Optimal flushing agents for integrated optical and acoustic imaging systems

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Abstract. An increasing number of integrated optical and acoustic intravascular imaging systems have been developed and hold great promise for accurately diagnosing vulnerable plaques and guiding atherosclerosis treatment. However, in any intravascular environment, the vascular lumen is filled with blood, a high-scattering source for optical and high-frequency ultrasound signals. Blood must be flushed away to provide clearer images. To our knowledge, no research has been performed to find the ideal flushing agent for combined optical and acoustic imaging techniques. We selected three solutions as potential flushing agents for their image-enhancing effects: mannitol, dextran, and iohexol. Testing of these flushing agents was performed in a closed-loop circulation model and *in vivo* on rabbits. We found that a high concentration of dextran was the most useful for simultaneous intravascular ultrasound and optical coherence tomography imaging. [DOI: 10.1117/1.JBO.20.5.056005]

Keywords: imaging system; optical coherence tomography; attenuation; ultrasound.

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1 Introduction

Integrated intravascular ultrasound and optical coherence tomography (IVUS-OCT) has the potential to provide better visualization of coronary lesions[1–4] and to improve the accuracy of atherosclerotic plaque characterization.[5] Great progress has been made in developing a fully integrated IVUS-OCT system and catheter. However, to our knowledge, no research has been performed to find optimal flushing agents that provide both the necessary clarity for OCT and IVUS.

Blood is a high-scattering source for OCT signals and high definition IVUS (HDIVUS). Either blood occlusion or continuous flushing is needed for intravascular OCT imaging. Although no flushing agents are needed in 40-MHz IVUS imaging, some OCT flushing agents may hinder the transmission of IVUS signals, such as perfluorocarbon,[6] when simultaneously using IVUS and OCT functions. Thus, it is critical to identify flushing agents that are effective for IVUS-OCT imaging. This research will also benefit acousto-optics (AO), photoacoustic (PA) imaging and spectroscopy, acoustic radiation force optical coherence elastography, and other imaging techniques that simultaneously use light and ultrasound (US).

X-ray contrast agents, such as iohexol and iodixanol, are commonly used for intravascular imaging to clear blood for OCT.[7] However, the use of contrast agents in some patients may lead to renal function disorder[8] or life-threatening reactions, such as cardiotoxic effects and seizures.[9] It was reported that one dominant reason that physicians avoid using intravascular OCT is the injection of extra contract agents.[10] Although combined light and sound-based techniques are very promising for improving health outcomes, the wide clinical utility of these techniques will not be achieved until the challenge of safe and effective flushing is addressed.

Dextran[11,12] and oxygen-carrying blood substitute perfluorodecalin (PFD; a type of perfluorocarbon)[13] have been previously studied as alternative flushing agents for OCT imaging. These have minimal toxicity compared to contrast agents.[12,13] Dextran reduces scattering of red blood cells by matching refractive indices between blood plasma and blood cells.[14] PFD, which has high viscosity, can displace blood and clear OCT images. However, PFD can cause significant reduction of the US signal.[6] In addition, PFD has not been approved by the Food and Drug Administration (FDA) and cannot be used in patients.[15] Accordingly, PFD was excluded from our quantitative experiments. We also considered using mannitol solution as a flushing agent, based on mechanisms of optical flushing. Mannitol injection is approved by the FDA and is typically used to promote diuresis and reduce intracranial/intraocular pressure. Last but not least, iohexol is a commonly used contrast agent for OCT flushing. Its toxicity is lower than iodized contrast agents.[16]

To pave the road for new imaging techniques with both acoustic and optical functions, we studied the principle of flushing and experimentally evaluated the attenuation characteristics of flushing agents using an integrated IVUS-OCT system. We selected three solutions as representative flushing agents for testing because of their image-enhancing effects and relatively low toxicities: mannitol, dextran, and iohexol.

While previous testing on flushing agents has been performed in static baths,[14,17,18] we chose to mimic complex,

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dynamic *in vivo* human coronary arteries using an *in vitro* circulatory system model, and live rabbits.

