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Carbon dioxide coronary angiography: A mechanical feasibility study with a cardiovascular simulator

Ivan Corazza,[1,a] Nevio Taglieri,[1] Edoardo Pirazzini,[1] Pier Luca Rossi,[2,3] Alessandro Lombi,[2] Filippo Scalise,[4] James G. Caridi,[5] and Romano Zannoli[1]
[1] *Experimental, Diagnostic and Specialty Medicine Department, University of Bologna, Via Massarenti, 9, 40138 Bologna, Italy*
[2] *Department of Physics and Astronomy, University of Bologna, Viale Berti Pichat 6/2, 40127 Bologna, Italy*
[3] *INFN Bologna, Viale Berti Pichat 6/2, 40127 Bologna, Italy*
[4] *Department of Interventional Cardiology, Monza Hospital, Via Amati 11, 20900 Monza, Italy*
[5] *Health Sciences Center, Tulane University, 1430 Tulane Avenue, New Orleans, LA 70112-2699, USA*

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The aim of this study was to carry out a bench evaluation of the biomechanical feasibility of carbon dioxide (CO_2) coronary arteriography. Many patients among the aging population of individuals requiring cardiac intervention have underlying renal insufficiency making them susceptible to contrast-induced nephropathy. To include those patients, it is imperative to find an alternative and safe technique to perform coronary imaging on cardiac ischemic patients. As CO_2 angiography has no renal toxicity, it may be a possible solution offering good imaging with negligible collateral effects. Theoretically, by carefully controlling the gas injection process, new automatic injectors may avoid gas reflux into the aorta and possible cerebral damage. A feasibility study is mandatory. A mechanical mock of the coronary circulation was developed and employed. CO_2 was injected into the coronary ostium with 2 catheters (2F and 6F) and optical images of bubbles flowing inside the vessels at different injection pressures were recorded. The gas behavior was then carefully studied for quantitative and qualitative analysis. Video recordings showed that CO_2 injection at a precise pressure in the interval between the arterial dicrotic notch and the minimum diastolic value does not result in gas reflow into the aorta. Gas reflow was easier to control with the smaller catheter, but the gas bubbles were smaller with different vascular filling. Our simulation demonstrates that carefully selected injection parameters allow CO_2 coronary imaging without any risk of gas reflux into the aorta.
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NOMENCLATURE

CO_2 = carbon dioxide
ECG = electrocardiogram
InP = injection pressure
AP = arterial pressure
Vi = injected gas volume
ΔP = gas pressure increase

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[a] Address for correspondence: Ivan Corazza, Medical Physics Activities Coordination Center Experimental, Diagnostic and Specialty Medicine Dept. (DIMES), University of Bologna, Via Massarenti, 9, 40138 Bologna, Italy, Phone: +390512143588, Mail: ivan.corazza@unibo.it

INTRODUCTION

Peripheral arterial and venous carbon dioxide (CO_2) angiography is becoming more widespread due to the improved quality of the images obtained with the latest radiological apparatuses. In addition, CO_2 lacks nephrotoxicity, a growing medical problem related to the wide use of iodinated contrast media.[1–8] The caveat is that CO_2 angiography is not performed in the thoracic arterial or coronary structures to avoid the risk of gas bubbles in the cerebral circulation, possibly leading to ischemic damage.[5,9–11]

Coronary arteriography is the most frequent angiographic procedure performed for diagnosis and/or intervention, and iodine contrast intolerance or reduced renal function is a common problem, increasing patient management complexity and related costs.[4,12,13] If the radiological procedure could be executed in these patients using CO_2 instead of iodine for angiographic imaging, it would not only benefit patients but also reduce the overall cost of the procedure.

Precluding this possibility is the risk of introducing CO_2 gas bubbles into the cerebral circulation. Coronary imaging can be studied applying algorithms to enhance the radiological information in the peripheral circulation, namely radiological image subtraction and subsequent frame superimposition (stacking)[14–16] to a moving vascular tree. This technological problem may be solved by using cardiac synchronism (ECG) to control the X-ray emission and frames acquisition, and developing procedure-specific software for image subtraction, frame selection and stacking. Nevertheless, it seems useless to improve and test the technological aspects if the clinical risk of thoracic aortic refluxed gas is not solved.

