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ORIGINAL PAPER

Optimizing flushing parameters in intracoronary optical coherence tomography: an in vivo swine study

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Abstract Intracoronary optical frequency domain imaging (OFDI), requires the displacement of blood for clear visualization of the artery wall. Radiographic contrast agents are highly effective at displacing blood however, may increase the risk of contrast-induced nephropathy. Flushing media viscosity, flow rate, and flush duration influence the efficiency of blood displacement necessary for obtaining diagnostic quality OFDI images. The aim of this work was to determine the optimal flushing parameters necessary to reliably perform intracoronary OFDI while reducing the volume of administered radiographic contrast, and assess the influence of flushing media choice on vessel wall measurements. 144 OFDI pullbacks were acquired together with synchronized EKG and intracoronary pressure wire recordings in three swine. OFDI images were graded on diagnostic quality and quantitative comparisons of flushing efficiency and intracoronary cross-sectional area with and without precise refractive index calibration were performed. Flushing media with higher viscosities resulted in rapid and efficient blood displacement. Media with lower viscosities resulted in increased blood-media transition zones, reducing the pullback length of diagnostic quality images obtained. Flushing efficiency was found to increase with increases in flow rate and duration. Calculations of lumen area using different flushing media were significantly different, varying up to 23 % ($p < 0.0001$). This error was eliminated with careful refractive index calibration. Flushing media viscosity, flow rate, and flush duration influence the efficiency of blood displacement necessary for obtaining diagnostic quality OFDI images. For patients with sensitivity to contrast, to reduce the risk of contrast induced nephrotoxicity we recommend that intracoronary OFDI be conducted with flushing solutions containing little or no radiographic contrast. In addition, our findings show that careful refractive index compensation should be performed, taking into account the specific contrast agent used, in order to obtain accurate intravascular OFDI measurements.

Keywords Optical coherence tomography · Intracoronary imaging · Optical frequency domain imaging · Refractive index · Viscosity · Flushing

Introduction

Optical coherence tomography (OCT) is an infrared light-based imaging modality that can be used to generate cross-sectional images of the coronary wall in vivo with sufficient resolution and contrast to enable identification of

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many of the features associated with the vulnerable plaque [1–6]. Such features include the identification of fibrous plaques [7, 8], lipid-rich plaques [7–9], calcium deposits [7, 8], macrophages [10, 11], cholesterol crystals [2, 12], and red and white thrombus [4, 13]. Intracoronary OCT may additionally be useful for evaluating coronary stent placement [11, 14, 15], apposition [11, 16–18], and strut coverage [6, 19–22]. One challenge faced when conducting intravascular OCT is the high light scattering property of blood that causes significant attenuation of the OCT imaging signal, and therefore prevents clear imaging of the artery wall. To acquire images of the artery wall the blood must be first cleared from the imaging field of view. The two techniques routinely used to displace blood from the OCT imaging window are non-occlusive flushing of the vessel through the guiding catheter with an optically transparent media, such as lactated ringers solution or radiographic contrast [11, 23, 24], or by performing a combination of proximal balloon occlusion and vessel flushing through the OCT imaging catheter [25, 26]. To mitigate risks, such as myocardial ischemia, that may occur as a result of the disruption to blood flow in the artery, the duration of these methods are limited to only a few seconds, which in turn limits the volume of artery that can be safely imaged with OCT. Second-generation OCT systems, termed Fourier domain OCT (FD-OCT) [27] or optical frequency domain imaging (OFDI) [28], are capable of imaging at significantly higher image acquisition rates while preserving the resolution and contrast of the first generation time-domain OCT systems. OFDI systems are therefore capable of comprehensively imaging entire coronary artery segments at a microscopic resolution during a brief flush (~7 cm coronary segments in <4 s) [23, 29].

While the advent of FD-OCT systems has resulted in a reduction in the imaging time required, and a corresponding reduction in the administered volume of flushing media necessary, the optimal flushing parameters and media have yet to be determined. As radiocontrast agents typically have a higher viscosity than saline or lactated ringers solution, they typically have superior blood displacement performance [30, 31] and are therefore often the OCT flushing media choice, however physicians must be mindful of the increased contrast burden and take preventative steps to ensure that the maximum allowable contrast dose, typically around 250–350 mL [32, 33], is not exceeded. Although the volume of contrast delivered during intracoronary OCT is small relative to the volume used in standard PCI procedures, radiocontrast is not required for successful OCT imaging and therefore may unnecessarily add to the contrast burden. The primary objective of this study is to determine the optimal intracoronary flushing media, flow rate and duration in order to reliably acquire high quality OFDI images of long coronary segments while minimizing the potential risks to the patient. We will additionally assess the refractive index of the flushing media and will determine the effect OCT measurement of vessel area.

Methods

OFDI imaging system

The OFDI imaging system used in this study has been described previously [29]. The system utilized dual-balanced polarization diverse detection and acquired axial depth profiles at a rate of 52 kHz, corresponding to 100 frames per second (frame size: 1536 × 512). The axial resolution was 7 μm, and the imaging depth was 6.14 mm in air. A helical scanning 2.4 Fr (0.8 mm diameter) intracoronary OFDI catheter was used in this study with a mean focal length and transverse resolution of 2.1 mm and 47 μm. The inner optical core of the catheter was rotated at 100 revolutions per second with a longitudinal pullback speed of 20 mm/sec corresponding to a frame-to-frame spacing of 200 μm. The catheter incorporated a distal 0.014 guide-wire provision and radio-opaque markers both on the imaging lens and the outer sheath to increase visibility for catheter placement determination on angiography.