2 Methods and Materials

2.1 *In Vitro Circulatory System Model*

To avoid unknown variables as in animal experiments, a well-controlled phantom test was first performed for comprehensive quantitative analyses of different flushing agents. An *in vitro* circulation model was built (as shown in Fig. 1) according to the dimensions of a human arterial system, to best mimic the circulation system *in vivo*. This model was a closed-loop system, simulating the heart-artery-vein-heart closed-loop circulation, and made from Masterflex L/S® tubes, tube adapters, three-way luer valves, a glass jar, and a peristaltic pump. Similar to the middle of the human left anterior descending coronary artery, where intravascular imaging is usually performed, the tubing had an inner diameter of 2.4 mm. The total length of all tubes with blood flow was 3 m, which simulated the blood circulation through the entire arterial and venous system. Since the distance between the imaging region and the guiding catheter influences the efficiency of flushing,[19] this distance was also controlled to be similar to the *in vivo* distance. The peristaltic pump's parameters were then set to mimic the pressure profile of human circulation. The fluid reservoir was physically located 1 m above the imaging region which raised the minimal blood pressure to 78 mm Hg, approximately the diastolic pressure of a healthy human. The peak pressure during pumping was approximately 40 mm Hg higher than minimum, mimicking a systolic pressure of 120 mm Hg. The pump was then set to ~60-80 times/ min, mimicking the normal heart rate.

Three flushing agents, dextran [40,000 molecular weight (MW)], 20% mannitol in normal saline, and iohexol (350 mgI/ml, NOVAPLUS), were examined in our quantitative experiments. Because the concentration of dextran solution was reported to affect the enhancement of OCT image quality,[14] we tested the effect of dextran with different concentrations at 1%, 3%, and 5%. Although dextran with high MW, such as MW 500,000 or 70,000, may provide better blood optical clearing,[20] high MW dextran takes a longer time to be extract from human body.[21] Thus, we used dextran MW 40,000 in our experiments.

The maximal injection speed of a flushing agent commonly used in patients is 4 ml/s at the coronary artery proximal.[12,22] To keep the volumetric delivery of flushing agent comparable to the *in vivo* setting, we chose 1 ml/s as the maximal testing speed, because the inner diameter of our tube is one-half of the inner diameter of the coronary artery proximal end, where flushing is usually performed. All three flushing agents were tested at flushing speeds 0.1, 0.5, and 1 ml/s.

During the experiment, 500 ml EDTA-added (anti-coagulated) porcine whole blood was circulated inside the circulation model. Imaging was performed using our previously published IVUS-OCT system[23] with a 1310-nm OCT system and 40-MHz IVUS transducer. We obtained 1000 A-lines in each frame.

An ideal flushing agent should provide minimal attenuation with the lowest possible delivery; therefore, we measured the attenuation during imaging for each agent at each speed setting. In each A-line, the attenuation coefficients (ACs) of each flushing agent at each speed setting were calculated in the equations provided next using MATLAB:

$$R(z) = I_0 T(z) e^{-2\alpha z}$$

$$R(z) = I_0 T(z) e^{-\mu z},$$

where R is the intensity of the signal obtained in US or OCT system, I_0 is the intensity of the outgoing sound signal or the incident light intensity. T is the reflectivity of the sample as a function of scanning depth, α is the ultrasound AC, and μ is the optical AC.[24]

To minimize the effects of tube heterogeneity and speckles in images, 10×10 pixel windows were averaged. The means and standard deviations of the AC for all 1000 A-lines were then calculated. The AC of an adjacent three-image unit was then averaged to obtain the final AC value of the corresponding flushing agent at its corresponding speed. Summaries of these final values for each setting are shown in Figs. 2 and 3.