In this paper we define and test a potential solution allowing CO_2 angiography of the coronary arteries without gas contamination of the cerebral vessels. The core points of the proposal are the knowledge of the physiological behavior of coronary blood perfusion, and the possibility to inject CO_2 at a very precise pressure using the new Angiodroid (Angiodroid Srl, Bologna, Italy) gas injector.[5,17]

The idea is to insert the contrast injection catheter into the coronary artery input ostium as usual, but setting an unusually low gas injection pressure (*InP*). Coronary artery blood flow is mainly diastolic due to the arteriolar constriction during ventricular contraction, and the pressure signal is the same as the aorta, with a roughly triangular shape. Let us now describe what happens when the gas *InP* of a catheter positioned in the coronary artery is progressively increased. Since our objective is a feasibility study, we simulated the aortic pressure pulse of a normal adult (130/75mmHg with a dicrotic value of 120mmHg).[18] Up to the arterial minimum pressure (75mmHg) there is no gas injection as the pressure in the artery is always higher than the gas pressure in the catheter. When the pressure of the gas controlled by the injector overcomes the minimum pressure in the artery, small bubbles of gas are emitted by the catheter, enter the coronary flowing blood and are rapidly transported towards the periphery. In this condition, if the catheter is correctly inserted in the coronary ostium, it is practically impossible for a bubble to move retrogradely into the aorta as the coronary blood flow is quite high with respect to the gas inflow. This behavior is maintained up to an *InP* corresponding to the arterial notch, where the diastolic coronary blood flow stops and bubble dragging is no longer guaranteed. On the basis of this simple description we have a range of possible gas *InP* settings from the minimum arterial value (i.e. 75mmHg) to the arterial notch value (about 120mmH). By increasing the *InP* in this range, we can change the gas-blood filling ratio of the arterial tree: the higher the pressure, the greater the gas filling. The result obviously depends also on the hydraulic resistance of the catheter and connection line. If the gas injection flow overcomes the blood flow in the vessel, a retrograde reflux is detected. This aspect must also be taken into account to fix the pressure setting.[19,20]

METHODS

To test the proposal we built a mechanical model of the coronary circulation using transparent glass pipes with an internal diameter of 2.5mm for observation of the injected gas behavior, and a mechanical pumping apparatus to produce a physiologically shaped arterial pressure (AP) and flow (Fig. 1).

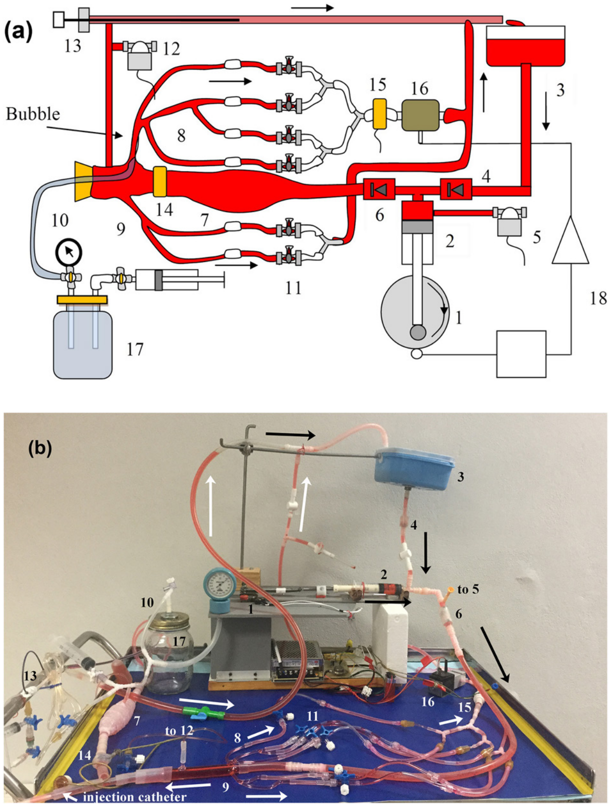

FIG. 1. (a) Scheme and (b) picture of the cardiovascular mock - (1) Motor, (2) Pumping syringe; (3) Atrium; (4) Mitral valve; (5) Ventricular pressure transducer; (6) Aortic valve; (7) Aorta; (8) Left coronary branch; (9) Right coronary branch; (10) Catheter; (11) Stopcocks; (12) Aortic pressure transducer; (13) Aortic hydraulic resistance regulator; (14) and (15) Electromagnetic flowmeter probes; (16) Electric valve; (17) Rigid chamber filled with CO_2; (18) Feedback circuit to drive the electric valve.

For most aspects the model is similar to others previously described,[21–23] but a particular device (Fig. 2) has been developed specifically for this research. This device simulates the systolic constriction of myocardial coronary vessels and produces a fully diastolic coronary flow, as happens in a physiological setting for the left coronary artery. The result is obtained by delivering an electric hydraulic valve in series with the coronary artery. The valve is actuated by a trigger pulse generated when syringe pumping starts. The closure time corresponds to the mid pumping cycle. This systolic closure and diastolic opening repeats with each beat resulting in a periodic fully diastolic flow.

