the P transition. Hence stratified flow is not expected at any considered CO₂ flow rate. The transition from intermittent flow to annular flow in is in the range of 20 mL/sec. Ideal opacification of a 5-mm vessel should hence be achievable at flow rates greater than 20 mL CO₂/sec, which are readily achievable by manual injection. Increasing the flow rate further is not expected to yield additional benefit. Once the flow pattern is annular it cannot be further improved on for imaging purposes.

In a 2-cm artery, such as a small aorta, intermittent flow with large periodic bubbles is the best the angiographer can hope for based on the theoretical predictions (Fig 2b). Continuous floating bubbles (stratified flow pattern) need not be of concern, but CO₂ flow rates need to exceed 100 mL/sec to produce optimal large, elongated bubbles (intermittent flow pattern). At lower CO₂ flow rates, the flow pattern would still be intermittent but bubbles would be smaller and break up readily. Based on the flow regime map, the A transition (beyond which flow assumes the ideal annular form) is around 1,000 mL/sec. Such a flow rate is only hypothetical since there is no injector capable of this delivery, and even if available, its usage would be unreasonable because of the associated pressure surge.

When vessel size increases to aneurysmal dimensions (5-cm ID) (Fig 2c) filling of the entire vessel lumen cannot be expected at any reasonable CO₂ flow rate. The angiographer can only expect the stratified flow pattern (continuous floating bubbles). Hypothetically, annular flow is realized at flow rates higher than 7,000 mL/sec, a value beyond reach and reason. Consequently, large aortae cannot be filled in their anterior posterior extension and positional changes are required to image all vascular segments.

- **Experimental Validation of the Analytical Predictions**

To test whether increases in CO₂ flow rate are indeed associated with larger bubble sizes in an intermittent flow pattern and whether the predicted A transition into the annular flow pattern coincides with experimental observations, a circuit with 6.8-mm Tygon tubing was used. When intravascular pressure and CO₂ injection volume were held constant and CO₂ injection pressure was increased, the number of individual bubbles decreased. Accordingly, the average size of bubbles and the size of the largest individual bubble increased (Fig 5). At greater differentials between injection pressure and intraluminal pressure, annular flow was favored. Experimental A transitions typically occurred gradually around a 20 mL/sec CO₂ delivery rate confirming the theoretical predictions and validating the analytical method.

Annular flow tended to convert into intermittent flow in the most downstream coils of the spiral (Fig 4). Toward the end of the injections bubbles became smaller but remained distinct. This agrees with the theoretical predictions since the downstream flow rate of the CO₂ will adapt to the one of the flowing liquid in the tubing, that is, decrease thus favoring periodic intermittent flow. Dispersed bubble flow and stratified flow were not observed as predicted.

Validation of the flow regime maps obtained for large vessels was limited by the ability of the injector to generate flow rates high enough to reach the values needed for an A transition. In the realm of the injector (prepressurization of CO₂ to 500 mm Hg, maximal flow rate 34 mL/sec) no annular flow was observed. Flow was stratified at all available settings; that is, only floating bubbles were obtained.

DISCUSSION

Conventional vascular contrast media provide radiographic contrast as a bolus and after dissolution in fluids. CO₂ provides radiographic contrast only in gas phase, not after dissolution. Gas and fluids assume specific flow patterns. From an imaging point of view, annular flow in which most of the vascular lumen is filled with CO₂ is the most desirable regime. Periodic intermittent flow is useful, as long as individual bubbles are large.

Based on the theoretical predictions and experimental validation with an in vitro model the following conclusions emerged:

(i) In small and medium sized vessels (< 10 mm) ideal circumferential vascular opacification (annu-
lar flow) can be achieved relatively easily with injection rates above 20–30 mL/sec. Higher rates are not expected to produce superior results.

(iii) When imaging the aorta, the best an angiographer can expect is intermittent flow with large bubbles. Bubbles size and imaging potential increase with increasing CO₂ flow rate.