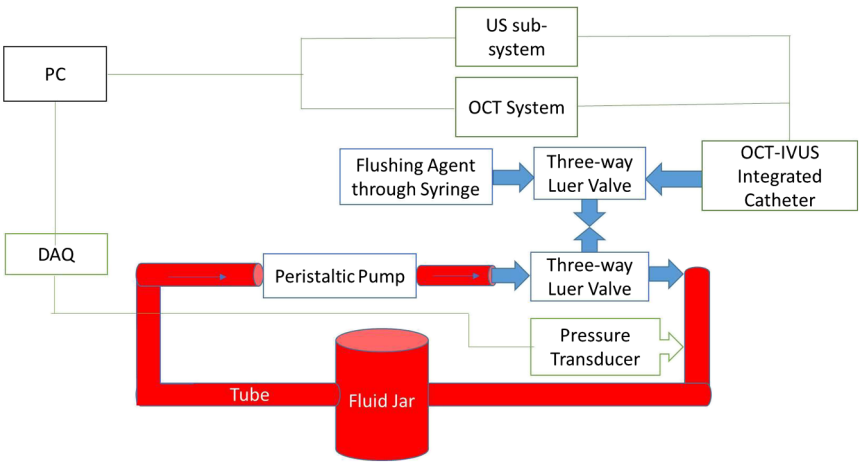

Fig. 1 Schematic of the *in vitro* circulatory system model with signal acquisition devices. The personal computer (PC) acquired the optical coherence tomography (OCT) signal, intravascular ultrasound (IVUS) signal, and fluid pressure signal. Three-way luer valves were used to provide access to the closed-loop tube system and allow the imaging probe and chemicals to enter. Red areas denote where blood circulates.