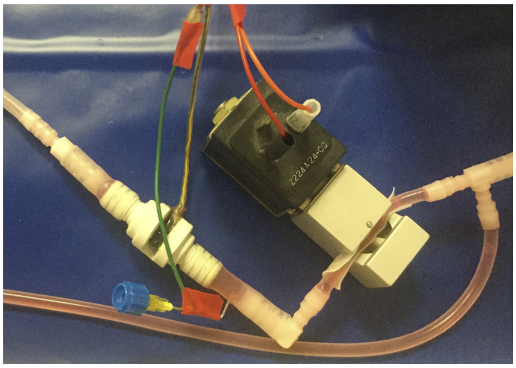

FIG. 2. Electric hydraulic valve synchronized to the ECG to stop left coronary flow during systole and open during diastole.

Physiologically, this behavior is limited to the left heart and mainly to the left coronary circulation. Right coronary flow is not very diastolic, but also has a reduced systolic value. For this reason we did not use the device for the simulated right coronary artery.

We decided to use 2F and a 6F catheters in order to cover the range of catheter sizes used in the clinical setting for CO_2 injections.[14] The pumping frequency was fixed at 72bpm, the stroke volume at 10ml, and the aortic pressure at 130/75mmHg (settable by hydraulic resistance regulation, Fig. 1, part 13). Aortic and coronary blood flows were monitored by the electromagnetic Biotronex BL610 system with 7mm and 3mm probes. To inject CO_2 gas a Cordis® ARIMOD100cm, 6F catheter and a Jomed® 100cm 2F catheter were used (1F=1/3mm). Room temperature was 20°C and medical grade 99.8% CO_2 gas was used.

Ventricular, aortic and gas *InPs* were monitored by three Statham P23 transducers and conditioned with an Esaote EP12 polygraph. Analog signals were sampled, digitally converted and stored by the Anscovery System (Sparkbio Srl, Bologna, Italy).[24]

The optical images of the gas filling the coronary arterial tree during mock operation with the two catheters and different *InPs* were sampled by an EX-SH20 high frame rate video recording camera (Casio Computers Co., Tokyo, Japan). The camera was positioned above and a light screen was positioned under the transparent mock filled with colored saline. A frame-by-frame image subtraction algorithm similar to that used for radiological images was implemented to enhance gas bubble

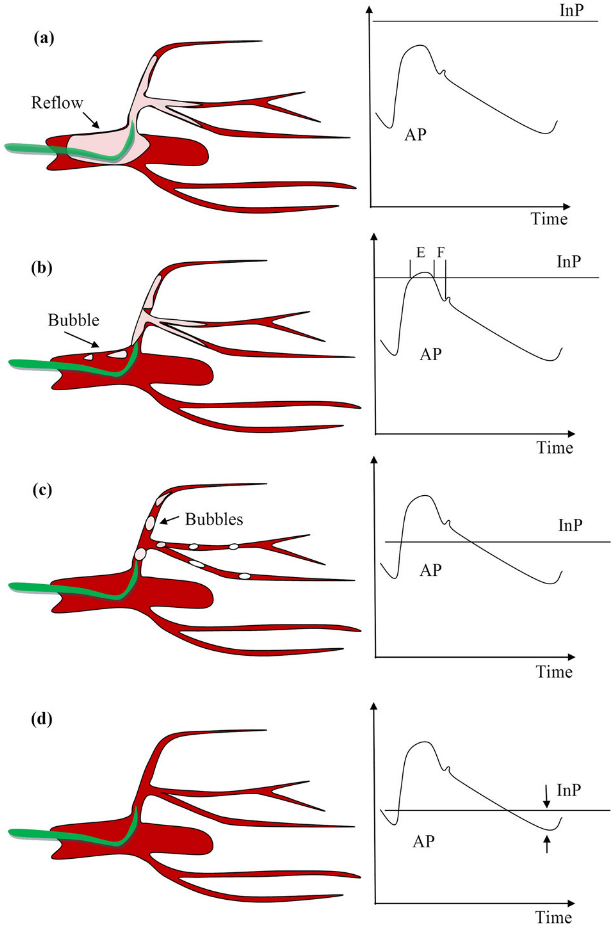

FIG. 3. Gas behavior at different injection pressure (*InP*). (a) The *InP* is higher than maximum arterial pressure (AP): input gas flow overcomes artery blood flow and gas reflow arises. (b) *InP* is slightly lower than systolic AP: small gas bubbles may reflow due to the systolic coronary perfusion stop. (c) *InP* is lower than arterial dicrotic pressure: gas bubbles injected by the catheter move forward, dragged by the coronary diastolic blood flow. (d) *InP* is still higher than minimum AP, but gas injection stops, due to the flow and reflow of blood in the catheter lumen.

visualization. A final stacking algorithm was then applied to visualize the coronary tree. Before these last two steps, the acquired color images were coded as grayscale to simulate angiographic images.