The findings of this study agree with empirical clinical practice described by Seeger et al and Kerns et al (5,6). These authors advocate CO₂ flow rates of 100–150 mL/sec for aortic injections, and 10–40 mL/sec for peripheral arteries in humans. These CO₂ flow rates are in the realm of our analytically derived values for the A transition. Experimentation in dogs yielded similar observations with regard to CO₂ flow rates and vessel size.
Krasny et al. assessed vascular filling with CO₂ during selective arteriography of aortic branch vessels in dogs (7). When vessels up to 10 mm in diameter were injected with CO₂, low gas volumes and flow rates were associated with formation of discontinuous bubbles (presumed intermittent flow). Increases in flow rate to 3.5–10 mL/sec and volumes to 4–10 mL lead to complete vascular filling with CO₂ (presumed annular flow). When imaging canine aorta with CO₂, flow rates of at least 20 mL/sec were required to prevent formation of discontinuous bubbles (8). The same authors were not able to fill the entire lumen of the canine aorta at any setting of their injection apparatus. At flow rates of 40 mL/sec retrograde flow of CO₂ up to 10 times the relative radius of the aorta was observed (7).

With the need of higher flow rates for achieving annular flow in larger vessels, optimization of CO₂ arteriography is hence limited by what an angiographer would consider as a "reasonable" flow rate of CO₂. To our knowledge there are no data available of what constitutes innocuous flow rates and intravascular pressure surges.

On the basis of theoretical predictions, there is not much gained in increasing the CO₂ flow rate beyond the A transition (provided the FRI is above the P transition; ie, flow is not stratified). This correlates with observations during in vivo CO₂ arteriography that no improvement of image quality resulted from further increases in CO₂ injection rates (9).

The aware angiographer can adapt to these physical limitations of CO₂ arteriography. Imaging the entire circumference of a large vessel may require imaging in two different patient positions exposing opposite wall segments to the floating CO₂ layer. On the other hand, injection parameters that produce limited distribution of CO₂ in the aortic lumen can be exploited: anteriorly located intestinal vessels can be imaged with little superposition of more dependent vessels.

Dispersed bubble flow was not observed experimentally. This is consistent with the analytical predictions. Dispersed bubble flow is to occur only under very rare flow conditions in a large diameter vessel with a large blood flow rate and a very low gas delivery rate.

The flow rate of CO₂ depends on the pressure to which CO₂ is precompressed in the injector and on the resistance of the connectors and catheters through which CO₂ travels. Since delivery pressure decreases toward the end of the injection, flow regimes may change during the same injection. For example, smaller bubbles follow larger bubbles at the end of the injection (Fig 4c).

In the pulsatile circuit the intermittent flow regime assumed a periodic intermittent pattern. The larger bubbles were similarly sized and spaced. This periodicity is inherent to a given "vascular" system and its intraluminal pressure fluctuations. Large bubbles were encountered during the "pressure valleys," for example, the diastoles of the cycles. At the systolic peaks, trains of fluid with tiny bubbles were seen. Transitions between the annular and the periodic intermittent flow regimes were gradual around the A transition during experimentation. Periodicity was also observed early after transition into the annular flow regime. It is important not to mistake the periodic indentations of the gas column asstenoses. Von Zwaan et al described the depiction of such presumed ste-
noses ("concentric indentations of the gas meniscus") during CO₂ arteriography of patent vessels in pigs (10); these authors also noted disappearance of these "stenoses" when CO₂ was injected distal to an occlusion balloon (elimination of pulsatility) or when the CO₂ flow rate was further increased. A periodic waviness correlating with the cycle rate of the system is also expected in stratified flow patterns (Fig 1).

Limitations of the model presented are its in vitro character and the absence of stenoses or features such a bifurcation. The correlation of experimental findings and analytical flow regime maps, however, is encouraging and validates the principal approach using flow regime maps as predictor of CO₂ distribution. Since flow regime maps can be constructed for different fluids and systems with various physical conditions, they seem a promising model for future applications.

