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Flow of blood-saline mixtures studied by time-domain optical coherence tomography

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ABSTRACT

In-vitro analysis of flowing blood-saline mixtures is performed by time-domain optical coherence tomography imaging. The mixtures contain blood in concentrations ranging from 100% to 20%. For each image, a corresponding compounded profile is obtained by adding one thousand adjacent A-scans. The compounded profiles are used for characterizing the optical coherence tomography signal as it propagates within the studied blood-saline mixtures. The results obtained point toward the possibility of acquiring intra-vascular images of arterial tissue that is located behind slabs of flowing blood-saline. A threshold in the propagation distance beyond which the recorded signal becomes dominated by its multiple scattered components is established along the compounded profiles. The threshold location, at a depth of ~ 0.6 mm, is independent of blood concentration. Further investigation of the compounded profiles reveals that the region extending to a maximum depth of about 200 μm from the point where the probing beam enters blood-saline mixtures could reveal information about the flow regime. This opens the possibility of another application for time-domain optical coherence tomography in intravascular imaging: assessing the flow regime, i.e. laminar or turbulent.

Keywords: time-domain optical coherence tomography, blood, light propagation, attenuation, multiple scattering of light, blood cells, blood-saline flow

1. INTRODUCTION

Technological advances made in the last decade have transformed intravascular optical coherence tomography (OCT) into a serious candidate for becoming the method of choice to be used for assessing and monitoring various clinical conditions specific to arterial tissue. One of these conditions, atherosclerosis in coronary arteries has been recognized as a complex process that needs to be investigated using an imaging technique that has a higher spatial resolution than the resolution provided by the current imaging methods. As a comparison, one of the most used imaging methods, intravascular ultrasound (IVUS) provides too little information about plaque characteristics or other details of the vessel wall due to a spatial resolution threshold of ~ 100 μm . Another frequently utilized technique, X-ray angioplasty, has even a lower spatial resolution, with the geometrical size of the smallest detail discernable being around 0.5 mm. X-ray angioplasty is also performed through imaging the X-ray-generated fluorescence from a dye that is injected in the aorta through a catheter. Besides putting a strain on kidneys, which have to eliminate the dye from the body, this method shows only *post factum* if and where plaque blocks the artery and does not give any indication about existing plaque that has not yet obstructed the lumen.

Meanwhile, OCT has an axial spatial resolution that allows the imaging of structures dimensionally comparable to the coherence length of the light source used in the OCT system. The coherence length of sources used in OCT systems is usually of the order of 10 μm . Such level of detail renders the OCT technology as the suitable method for investigating arterial surface as well as the tissue underneath, region where atherosclerotic clinical conditions appear and develop¹. A spatial resolution of 10 μm 's offers the possibility to investigate details such as arterial morphology, incipient plaque, fat streaks, endothelium layer injuries, lipid pools, fibrous caps and macrophage accumulations.

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Besides higher resolution there are other advantages for OCT. It uses the least intrusive and cleanest probing tool available, light, with the existence of a multitude of spectral sources available from ultraviolet to infrared that can be tailored according to specific needs. Also, OCT technology rides on the demands from the telecommunication market, a high-volume consumer industry that constantly decreases the costs for the necessary hardware. Additionally, the standard optical fiber-based OCT systems could be easily integrated with the existing intravascular catheter technology.

A schematic diagram of the probe head that can be part of an OCT arterial catheter collecting images in an in-vivo clinical setting is presented in figure 1. The probe head could be seen as part of the sample arm of an OCT system designed around a fiber-based interferometer. The main possible routes along which light propagates are indicated in the figure. Shown is light passing through the catheter sheath and entering an environment that could be exclusively blood or a mixture of blood and isotonic saline in various concentrations. After propagating through blood or blood-saline mixture, the probing light reaches the arterial wall and a part of it is reflected back toward the detection system. Biomorphological variations in the arterial tissue generate changes of optical properties such as scattering, absorption and refractive index. These changes in the intrinsic optical properties of the tissue leave their marks on the recorded OCT signal. Therefore by analyzing the OCT signal recorded after back-reflection from within the arterial tissue it is possible to assess the optical properties of the studied sample and to establish their correlation with specific clinical states.