Swine

The Skirball Center for Cardiovascular Research (Orangeburg, NY) Institutional Animal Care and Use Committee approved this study. The study was conducted in three female Yorkshire swine each weighing 52 kg.

Surgical preparation

On days 0 and 15, the swine were pre-anesthetized with an intramuscular injection of Glucopyrrolate (0.004–0.01 mg/kg), Telazol (3–5 mg/kg), and Xylazine (1–2 mg/kg), and inhaled isoflurane (1–3 %). Once an adequate anesthetic plane was reached, the animals were intubated and mechanically ventilated. General anesthesia was maintained with inhaled isoflurane (1–2 %), and intravenous fluids (lactated ringers) were administered throughout the procedure. A vascular access sheath was positioned in the femoral artery using a standard cut-down procedure and a bolus of heparin was administered to achieve an Activated Clotting Time of 250 s. Blood pressure, heart rate, respiration rate and blood oxygenation were routinely monitored and recorded throughout the procedure.

Day 0: Stent placement

On day 0, 15 days prior to OCT imaging, all three major epicardial arteries were implanted with bare metal stents using standard percutaneous coronary interventional techniques and under fluoroscopic guidance. Baseline coronary angiography was performed to determine appropriate stent sizing with approximately a 10 % overstretch ($\leq$1.1:1 stent-to-artery diameter ratio). Stent lengths were additionally selected using baseline angiography calculations. Details of the stents used are provided in Table 1.

Day 15 and 16: Catheterization and OFDI imaging

Catheterization

On day 15, OFDI imaging was conducted in 2 swine (#23483 and #23484) and was concluded in the 3rd swine (#23485) on day 16. Using standard percutaneous coronary interventional techniques a 6 Fr guide catheter was advanced under fluoroscopic guidance to fully engage the coronary artery. A 0.014 PressureWire(R) Certus guide wire (RADI Medical Systems Inc., Reading MA) was positioned within the target coronary artery and the OFDI imaging catheter was advanced over the guidewire into the coronary artery immediately proximal to, but not covering, the sensor location on the PressureWire.

Throughout the procedure heparin was administered as needed to ensure appropriate Activated Clotting Times, and Nitroglycerin was administered as needed to alleviate vasospasm.

Flushing

To determine the optimal flushing parameters, OFDI imaging was performed with 8 different flushing media at 2 and 3 ml/sec for a total duration of 3 s using a Medrad Mark V ProVis automated injection system (Medrad Inc., Warrendale, PA, USA) providing a total of 144 OFDI pullback datasets (3 vessels × 3 swine × 2 flushing rates × 8 flushing media = 144 OFDI pullbacks). All media were pre-mixed and warmed to a temperature of 37 °C. The flushing media was manually advanced through the guide catheter prior to imaging to ensure that there was no mixing of flushing solutions. In a small subset of vessels additional flushing parameters were testing including infusion rates of 4 ml/sec in the RCA of swine 23485, and increased flushing durations of 4 s in the LCX of swine 23484 at 3 ml/sec.

Table 2 provides a list of the flushing solutions together with the respective optical refractive index and the viscosity. Viscosity values were calculated using a ViscoLab3000 with T480 Sensor (Cambridge Viscosity Inc., Medford, MA, USA) at 37 °C. Optical refractive indices were measured using a hand refractometer (Milton Roy, Reviera Beach, FL, USA). Figure 1 shows a plot of the relationship between viscosity and dilution of contrast media in Lactated Ringers solution. From this figure it can be noted that viscosity does not appear to scale linearly with dilution.

Flushing and imaging procedure

The OFDI catheter rotation was initiated prior to commencement of flushing. Flushing, OFDI data acquisition, and time stamping for the continuously recorded pressure wire and EKG traces were all synchronized. Upon visualization of the clearing of the blood in the coronary artery by OFDI, the OFDI pullback was initiation at a pullback speed of 20.0 mm/sec. A minimum recovery time of 2 min was observed between flushing events. This time was additionally extended when indicated as necessary based on physiologic monitoring of the EKG, blood pressure or intracoronary pressure values.

In addition to EKG and pressure wire readings further study controls were incorporated including blood analysis at the completion of imaging in each vessel, angiography

Table 1 Stent implant matrix

Animal number—artery	Stent manufacturer	Stent size (dia. × len. mm)
23483—RCA	Medtronic—Driver	3.5 × 15
23483—LAD	Medtronic—BeStent 2	3 × 9
23483—LCX	Cordis—BX Sonic	3 × 18
23484—RCA	Medtronic—Driver	3.5 × 15
23484—LAD	Abbott—ML vision	3.5 × 15
23484—LCX	Medtronic—Driver	3.5 × 12
23485—RCA	Medtronic—Driver	3.5 × 12
23485—LAD	Boston Scientific—Express 2	3 × 20
23485—LCX	Medtronic—BeStent 2	3 × 9

RCA right coronary artery, *LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery

Table 2 Intracoronary OCT flushing solutions with optical refractive indices and viscosity values

Index	Flushing solutions	Refractive index (n)	Viscosity (cP)[a]
A	100 % Lactated ringers (LR)	1.334	0.825
B	30 % Iodixanol 320 in LR	1.404	1.042
C	30 % Iohexol 350 in LR	1.349	2.198
D	60 % Iohexol 350 in LR	1.355	2.418
E	60 % Iodixanol 320 in LR	1.350	4.229
F	5 % Dextran 40 in Dextrose	1.394	4.375
G	100 % Iodixanol 320	1.458	12.271
H	100 % Iohexol 350	1.443	13.146
I[b]	5 % Dextran 40 in LR	1.365	3.556
J[b]	5 % Dextran 40 in 0.9 % NaCl	1.370	3.845