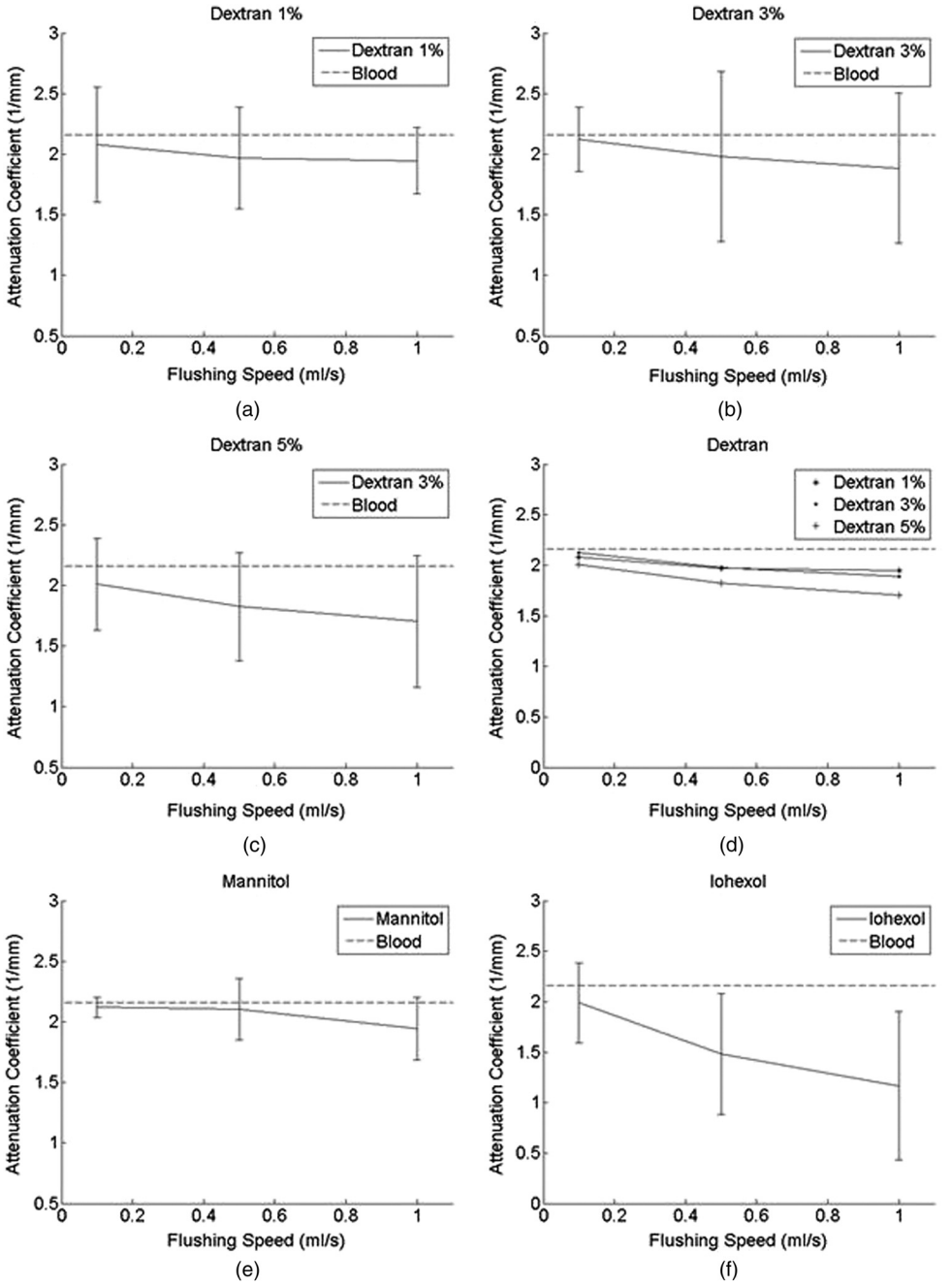

Fig. 2 OCT attenuation coefficients (ACs) using different flushing agents (a) dextran 1% (b) dextran 3% (c) dextran 5% (d) dextran 1%, 3%, and 5% (e) mannitol (f) iohexol. Dashed lines represent the AC of blood at 2.16 mm^{-1}.[14] The error bars represent the standard deviation of ACs encountered when rotating the imaging probe along the tube wall.

2.2 *In Vivo Studies*

To demonstrate the clinical applicability of these flushing agents, simultaneous optical and acoustic imaging of rabbit abdominal aortas was performed *in vivo*. The experimental protocol was approved by the University of California, Irvine, Institutional Animal Care and Use Committee. All animals were treated in accordance with federal and state regulatory guidelines. During the imaging procedures, rabbits were anesthetized, intubated, and mechanically ventilated. Laparotomy was performed. The abdominal aorta was then isolated and exposed. At this opening, a 6-F arterial catheter was inserted into the aorta.[26] The IVUS-OCT catheter was advanced through the 6-F arterial catheter and into the abdominal aorta. We examined three flushing agents, 10% dextran (40,000 Da MW) in normal saline, 20% mannitol in normal saline, and iohexol (350 mgI/ml, NOVAPLUS), in the abdominal aortas of three anesthetized rabbits, which mimic the diameter of human coronaries.[13] To evaluate the effect of different flushing agents in the *in vivo* experiment, a clear image frame (CIF) was used as a criteria. A CIF is defined as the image frame where over 270 deg continuous arc of artery wall can be visualized, similar to previously published concepts.[11,12]