To simplify the procedure and to have a continuous recording, the gas *InP* was progressively decreased from a pressure value above the arterial maximum up to the limit value to observe injected gas bubbles (Fig. 3). Coronary flow was recorded immediately before gas injection (to avoid the noise due to the running bubbles). For each 5mmHg step decrease a ten second video record was stored together with pressure and flow signals. The whole procedure was repeated for the two catheters positioned in the left and right coronary artery ostia.

Since the mechanical mock always works in stable conditions, the hemodynamic parameters (pressures and flows) are repeatable. Nevertheless, repeating the test with different CO_2 InPs, bubble size, number and shape change, with different interventions of the stacking process.

The apparatus described in Fig. 4 was used to measure the hydraulic resistance of the catheters and the whole injection line. A rigid wall container (Fig. 4a, volume 1000ml) was steeply filled up to 200mmHg (for the 2F catheter) and 100mmHg (for the 6F catheter) pressure with CO_2 gas, using a 50mL syringe. The bottom of the container was partially filled with water to have a simple correspondence between injected gas volume (Vi) (at ambient temperature and pressure) and pressure increase (Vi = 50ml, ΔP = 50mmHg). Then the container was opened towards the connection line and the internal pressure had a roughly exponential decrease with time. The instantaneous remove slope of the curve indicates the instantaneous gas flow (ml/s), which can be related to the instantaneous remove driving pressure. The pressure/flow ratio along the curve indicates the instantaneous hydraulic resistance of the connection line (Fig. 4b).

The feasibility of the proposal was evaluated by monitoring the mechanical behavior of the bubbles in the simulated coronary tree at progressively decreasing *InP*. Monitoring focused first on aortic gas reflow, then on coronary bubble size and vascular filling. The results were both qualitative

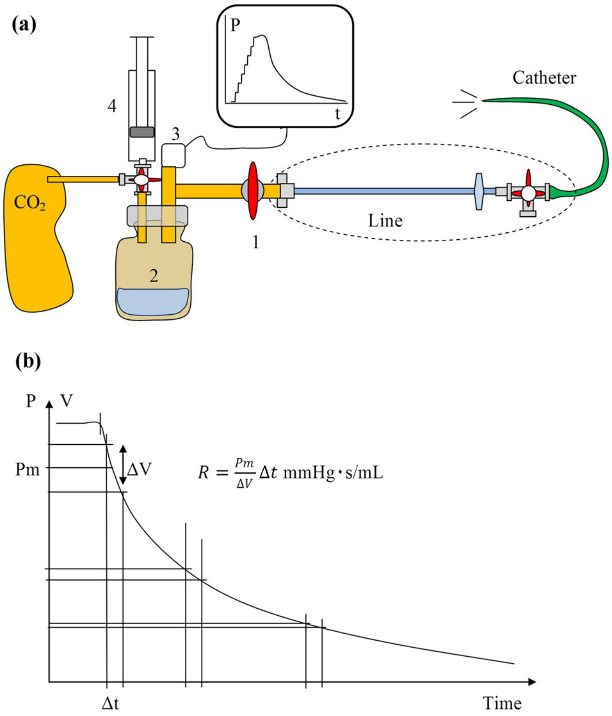

FIG. 4. (a) Apparatus to measure hydraulic resistance: (1): Stopcock; (2): Rigid chamber; (3): Pressure transducer; (4): Syringe; (b) Example of pressure and volume decays against time. Since the ratio pressure/flow along the curve indicates the instantaneous hydraulic resistance of the connection line, by measuring the mean pressure (Pm) and the mean flow (Fm= DV/DT) at a certain time, the resistance can be easily calculated (R=Pm/Fm=Pm/DV*Dt).

TABLE I. Qualitative and quantitative results. Legend: “+++” (maximum value/dimension) to “---” (absence).