All values reported in the table were measured by Cambridge Viscosity Inc (Medford, MA). Supplier reported viscosity values for Iodixanol (Visipaque 320) and Iohexol (Omnipaque 350) were 11.8 and 10.4 cP respectively

[a] Viscosity measured at 37 °C

[b] Solution properties for I, and J are provided for reference only and were not tested in this study

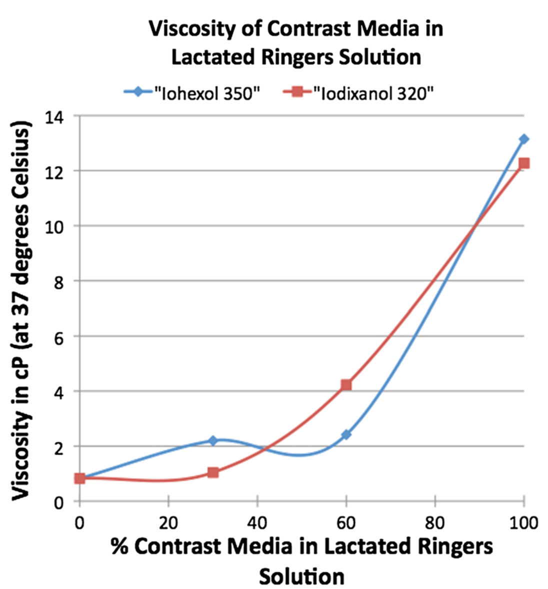

Fig. 1 Viscosity of contrast agents Iohexol 350 and Iodixanol 320 diluted in lactated ringers solution at 37 °C

of guide catheter placement, guidewire and OFDI imaging catheter placement, and during each OFDI imaging pullback.

Data analysis

Each frame in the acquired OFDI datasets were graded as either (Fig. 2a) blood obscures visualization of the vessel wall, (Fig. 2b) vessel lumen is visible, (Fig. 2c) diagnostic quality images of the artery wall acquired, or (Fig. 2d) no blood visible in the artery lumen. Unless otherwise noted, comparisons of flushing efficiency were calculated using the diagnostic quality images. Paired two-sided student t-tests were used to calculate statistical significance of flushing efficiency.

The change in intracoronary pressure was calculated corresponding to each of the flushing and OFDI imaging events. The purpose of recording the intracoronary pressure changes was to ensure that the flushing solution was fully delivered to the target vessel. A 5 s window prior to the time stamped event and 15 s post initiation of the flush was assessed. Statistical assessment of changes in intracoronary pressures resulting from different flushing media, were calculated using paired 2-sided Student *t* tests. To determine the potential influence of intracoronary pressure on flushing efficiency or solution viscosity, square Pearson's correlation coefficients were calculated.

The refractive indices varied approximately 9 % across each of the flushing media used in this study (Table 2). Therefore, when measuring lumen areas, incorrect refractive index values could potentially result in errors as high as 19 %. To determine the influence of flushing media choice on OFDI metrics we calculated and statistically compared lumen areas in each of the 9 vessels using the different flushing solutions at a flush rate of 3 ml/sec. Initial calculations were performed using a refractive index of n = 1.4, which is the standard default for intracoronary OCT systems. In order to accurately compare comparable frames within each dataset, frames were registered using stent and anatomical landmarks visible in each of the OFDI sets. If a precise frame match was not possible due to, for example, insufficient flushing, the frame was discarded. These measurements were calculated across a mean number of 165 registered frames for each flushing media. The results were then corrected using the measured refractive indices of the flushing media and were again statistically compared using paired student t tests.