We conclude that optimization of CO₂ arteriography is much more complex than that of arteriography with water-soluble contrast media. While ideal flow regimes can be obtained easily in small and medium sized vessels, ideal opacification of large vessels may be limited to what can be considered reasonable injection pressure. Cognizance of the CO₂ flow regime aids optimization of arteriography and can avoid diagnostic pitfalls.

APPENDIX

• Flow Regime Maps

Taitel and Dukler developed flow regime maps for steady gas liquid flow predicting the transition between stratified smooth, stratified wavy, intermittent, annular, and dispersed flow (1). Their analytical results compared well with experimental findings under conditions of horizontal and near horizontal steady flow (11) and served as a basis for subsequent development of flow regime maps for pulsatile cocurrent gas liquid flow in this laboratory (3).

Flow regime maps may be non-dimensionalized and use the Marti- nelli parameter X as the independent variable on the x-axis (L2). The Martinielli parameter is given by

\[
X = \left[ \frac{4C_1 \left( \frac{jD}{v_t} \right)^{n} \rho_f \left( jD \right)^2}{2} \right]^{\frac{1}{2}}
\]

where the subscripts 1 and g refer to the liquid or gas phases, respectively, the variables C, n and m are constants selected according to laminar or turbulent flow for the considered phase, D is the vessel diameter, j is the superficial velocity, v is the kinematic viscosity, and p is the density. Please note that effects of temperature are indirectly accounted for by their effects on viscosity and density.

Non-dimensional analysis is a fundamental approach to the analysis of flow problems. It is a method for reducing the number and complexity of experimental variables over a class of flows (12). The non-dimensional forms of the flow regime maps using the Martinielli parameter are broadly useful and are applicable to widely different flow conditions. For example, use of the non-dimensional forms allowed experiments to be conducted in circuits using water rather than a blood analog. However, the non-dimensional forms seemed complex for clinical understanding and we therefore present the flow regime maps in a more accessible form by restricting their construction to specific circulatory conditions. Hence, each flow regime map is constructed for a given set of flow conditions of a vascular flow circuit and for a range of injection parameters. Conversions into CO₂ flow rates were based on converting any measures containing spatial parameters into fractions or multiples of the vessel diameter. This model assumes a constant vessel diameter. Including different degrees of wall elasticity would further significantly complicate the already complex system of equations involved in the flow regime maps. Also, vascular compli-

cance depends on a variety of parameters and is not necessarily predictable in a clinical setting (13).

On the flow regime map, the PRI is the ratio between inertial to gravitational forces of the gas phase modified by a density ratio between gas and fluid phase and defines the predicted flow regime as a function of the CO₂ flow rate (for detailed formulas see reference 3). Stratified flow is predicted to occur only when the PRI (solid line in Fig 2) falls below the P transition (dashed line, Fig 2); when the PRI is above the P transition, flow is either intermittent or annular. The transition between intermittent and annular flow regimes occurs at the "A" transition (vertical dashed line, Fig 2); flow to the left of the line is predicted to be intermittent; to its right it is predicted to be annular.

As the liquid velocity in a tube increases, turbulence increases such that random fluctuations are expected to dominate, masking periodic flow components. The transition from intermittent to dispersed bubble flow is determined by a parameter T, a ratio of turbulent drag to gravity forces (Formulas see reference 3). The T parameter is a line parallel to the x axis. However, as a further simplification of the applied flow regime maps, the dispersed flow regime is omitted. Dispersed flow can be achieved with a combination of very low gas delivery rates and extremely high blood flow rates. In using larger gas flow rates for vascular imaging, the dispersed flow regime need not be a concern under typical human circulatory conditions.

By using the formulas for the various parameters and transitions (3) flow regime maps were constructed with a spreadsheet program using an implicit solver function (Microsoft Excel 4.0, Microsoft Corp, Bothell, WA).

References

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