Catheter	Injection Pressure (InP) vs Arterial Pressure (AP)	Reflow	Bubble dimensions	Number of bubbles	Vascular filling
2F	InP> Systolic Pressure	+++	++-	++-	+++
	Systolic <InP<Dicrotic Pressure	+--	+--	+++	+++
	Dicrotic pressure <InP< Diastolic Pressure	---	+--	++-	++-
	InP near Diastolic Pressure	---	+--	+--	+--
6F	InP> Systolic Pressure	+++	+++	+++	+++
	Systolic <InP<Dicrotic Pressure	+--	+++	+++	+++
	Dicrotic pressure <InP< Diastolic Pressure	---	++-	++-	+++
	InP near Diastolic Pressure	---	---	---	---

and quantitative as shown in Table I. Due to the specific purpose of the research, no statistical analysis was necessary.

RESULTS AND DISCUSSION

Fig. 5 shows a specimen of complete recording of the analog sampled signals. Fig. 6 shows an example of a plot obtained by the apparatus to measure the hydraulic resistance of the catheters. The resultant resistances were 5mmHg/ml/s for the 6F catheter and 80mmHg/ml/s for the 2F catheter. An example of frames in each simulated condition (Fig. 3) for both catheters of the left coronary is shown in Figs. 7 and 8. Fig. 9 shows an example of subtracted frame and the final stacked image.

The discussion is divided into two parts. Part one focuses on the clinical, biomechanical and procedural aspects, while part two analyzes and discusses the results.

Concern over CO_2 delivered to the cerebral circulation is related to case reports describing transient neurologic alterations of patients’ stability.[10,25–28] There is no proof of a permanent real risk for the patient and in most cases the normal situation is rapidly restored. CO_2 does not produce vascular embolism, as demonstrated in peripheral injections. The potential origin of the cerebral effects, highlighted by the symptoms described, is most likely the trapping of gas in the upper domes of the tortuous cerebral arteries. This is due to gas buoyancy and can produce a biomechanical obstacle to the circulation. This event is less likely in the small vessels, where the bubble completely fills the vascular volume, but it could occur in larger vessels where the gas stops in the upper position of the dome producing a mechanical obstruction for the incoming blood. What is not well known

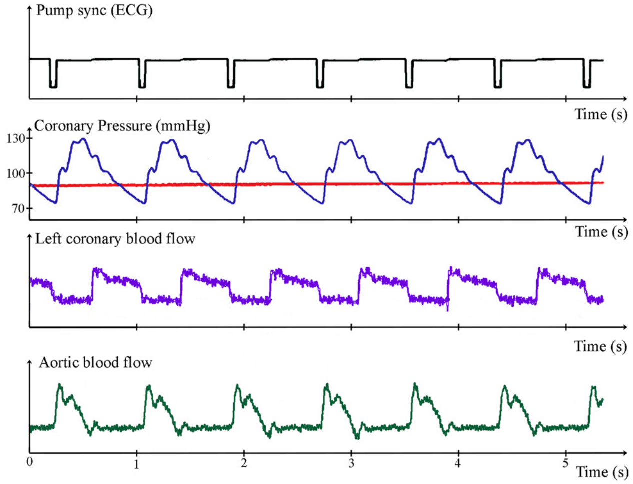

FIG. 5. Example of analog signals acquired with the Anscovery System.

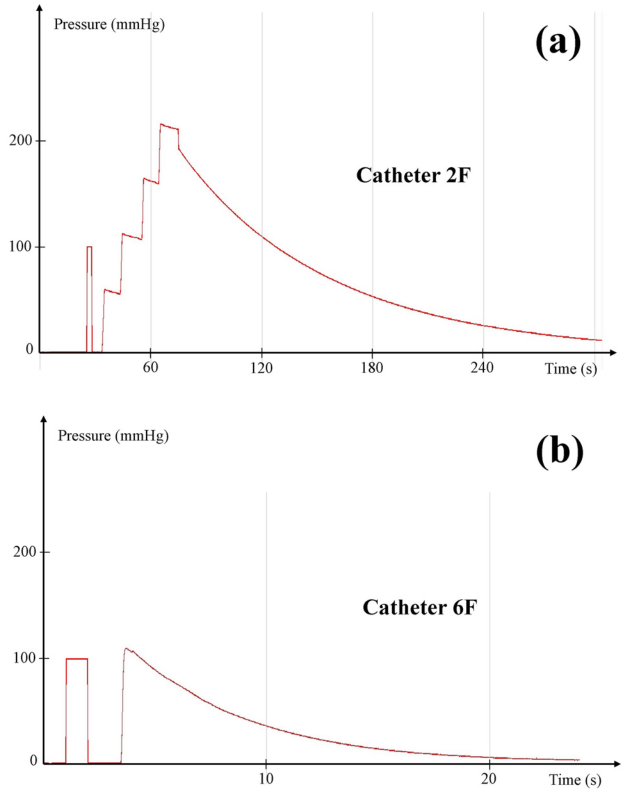

FIG. 6. Pressure decay while measuring the hydraulic resistance of the (a) 2F catheter and (b) 6F catheter.