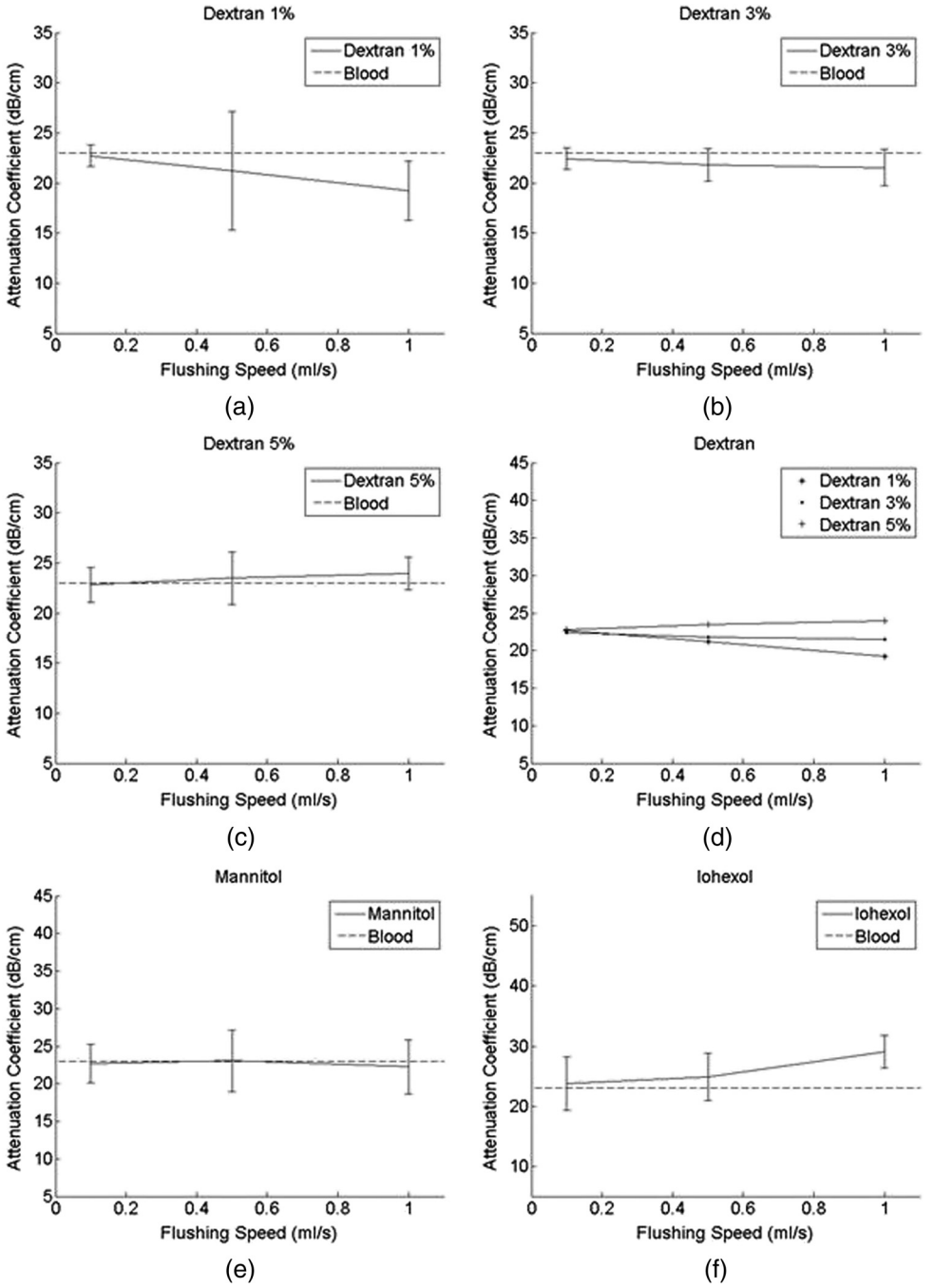

Fig. 3 IVUS ACs using different flushing agents (a) dextran 1% (b) dextran 3% (c) dextran 5% (d) dextran 1%, 3% and 5% (e) mannitol (f) iohexol. The AC of blood is 23 dB/cm (shown as dashed lines).[25]

3 Results

3.1 *Phantom Result*

OCT image quality increases as the flushing speed increases. Dextran at 5 g/dL and flushed at 1 ml/s had strong effects on both OCT and IVUS signals (10.3% μ decrease, 4.16% α increase). Mannitol at 1 ml/s had marginal effects on both OCT and IVUS signals (4.6% μ decrease, 3.37% α decrease). Iohexol at 1 ml/s dramatically improved OCT signals (23% μ decrease) but hindered IVUS signals (17% α increase). Iohexol had the best effect for OCT flushing. The high concentration of dextran, when flushing at a high speed, can provide a flushing effect similar to that of low-speed iohexol.

3.2 *In Vivo Result*

From the acquired OCT images, CIFs are 99%, 97.5%, and 50% for iohexol, dextran, and mannitol flushing, respectively. There were many image frames acquired with mannitol flushing that were partially clear, see Fig. 4(c), but most image frames acquired with dextran were clear. Based on the semi-quantitative criteria of CIFs, different flushing agents showed a similar effect on IVUS images.