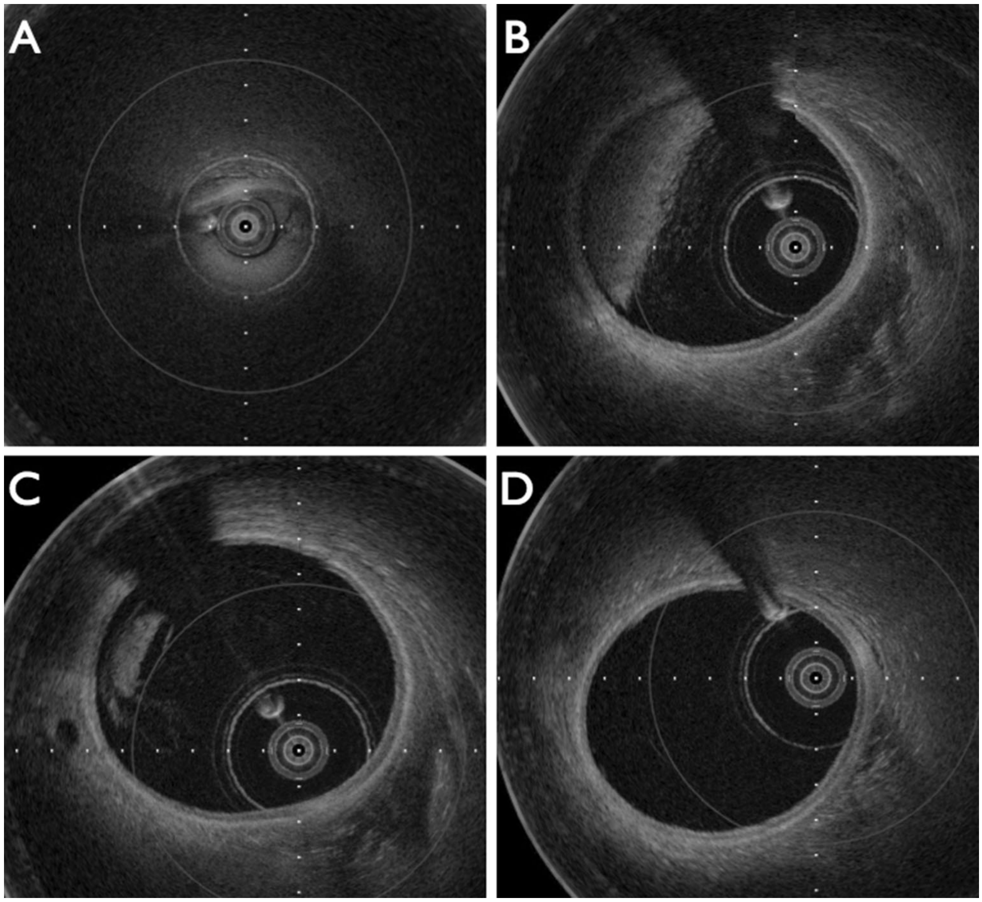

Fig. 2 Example OFDI images of **a** blood obscuring visualization of the vessel wall, **b** a visible vessel lumen, **c** diagnostic quality images, and **d** a fully clear vessel with no visible blood

Results

Analysis of the pressure wire, EKG, OFDI and angioscopy results were performed on each of the 144 flushing datasets plus the added extra flushes of increasing duration and flush rate. Data from a 3 s, 3 ml/sec flush of Iodixanol 320 from the RCA of swine 23485 is provided in Fig. 3. In Fig. 3d a slight increase in the intracoronary pressure can be observed at 2.36 s corresponding to the commencement of the displacement of blood from the OFDI imaging window. No appreciable difference in the EKG was noted.

Figure 4 shows the calculated pullback length for each of the chosen flushing solutions averaged over the 9 coronary vessels. As anticipated, the flushing solutions with the higher viscosity values more successfully displaced the blood from the vessel allowing for longer imaging segments. Significantly longer pullback lengths were achieved with the 3 ml/sec flush rate, and therefore increased flush volume, when compared to the values obtained for the 2 ml/sec flush rates. There was no significant difference in the flushing efficiency between Iohexol 350 and Iodixanol 320 at equivalent concentrations ($p = 0.33$). The flushing efficiency was highly correlated to the rate of flow ($p < 0.00001$). It should also be noted that 5 % Dextran 40 in Dextrose performed comparably well to the higher contrast agent concentrations, although not as well as the full strength radiocontrast concentrations.

The maximum change in intracoronary pressure values were not found to correlate to flushing efficiency determined by diagnostic quality OFDI images ($R^2 = 0.005$), or to solution viscosity ($R^2 = 0.003$). As expected, there was a significant increase in intracoronary pressure values with a corresponding increase in the flushing rate ($p < 0.00002$).

Figures 5 and 6 show the result of the extra flush rates and durations performed. Figure 5 suggests that both flushing efficiency (Fig. 5a) and intracoronary pressure (Fig. 5b) increase significantly with increases in flushing rate. Corresponding p values are provided in Table 3. Figure 6 shows the effect of flush duration on flushing efficiency (Fig. 6a) and on intracoronary pressure change (Fig. 6b). No significant increase in pressure was noted corresponding to the increase in flush duration ($p = 0.24$), however there did appear to be a notable increase in the flushing efficiency. At the increased flushing duration of

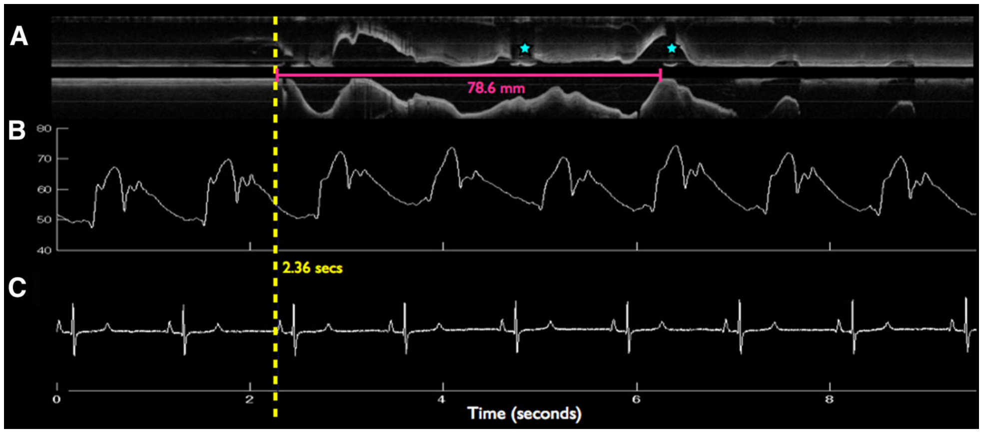

Fig. 3 Time correlated *a* a longitudinal reconstruction of the OFDI pullback, *b* pressure wire, and *c* EKG data obtained from the right coronary artery of swine 23485 with a 100 % Iodixanol 320 flush at 3 ml/sec for 3 s. The blood clearing was observed at the OFDI catheter 2.36 s following the flushing initiation (*a*) and corresponded to a mean intracoronary pressure elevation (*b*), with no change in the EKG (*c*). *Yellow dashed line*—time for flush to clear blood from OFDI field of view, *magenta solid line*—length of clear OFDI pullback