and not published, is how to overcome this situation. If no intervention is applied, the CO_2 bubble progressively disappears by diffusing and dissolving the gas in the flushing blood. This takes some time (minutes) and the patient may have symptoms of reduced local cerebral perfusion. However, gas removal from the trapped position will probably be expedited by rotating the patient's head in all the possible directions. In some cases, X-ray will depict the trapped gas allowing direct observation of the effect of the different maneuvers. The object of this operative intervention is not to underestimate

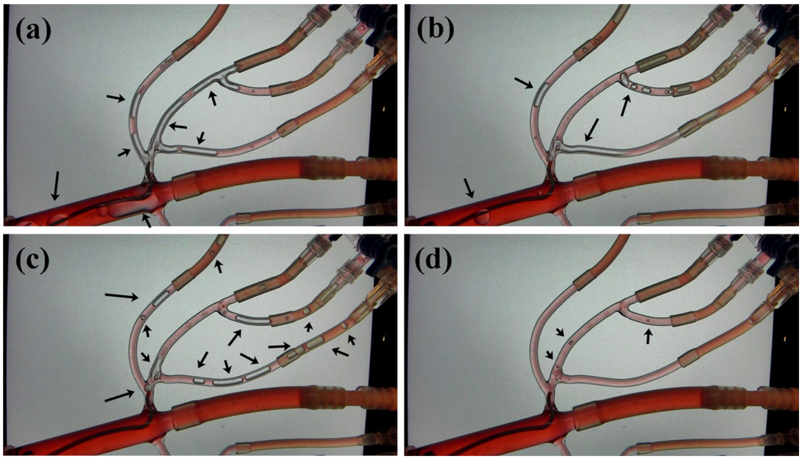

FIG. 7. Examples of acquired frames of the left coronary artery at the four different InPs with the 6F catheter: (a) Higher than the systolic value (145mmHg); (b) Between systolic and dicrotic notch (120mmHg); (c) Between dicrotic and diastolic pressures (90mmHg); (d) Slightly higher than the diastolic value (65mmHg).

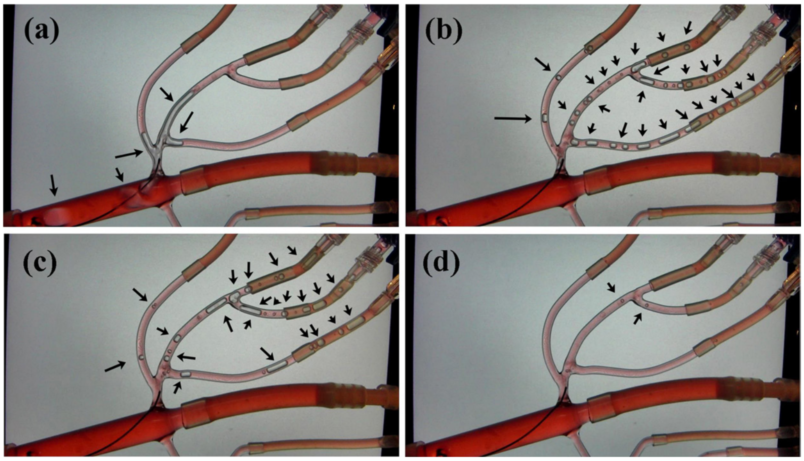

FIG. 8. Examples of acquired frames of the left coronary artery at the four different InPs with the 2F catheter: (a) Higher than the systolic value (145mmHg); (b) Between systolic and dicrotic notch (120mmHg); (c) Between dicrotic and diastolic pressures (90mmHg); (d) Slightly higher than the diastolic value (65mmHg).

the problem of cerebral CO_2, but to put it in the right context and to indicate how appropriate interventions may solve the problem were it to occur.

A second clinical aspect, more strictly related to the proposal, is the effect of the CO_2 gas injected in the coronary artery on mechanical and electrical ventricular function. Only one paper has been published on this topic, using swine and recording a depression of systolic and diastolic ventricular function together with electrocardiogram S-T elevation.[11] This will be a major limitation to CO_2 application in patients and must be carefully evaluated with a specific protocol. Our current focus is on the mechanical aspects of the procedure.

The proposed CO_2 coronary angiographic procedure is based on the appropriate setting of the gas pressure and flow, with gas injection only during the cardiac diastolic phase, with the gas dragged by the coronary flow and no gas reflux into the aorta. This raises two questions.