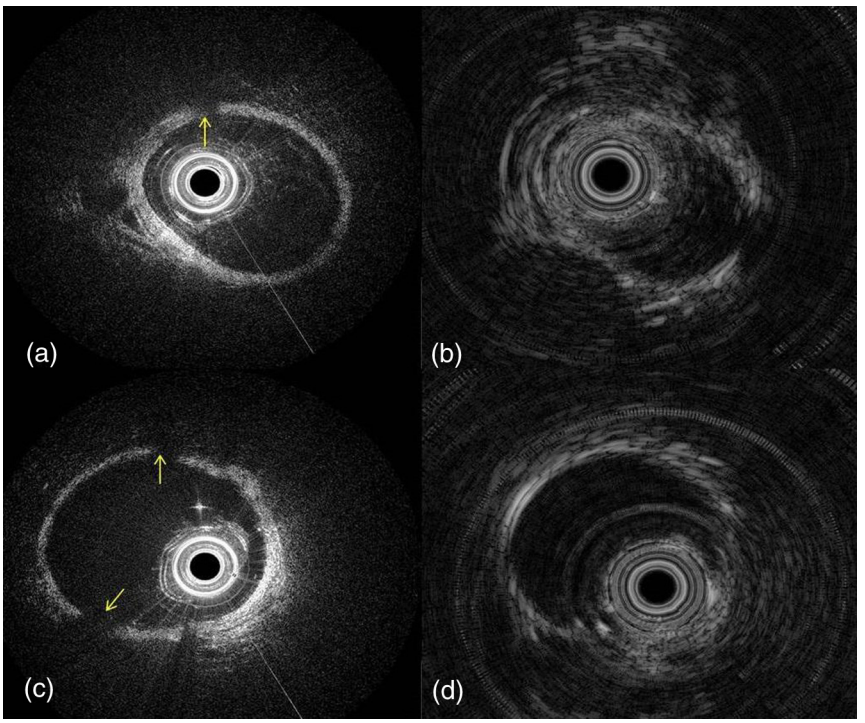

Fig. 4 Representative images acquired with alternative flushing agents: (a, b) dextran (c, d) and mannitol. (a, c) are the OCT images of rabbit artery. (b, d) are the corresponding IVUS images. Arrows denote areas where the artery wall is not visible in the image.

4 Discussion

From our phantom testing and *in vivo* experiments, we found that dextran at a high concentration worked well for both IVUS and OCT signals, as measured by a low optical and US attenuation and a high CIF rate. Mannitol was not very effective for OCT flushing while iohexol reduced the US signal. Here, we attempt to explain these results by the mechanisms behind OCT and US flushing.

4.1 *Mechanisms of Improving Optical Coherence Tomography Image Quality*

Two mechanisms are associated with the increase of OCT imaging quality: index matching and the displacing of blood.

Attenuation of optical signals is caused by absorption and scattering. At 1310 nm, where water absorption is negligible compared with scatterings, and where the absorption of hemoglobin is also low, scattering is the dominant source of attenuation. Scattering of light is generated by the difference in the index of refraction between the scatterer and surrounding medium.[14] By employing index matching chemicals and raising the refractive index of blood plasma ($n = 1.33$) to match that of blood cells ($n = 1.40$),[11] the OCT light experiences a lesser change in the refractive index at the plasma–cell interface. During the *in vivo* experiment, 10% dextran ($n = 1.349$), mannitol ($n = 1.357$), and iohexol ($n = 1.46$), which have higher refractive indices than plasma ($n = 1.33$), increased the refractive index of the mixed solution toward that of RBC (1.40). Extensive studies of index matching and optical clearing were investigated for reducing scattering in the stagnant blood imaging.[14,18]

In flowing blood, however, there is another mechanism associated with reducing scattering. As shown in our results, 1% dextran, which has a refractive index (1.334) similar to that of blood plasma (1.33), can still improve OCT image quality. A flushed chemical may completely displace blood in which case refractive index matching does not matter because no plasma–cell interface exists. In a completely displaced medium with a constant refractive index, very little scattering occurs. Flushing low concentration dextran displaces some blood, decreasing the number of plasma–cell interfaces and thus reducing scattering. This explains why flushing low concentration dextran improved the OCT signal despite its refractive index similar to that of blood plasma (Table 1).

4.2 *Mechanisms of Improving IVUS Image Quality*

Similar to light attenuation, the attenuation of sound is caused by acoustic absorption and scattering. The strength of absorption is related to the viscosity of material and the velocity of the flow. More friction and thermal consumption of energy will be induced when sound propagates through high viscosity media at a high speed.[37] The higher the viscosity is, the stronger the resistance to shearing flow and thus the larger friction that is generated. In addition, a higher flushing speed in a high viscosity medium causes a larger speed difference between the medium flowing over the surface of the tube/artery wall and the medium flowing in the center of the tube/artery wall. As a result, a high speed flushing may generate stronger friction. Iohexol, which has the highest viscosity, caused a stronger US signal reduction than other tested chemicals (see Fig. 3), and a high flushing speed of iohexol induced an even stronger reduction than at a lower speed [see Fig. 3(f)].

High viscosity is a double-edged sword for acoustic-optical imaging. Chemicals with higher viscosity most likely displace more blood because they have stronger internal "stiffness" in

Table 1 Comparison of viscosities and refractive indices.