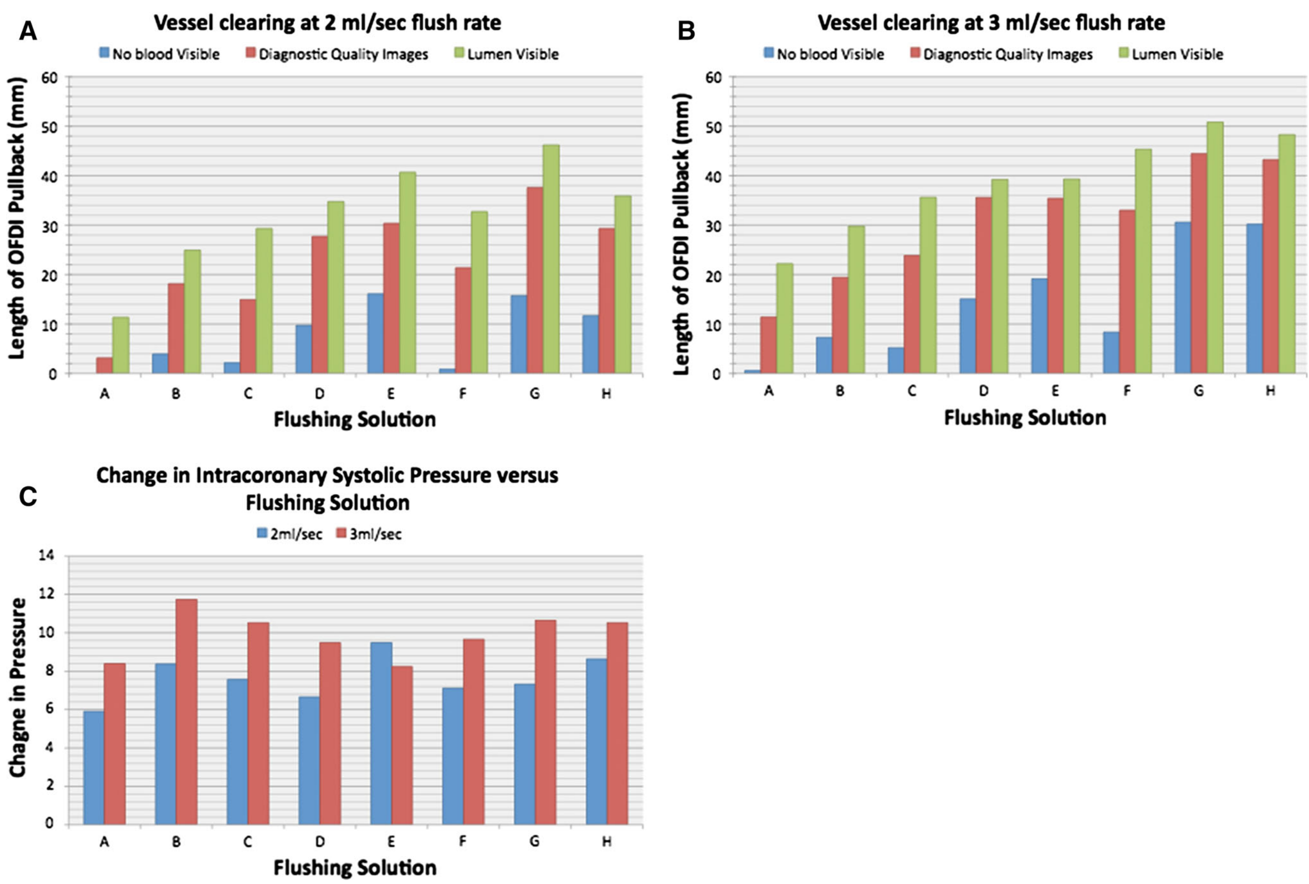

Fig. 4 The length of the OFDI pullback obtained averaged over the 9 coronary vessels for each flushing solution at **a** 2 ml/sec flush for 3 s, and **b** a 3 ml/sec flush for 3 s. **c** The increase in intracoronary systolic pressure averaged over the 9 coronary vessels for each flushing solution at 2 and 3 ml/sec flush rates for a duration of 3 s

4 s, all OFDI pullbacks maintained diagnostic quality images until reaching the maximum pullback length terminating in the guide catheter. None of the OFDI pullbacks maintained diagnostic quality until the guide catheter at flush durations of 3 s. The calculated *p* value for the flushing efficiency for the increased flushing duration was

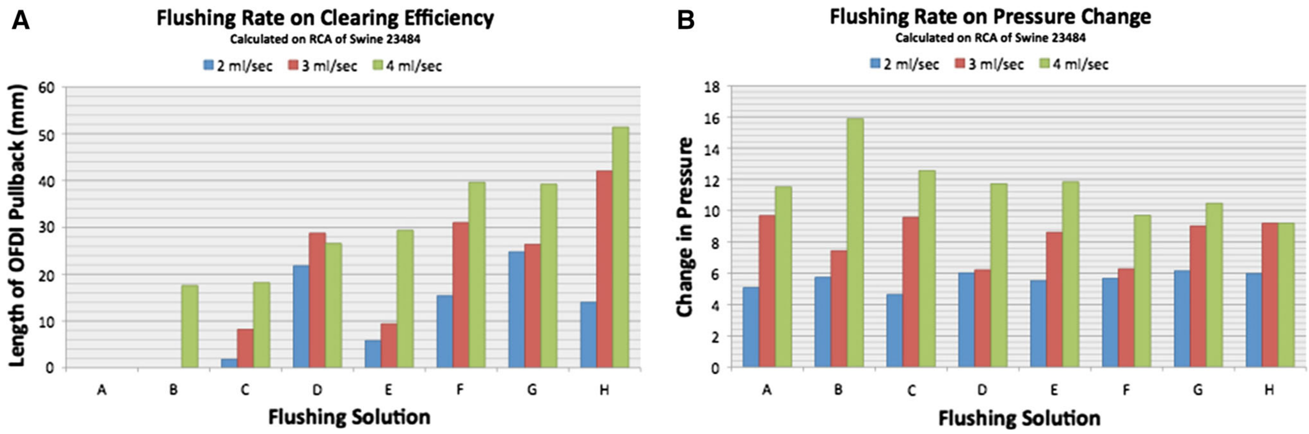

Fig. 5 The effect of increasing the flushing rate on **a** clearing efficiency and **b** intracoronary systolic pressure increase. Data collected for each of the 8 flushing solutions at 2, 3, and 4 ml/sec for 3 s assessed in the right coronary artery of swine 23484