The first is the rate of gas injection with the limited injector-artery pressure difference. We know that CO_2 flows easily even in very thin tubes, but here the pressure difference is quite limited and it must be verified if the resultant gas flow with standard catheters and connection lines is adequate to the need (for this we have to measure the hydraulic resistance of the line-catheter connection). The gas injection flow has to be lower than the blood flow in the target vessel, to avoid gas reflux backwards. However it also must be sufficiently high to adequately fill the entirety of the coronary vascular tree with standard catheters and connection lines. Because the coronary pressure is pulsatile and the injection pressure is stable, the gas injection flow is not constant. This determines a wide variation of injection flow time course, with possible reflux in some instances and insufficient injection in others. If the hydraulic resistance of the line is low, small pressure changes produce major gas flow changes, with reflux risk. A higher hydraulic resistance line can be used to compensate this unfavorable situation and ensure a gas injection flow towards the lower pressure instantaneous coronary blood flow.

The second problem is the reflow of the blood inside the catheter lumen when the AP overcomes the settled catheter gas pressure. In normal angiographic procedures this is not a major problem because the catheter and the connection line are filled by saline solution and the vascular pressure changes produce a very limited, unappreciable liquid compression with no blood reflux into the catheter lumen. Besides, after a gas injection into an artery, the catheter and the injection line remain filled with gas at a pressure near the minimum value in the artery. As soon the AP starts to rise towards the new maximum value, the gas in the line is compressed and blood refluxes into the catheter with possible lumen obstruction and closure. The interventions to limit the effects of intracatheter reflux may interfere with the other procedural aspects. If we reduce the hydraulic resistance of the line to facilitate gas injection, we increase the tube diameters, thereby increasing the line volume and corresponding volume change and blood reflux during the pressure pulse. If we use thin catheters

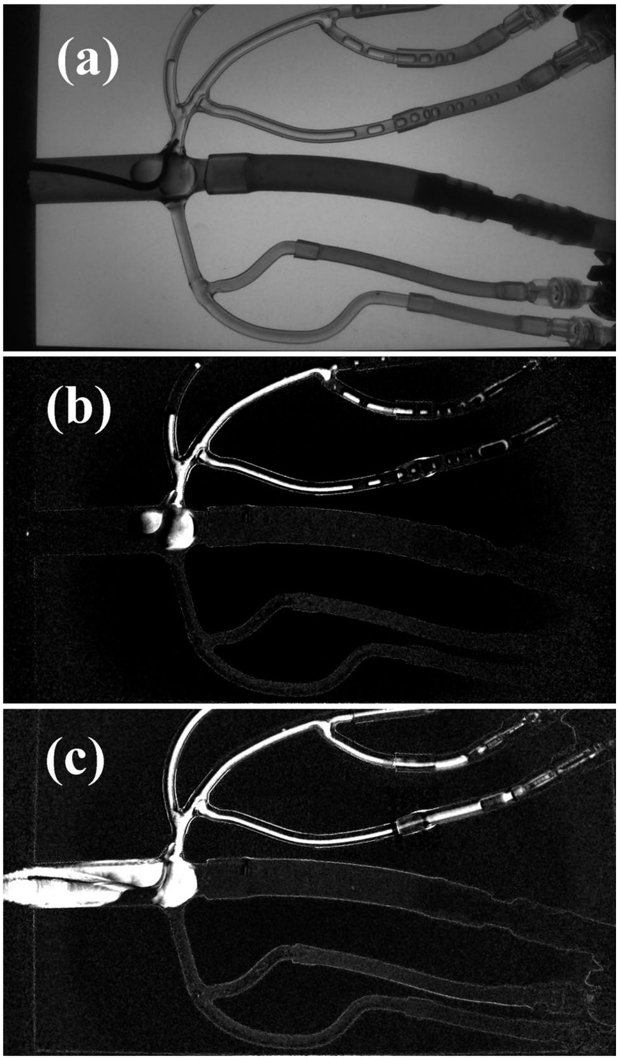

FIG. 9. (a) Example of a frame acquired during injection at a pressure higher than the systolic value; (b) Subtracted image; (c) Final stacked image. Gas can be seen flowing into the left coronary artery with reflow into the aorta.

and lines, we reduce the volumes and the reflux, but a thin catheter is more exposed to occlusion than a larger one. We calculated the volume change for a 2m line length and 1mm internal diameter. For a pressure increase of 50mmHg, roughly corresponding to the arterial pulse pressure, we obtained a possible blood reflow upstream of 10cm inside the catheter lumen with each pulse! This will not be the real value, due to the viscous behavior of blood, nevertheless the line volume must be low. This suggests the use of a line with a non-return valve and a catheter with a self-closing orifice.