Chemical	Viscosity at 20°C [cP]	Refractive index at 589 nm
Dextran 1%	3.23[a]	1.335[b]
Dextran 3%	4.34[a]	1.338[b]
Dextran 5%	5.89[a]	1.342[b]
Dextran 10%	12.18[a]	1.349[b]
Mannitol	5.2948[27]	1.357 (0.16 g/ml = 16%)[28c]
Iohexol	20.4[d]	1.46[29]
Blood plasma	1.39–1.64 [30,31]	1.33 [11]
Red blood cell	N.A	1.40[32–34]

[a]Refractive index of 20% mannitol was not available. Closest is 16%.
[b]Logarithmic interpolation of data from a paper.[35]
[c]Calculated by the equation from Ref. 36.
[d]NOVAPLUS Omnipaque (iohexol) injection.

pushing blood forward. This hypothesis is consistent with our results that both dextran 5% and iohexol had higher viscosities than mannitol and that they improved OCT signals better than mannitol. However, higher viscosities are known to cause more acoustic attenuation due to the increased damping of mechanical energy.[25] As revealed in Figs. 2(d) and 3(d), increasing the dextran concentration (and thus viscosity) deteriorated the IVUS signal and improved OCT image quality. Similarly, iohexol (a high viscosity chemical) increased IVUS attenuation but reduced OCT attenuation. In the context of simultaneous IVUS-OCT imaging, the medium's viscosity may serve as a critical parameter in determining the optimal balance between OCT and IVUS signal strengths. Dextran at a high concentration, with an intermediate viscosity, worked well for both IVUS and OCT. It is also significantly less toxic than iohexol, which may also enable us to perform IVUS-OCT imaging even on patients with renal insufficiency.[12] Thus, we believe dextran is a good contrast agent for simultaneous IVUS-OCT imaging.

4.3 *Effect of Blood Aggregation*

Occurring when blood cells "stick" onto one another through fibrinogen protein interactions, aggregation alters the blood's state and hence its AC. More specifically, aggregation is hypothesized to affect the OCT AC because it reduces the number of interfaces with different refractive indices.[14] Additionally, aggregation is believed to affect the ultrasound AC because of sound reflectivity's dependence on particle size.[25] Aggregation, however, typically occurs in stagnant blood or flowing blood with very low shear rates. For our experiment, the average shear rate across the pump's tube diameter was at 56 inverse second (s^{-1}), which was highly relative to lower shear rates at 0 to 15 s^{-1}.[38] Thus, aggregation was assumed to not occur. In addition, we did not observe any aggregation or sedimentation processes in the experimental images, as shown in Fig. 4, so changes in ACs must be caused by the introduced chemicals and their interactions with blood, not the blood interacting with itself to form cellular aggregates.

4.4 *Outlook*

Flushing, or optical clearing, is not only necessary in OCT but also in other optical-based imaging methods, such as optical elastography, acoustic-optics, and photoacoustic imaging.[39] For example, stronger intravascular photoacoustic signals were detected in a vessel without blood than the case with blood, which indicate the necessity for effective flushing agents.[40] In addition, optical clearing has also proven to be useful for enhance imaging performance and sensitivity in photoacoustic microscope[41,42] and flow cytometry.[43] HDIVUS (with a center frequency of over 50 MHz) recently received FDA approval and has caught physicians' attention at prestigious medical conferences due to its remarkable resolution.[44,45] However, unlike common IVUS, HDIVUS also suffers from reduction in image quality from blood scattering and performs better with a flushing agent.[46] With the system setup mentioned in this paper, the ideal nontoxic flushing agent for HDIVUS can easily be found. This study will also potentially benefit the clinical adoption of HDIVUS. Based on our research, we would argue that the optimal IVUS-OCT flushing agent should have an index of refraction over 1.34 and a viscosity lower than 15 cp.

In this paper, we quantitatively investigated three representative flushing agents. However, more optical clearing agents, such as glucose solutions, propylene glycol,[17] and hemoglobin,[47–49] can be investigated using the methods proposed in this paper. Before *in vivo* experiments, a preliminary theoretical analysis and low-cost phantom testing would be useful for initial screening.

5 Conclusion

This paper analyzed the effects of three flushing agents (dextran, mannitol, and iohexol) in a blood-filled closed-loop tube system and *in vivo* on rabbits. Dextran improved intravascular OCT signals, with higher concentrations leading to stronger signals, but it had variable effects on IVUS signals depending on concentration. Mannitol had a marginal impact on both OCT and IVUS signals. Iohexol significantly improved OCT signal but also significantly deteriorated the IVUS signal due to its high viscosity. From *in vitro* results, flushing high concentration dextran at 1 ml/s was most useful for simultaneous IVUS-OCT imaging. This conclusion confirms previous reports[12,14] that dextran performs well in intravascular OCT which can replace harmful contrast agents and thus reduce the side effects from intravascular imaging. *In vivo* result also validated the effectiveness of dextran for simultaneous IVUS-OCT imaging.

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