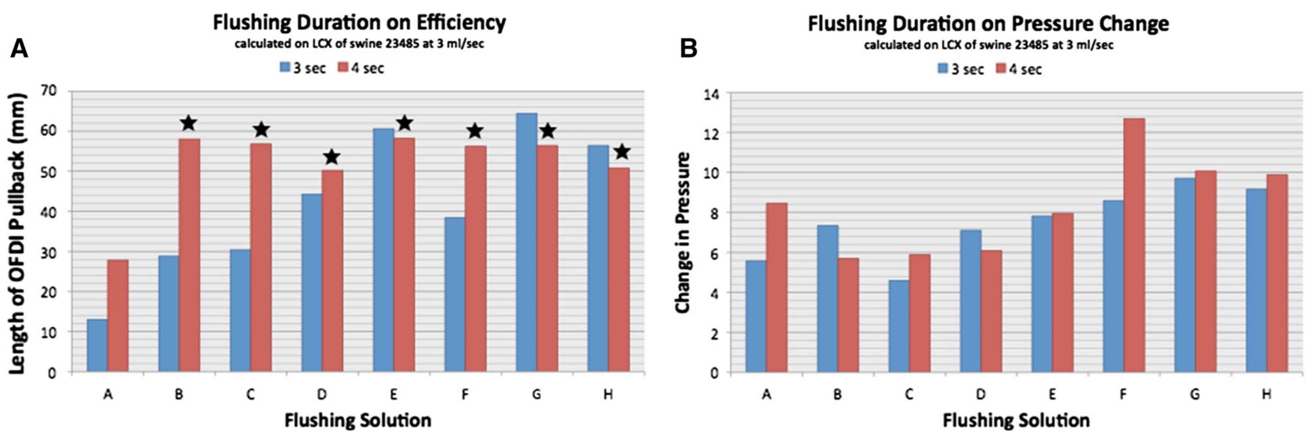

Fig. 6 The effect of increasing the flushing duration on **a** clearing efficiency and intracoronary systolic pressure increase. Data collected for each of the 8 flushing solutions at 3 ml/sec for 3 and 4 s durations assessed in the left circumflex of swine 23485. *Diagnostic quality OFDI images were obtained all the way to the guide catheter

Table 3 Paired Student *t* test on flushing rate versus clearing efficiency and increase in intracoronary pressure calculated on the RCA on Swine 23484 for a flushing duration of 3 s

Test comparison	Clearing efficiency (*p* value)	Intracoronary pressure change (*p* value)
2 versus 3 ml/sec	0.056	0.0033
3 versus 4 ml/sec	0.010	0.0084
2 versus 4 ml/sec	0.0041	0.00014

RCA right coronary artery

$p = 0.097$, however this was likely negatively influenced by the flushes terminating in the guide catheter as described above.

Table 4 highlights the importance of ensuring that the correct refractive index for the specific flushing solution is used when generating OCT or OFDI images. Using a default refractive index of n = 1.4, lumen area measurements of matched frames measured with each of the flushing media were found to be significantly different varying up to 23.0 % ($p < 0.0001$). When the correct refractive indices from Table 2 were applied, there was no statistically significant difference in matched lumen area measurements. The maximum difference in lumen area measurements across different flushing parameters following correction was 2.9 % ($p = 0.346$).

Discussion

In this study we have evaluated over 160 OFDI pullbacks with varying flushing media concentration, duration and flow rate combinations. Our results demonstrate, as expected, that increases in the flushing solution viscosity correspond to more efficient displacement of blood from the OFDI imaging window. Flushing efficiency was

Table 4 Paired Student *t* test and mean difference in lumen area provided for each flushing media against values from Lactated Ringers Solution before and after refractive index correction

		B	C	D	E	F	G	H
Default refractive index	A	0.010*, +5.1 %	0.002*, +6.3 %	<0.0001*, +10.2 %	<0.0001*, +10.4 %	0.033*, +4.2 %	<0.0001*, +19.6 %	<0.0001*, +23.0 %
Corrected refractive index		0.829, +0.4 %	0.703, +0.7 %	0.567, +0.9 %	0.577, +1.2 %	0.602, +1.0 %	0.239, +2.2 %	0.346, +2.9 %

* p values <0.05

calculated as the volumetric length of diagnostic quality OFDI images obtained. Increases in the rate of flow and the flushing duration were also correlated to increases in flushing efficiency.

The flushing radiocontrast agents (Iohexol 350, Iodixanol 320) were chosen based on those most commonly used during PCI at Columbia University Medical Center, New York. To assess the necessity for using contrast agents as opposed to routinely used Lactated Ringers solution for OCT/OFDI imaging we also evaluated dilutions of Iohexol 350 and Iodixanol 320. Dextran 40 in Lactated Ringers is routinely used as an OCT/OFDI flushing media in leading Japanese institutions, however due to difficulties in obtaining sufficient quantities of Dextran 40 in Lactated Ringers we did not select it as one of the flushing solutions evaluated in this study. To assist the comparison of Dextran 40 in Lactated Ringers with the evaluated flushing media, we provided measured viscosity and refractive index values for reference.