Obviously, due to its high complexity, CO_2 coronary arteriography would be justified only in patients with a serious intolerance to iodine or critically low renal function. Clinically speaking, however, the proposal may also have an unexpected positive impact. By setting the injection pressure in the range between minimum and arterial notch pressure values, the operator can change the ratio between intervals of gas introduction and intervals of blood perfusion. The operator can also lower the gas pressure with respect to the aortic notch and shorten the interval of gas injection with respect to the interval of blood perfusion. This may radically change the coronary angiographic procedure. In fact the reduced gas injection and blood perfusion may be maintained for some beats making the radiological process of imaging frame selection and enhancement completely different from iodine coronary angiography. During injection, traditional contrast practically stops the incoming blood. The radiological imaging management of this aspect is quite complex, both for the necessary technological improvements and radioprotection aspects. This will be the topic of a dedicated paper.

Analysis of the recordings (synchronous pressures, flows and images) highlights different behaviors for left and right coronary injections with low or high resistance catheters. We measured the hydraulic resistance of the catheters and the instantaneous coronary flows. For each known injection and AP value, we measured the ratio between blood flow and injection gas flow.

With the lower resistance catheter (6F, 4mmHg/ml) at an InP higher than the maximum arterial value, we observed a clear gas reflux into the aorta (Fig. 7a). This happens because coronary perfusion is stopped in the systolic phase, and the injected gas must reflow into the aorta. By progressively decreasing the *InP*, we observed that the thoracic aortic gas reflux progressively decreases and stops when the gas injection crosses the AP notch value indicating the onset of coronary blood flow.

For *InPs* between maximum arterial and notch value (Fig. 7b), there is no evident reflux but any small bubbles from the coronary ostium move to the aorta. This is probably due to the in-lumen blood reflow during the intra-systolic interval E and subsequent blood and gas output during the interval F. By continuing to decrease the *InP*, we observed a complete absence of aortic gas (Fig. 7c), with bubbles progressively decreasing in number and size and moving in the peripheral direction, steeply for the left coronary artery and more continuously for the right coronary artery. Continuing to decrease the *InP*, the bubbles become very small (fig. 7d) and completely disappear at an *InP* about 10mmHg higher than the minimum AP.

With the higher resistance catheter (2F, 80mmHg/mL/s) we observed the same general behavior but with some differences. Initially we still observed an aortic gas reflow but with a clearly reduced volume with respect to the previous condition (Fig. 8a). By decreasing the InP, the aortic gas reflux rapidly disappears with no gas bubbles in the aorta even at pressures higher than the notch value (Fig. 8b). This is probably due to the very high hydraulic resistance of the catheter and to the pressure drop when the gas moves inside. In comparison with the previous condition, the bubbles become progressively smaller during the InP decrease (Figs. 8c and 8d). The gas injection stops at a higher pressure difference with respect to the arterial minimum value (15 mmHg). For the right coronary artery, which also has a systolic blood flow, the problem is simpler to solve because the injected bubbles are dragged by the blood flow also during systole. Taking into account the driving pressure and catheter resistance, it is important to avoid a gas inflow higher than the instantaneous coronary blood flow. As left coronary artery flow stops during ventricular systole, if the *InP* is higher than the notch pressure, a small volume of gas is injected in late systole and cannot flow into the coronary so that a small gas reflux is possible. In the right coronary artery the blood flow exists also during systole and this possibility of aortic reflux is reduced.

On the basis of these observations, we can conclude that to avoid aortic gas reflux, it is sufficient to use an *InP* lower than the dicrotic arterial value, a catheter resistance corresponding to the maximum driving pressure, and gas injection flow lower than the estimated maximum instantaneous coronary blood flow. This avoids aortic gas reflux, but is the coronary gas filling obtained in these conditions (quite small bubbles) adequate to visualize the whole coronary network using a normal apparatus and X-ray emission? This question raises a new question focused on the radiological aspects of the procedure.

CONCLUSIONS

Our biomechanical simulations demonstrate that CO_2 injection into a coronary artery for radiological imaging with no aortic gas reflow is technically feasible. For this a stable gas InP lower than the dicrotic arterial value is required and a catheter with a sufficiently high resistance to ensure a gas input flow lower than the instantaneous coronary blood flow throughout the diastolic phase. Manual injection has poor pressure control and the above settings are applicable only after we integrate a constant pressure gas injector platform with accurate control.

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