Ensuring the correct temperature of the flushing solutions is extremely important in determining the solution viscosity, and therefore the efficiency of blood displacement for OFDI imaging. Viscosity is highly temperature dependent with lower temperature solutions having a higher viscosity. In this study all flushing solutions were warmed to a temperature of 37 °C as recommended by standard PCI procedures to avoid the risk of severe arrhythmia, including ventricular fibrillation, as a result of the introduction of un-warmed solutions into the coronary vessel [34]. It should also be noted that viscosity does not scale linearly with the dilution (Fig. 1) and therefore if dilution of the radiocontrast solution is considered in an attempt to reduce the potential of CIN, careful consideration of the final viscosity of the solution is needed.

Our study has highlighted the need for careful calibration of the OCT/OFDI images for the precise index of refraction for the flushing media choice (Table 4). Commercially available systems typically select a refractive index of approximately 1.4. However, based on the flushing media chosen in this study, length or lumen area measurements may vary up to 9 and 18 % respectively from the reported values if the incorrect refractive index calibration is used. When distance metrics are corrected using Table 2, there is no statistically significant difference in the measurements. As a result, we recommend that investigators use the values in Table 2 instead of the blanket refractive index of 1.4 to obtain more accurate results for intravascular OCT measurements such as vessel or stent areas and diameters.

A limitation of this study includes the evaluation of flushing efficiency in swine coronary arteries in vivo. Diseased human coronary arteries are expected to have significantly increased stiffness compared to the highly elastic healthy swine coronary arteries. In an attempt to mitigate the biomechanical influence on the flushing efficiency results and to better mimic the human condition, we implanted bare metal stents in each of the arteries 15 days prior to imaging. In practice we know that placement of the guide catheter is critical to effective blood displacement for OCT/OFDI imaging to ensure that the entire flush is directed into the target vessel. In this study we therefore made every attempt to fully engage the target coronary artery with the guide catheter ensuring minimal loss of flushing solution into adjacent vessels. During clinical PCI it may not be practical to fully engage the vessel due to the potential of the guide catheter to cause damage the vessel. Increased flushing rates or durations may therefore be necessary to accommodate this loss.

The results of this study suggest that flushing efficiency, calculated as length of diagnostic quality OFDI images obtained, is correlated to the viscosity and the flow rate of the flushing media. However, we also demonstrate in a smaller subset of flushing events that, given a sufficient flow rate, an increase in flushing duration can compensate for a reduction in fluid viscosity (Fig. 6). This is likely due to the knowledge that while a lower viscosity solution may have a longer fluid transition zone, once successful displacement of blood has been achieved it can be maintained. Therefore, in patients with a sensitivity to contrast agents, to decrease the contrast burden while simultaneously obtaining high diagnostic quality images we recommend that intracoronary OFDI be conducted with a longer flush duration (∼4 s) at a moderate flow rate (∼3 ml/sec) with a flushing solution containing little no or little radiocontrast agent. In addition, our results show that the images acquired should be carefully calibrated with the correct flushing media's index of refraction.

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Conflict of interest None.

References

1. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA et al (1991) Optical coherence tomography. Science 254(5035): 1178–1181
2. Tearney GJ, Jang IK, Bouma BE (2006) Optical coherence tomography for imaging the vulnerable plaque. J Biomed Opt 11(2):021002
3. Barlis P, Serruys PW, Gonzalo N, van der Giessen WJ, de Jaegere PJ, Regar E (2008) Assessment of culprit and remote coronary narrowings using optical coherence tomography with long-term outcomes. Am J Cardiol 102(4):391–395
4. Jang IK, Tearney GJ, MacNeill B, Takano M, Moselewski F, Iftima N, Shishkov M, Houser S, Aretz HT, Halpern EF, Bouma BE (2005) In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. Circulation 111(12):1551–1555
5. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, Tanimoto T, Matsuo Y, Masho T, Kitabata H, Tsuda K, Tomobuchi Y, Akasaka T (2007) Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. J Am Coll Cardiol 50(10):933–939
6. Gupta R, Raffel OC, Jang IK (2007) Severe intimal hyperplasia after sirolimus eluting stent deployment: evaluation by optical coherence tomography. Heart 93(6):754
7. Rieber J, Meissner O, Babaryka G, Reim S, Oswald M, Koenig A, Schiele TM, Shapiro M, Theisen K, Reiser MF, Klauss V, Hoffmann U (2006) Diagnostic accuracy of optical coherence tomography and intravascular ultrasound for the detection and characterization of atherosclerotic plaque composition in ex vivo coronary specimens: a comparison with histology. Coron Artery Dis 17(5):425–430
8. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, Kauffman CR, Shishkov M, Kang DH, Halpern EF, Tearney GJ (2002) Characterization of human atherosclerosis by optical coherence tomography. Circulation 106(13):1640–1645
9. Kume T, Okura H, Kawamoto T, Akasaka T, Toyota E, Watanabe N, Neishi Y, Sukmawan R, Sadahira Y, Yoshida K (2007) Relationship between coronary remodeling and plaque characterization in patients without clinical evidence of coronary artery disease. Atherosclerosis 197(2):799–805
10. MacNeill BD, Jang IK, Bouma BE, Iftimia N, Takano M, Yabushita H, Shishkov M, Kauffman CR, Houser SL, Aretz HT, DeJoseph D, Halpern EF, Tearney GJ (2004) Focal and multifocal plaque macrophage distributions in patients with acute and stable presentations of coronary artery disease. J Am Coll Cardiol 44(5):972–979
11. Bouma BE, Tearney GJ, Yabushita H, Shishkov M, Kauffman CR, Gauthier DD, MacNeill BD, Houser SL, Aretz HT, Halpern EF, Jang IK (2003) Evaluation of intracoronary stenting by intravascular optical coherence tomography. Heart 89(3):317–320
12. Tearney GJ, Jang IK, Bouma BE (2003) Evidence of cholesterol crystals in atherosclerotic plaque by optical coherence tomographic (OCT) imaging. Eur Heart J 24(15):1462
13. Kume T, Akasaka T, Kawamoto T, Ogasawara Y, Watanabe N, Toyota E, Neishi Y, Sukmawan R, Sadahira Y, Yoshida K (2006) Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol 97(12):1713–1717
14. Toutouzas K, Vaina S, Riga MI, Stefanadis C (2007) Evaluation of dissection after coronary stent implantation by intravascular optical coherence tomography. Clin Cardiol 32(7):E47–E48
15. Regar E, Schaar J, Serruys PW (2006) Images in cardiology. Acute recoil in sirolimus eluting stent: real time, in vivo assessment with optical coherence tomography. Heart 92(1):123
16. Raffel OC, Hannan JC, Jang IK (2006) Coronary stent malapposition as a result of a post-stenotic aneurysm detected by optical coherence tomography. J Invasive Cardiol 18(11):561–562
17. Sawada T, Shite J, Shinke T, Watanabe S, Otake H, Matsumoto D, Imuro Y, Ogasawara D, Paredes OL, Yokoyama M (2006) Persistent malapposition after implantation of sirolimus-eluting stent into intramural coronary hematoma: optical coherence tomography observations. Circ J 70(11):1515–1519
18. Takano M, Jang IK, Mizuno K (2006) Neointimal proliferation around malapposed struts of a sirolimus-eluting stent: optical coherence tomography findings. Eur Heart J 27(15):1763
19. Regar E, van Beusekom HM, van der Giessen WJ, Serruys PW (2005) Images in cardiovascular medicine. Optical coherence tomography findings at 5-year follow-up after coronary stent implantation. Circulation 112(23):e345–e346
20. Barlis P, Tanigawa J, Di Mario C (2007) Coronary bioabsorbable magnesium stent: 15-month intravascular ultrasound and optical coherence tomography findings. Eur Heart J 28(19):2319
21. Tanigawa J, Barlis P, Di Mario C (2007) Do unapposed stent struts endothelialise? In vivo demonstration with optical coherence tomography. Heart 93(3):378
22. Takano M, Inami S, Jang IK, Yamamoto M, Murakami D, Seimiya K, Ohba T, Mizuno K (2007) Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation. Am J Cardiol 99(8): 1033–1038
23. Tearney GJ, Waxman S, Shishkov M, Vakoc BJ, Suter MJ, Freilich MI, Desjardins AE, Oh WY, Bartlett LA, Rosenberg M, Bouma BE (2008) Three-dimensional coronary artery microscopy by intracoronary optical frequency domain imaging. JACC Cardiovasc Imaging 1(6):752–761
24. Gonzalo N, Tearney GJ, Serruys PW, van Soest G, Okamura T, Garcia-Garcia HM, Jan van Geuns R, van der Ent M, Ligthart J, Bouma BE, Regar E. (2010) Second-generation optical coherence tomography in clinical practice. High-speed data acquisition is highly reproducible in patients undergoing percutaneous coronary intervention. Rev Esp Cardiol 63(8):893–903
25. Garcia-Garcia HM, Gonzalo N, Regar E, Serruys PW (2009) Virtual histology and optical coherence tomography: from research to a broad clinical application. Heart 95(16):1362–1374
26. Gonzalo N, Serruys PW, Okamura T, van Beusekom HM, Garcia-Garcia HM, van Soest G, van der Giessen W, Regar E (2009) Optical coherence tomography patterns of stent restenosis. Am Heart J 158(2):284–293
27. Choma M, Sarunic M, Yang C, Izatt J (2003) Sensitivity advantage of swept source and Fourier domain optical coherence tomography. Opt Express 11(18):2183–2189
28. Yun S, Tearney G, de Boer J, Iftimia N, Bouma B (2003) High-speed optical frequency-domain imaging. Opt Express 11(22): 2953–2963

29. Yun SH, Tearney GJ, Vakoc BJ, Shishkov M, Oh WY, Desjardins AE, Suter MJ, Chan RC, Evans JA, Jang IK, Nishioka NS, de Boer JF, Bouma BE (2006) Comprehensive volumetric optical microscopy in vivo. Nat Med 12(12):1429–1433
30. Petitjeans P, Maxworthy T (1996) Miscible displacements in capillary tubes. Part 1. Experiments. J Fuild Mech 326:37–56
31. Prati F, Cera M, Ramazzotti V, Imola F, Giudice R, Giudice M, Propris SD, Albertucci M (2008) From bench to bedside: a novel technique of acquiring OCT images. Circ J 72(5):839–843
32. Cigarroa RG, Lange RA, Williams RH, Hillis LD (1989) Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. American J Med 86(6 Pt 1):649–652
33. Raposeiras-Roubin S, Abu-Assi E, Ocaranza-Sanchez R, Alvarez-Alvarez B, Cambeiro-Gonzalez C, Fandino-Vaquero R, Garcia-Castelo A, Garcia-Acuna JM, Gonzalez-Juanatey JR (2013) Dosing of iodinated contrast volume: a new simple algorithm to stratify the risk of contrast-induced nephropathy in patients with acute coronary syndrome: A new simple algorithm to stratify the risk of contrast-induced nephropathy in patients with acute coronary syndrome. Catheter Cardiovasc Interv 82(6):888–897
34. Jacobsen EA, Mortensen E, Refsum H, Klow NE (1992) The effect of the temperature of contrast media on cardiac electrophysiology and hemodynamics during coronary arteriography. Invest Radiol 27(11):942–946