In order to obtain high quality OCT arterial images it is necessary to eliminate or quench all the signals that are not coming from the region of interest. Most of the signal recorded outside the region of interest (i.e. the arterial tissue) is generated either by the specular reflections at various catheter interfaces or by light scattered from blood cells. If the specular reflections are easy to identify and to eliminate from the overall recorded OCT signal, the part of the signal generated through backscattering from blood cells presents a much bigger problem. Blood, as well as blood-saline mixtures, are highly turbid environments that strongly scatter light. In the presented context, scattering is damaging to OCT imaging in two ways: first, it decreases the amount of probing light flux that reaches the arterial wall and second, it decreases the amount of light that carries information back to the detection after being back-reflected within the arterial tissue. In addition to these two factors, signal detected after undergoing multiple scattering events decreases the contrast of the OCT image and delocalizes some of the photons received by the detector. Photon delocalization undermines the connection between the studied sample and its corresponding OCT image.

Fig. 1. Schematic design of an in-vivo OCT arterial catheter. The specular reflection corresponding to the sheath interface can be eliminated. The “good” signal coming from the arterial wall is attenuated due to scattering by blood cells and its contrast is diminished by signal detected after multiple scattering events.

An obvious solution for the blood problem is to surround the catheter probe head with a percutaneous coronary angioplasty (PTCA) balloon. The balloon is inflated in order to obstruct the arterial lumen and to block the blood circulation during the OCT image acquisition. Such a design for an OCT probe head is technically complex because, in addition to the incorporated optical elements, it also contains the balloon with all the attached gear. In addition this design also requires a system for injecting saline on the other side of the PTCA balloon in order to keep the pressure necessary within the arterial lumen to prevent the collapse of the vessel walls. Blocking the blood flow by pressing a PTCA balloon against a portion of the arterial wall generates its own set of problems. One of the problems is ischemia. Another one is the fact that the lumen shape is not preserved during the OCT image acquisition making the quantification of plaque difficult and the visualization of arterial wall ulcerations impossible. Also, the imaging itself is limited to the length of the PTCA balloon. Besides that, by suddenly inflating the balloon blood could be trapped between its surface and the luminal tissue further obstructing imaging. The last but not the least is the concern about the possible damage occurring due to the contact pressure applied by the PTCA balloon on the arterial wall. This pressure could damage the endothelium layer and this could lead later on to the development of stenosis.

In order to avoid and/or to minimize the aforementioned problems, OCT imaging through a slab of blood or blood-saline flowing between the probe head and the arterial wall should be taken into consideration.

2. EXPERIMENTAL SETUP AND DATA ACQUISITION

A super-luminescent SLD-571-HP diode is the low-coherence light source in the OCT system used for acquiring images of flowing blood-saline mixtures. This diode emits light at a wavelength of 1300 nm. Its measured coherence length is $\sim 10\text{ }\mu\text{m}$. The spectral region around the wavelength emitted by this source has the potential of becoming important for a number of bio-photonics applications because it is characterized by a lower degree of absorption and scattering in biological tissues in comparison to visible and shorter near-infrared wavelengths²⁻⁴.

The low-coherence light emitted by the diode is guided through single-mode fibers terminated with collimating lenses at the exits of both arms of the interferometer. In the reference arm, a rapid scanning optical delay line with a constant velocity of 655 mm/s modulates the optical path length. A lens with a 48 mm focal distance and a diameter of 14.5 mm was located near the exit of the sample-arm optical fiber to focus the collimated probing beam on the sample. This lens focuses the collimated probing beam to a diameter of $\sim 30\text{ }\mu\text{m}$ at the focus and to an estimated focal depth of $\sim 2\text{ mm}$.

In order to prepare the researched samples, fresh porcine blood is acquired from a local abattoir immediately after sacrifice. Before starting the experiment, the volume fraction of cells in the entire blood volume, i.e. the blood haematocrit, is measured to be 45%. During the protocol, the blood is mixed with 0.9% sterile sodium chloride isotonic solution (saline). Measurements are performed on blood-saline mixtures with blood concentrations ranging from 20% to 100%. In order to avoid coagulation, 2mL of heparin is mixed with blood immediately after blood collection and then added at a rate of 1mL at 1-hour intervals for the remainder of the protocol. The blood is kept at room temperature for the duration of the experiment. In total, the protocol duration was three hours.

During the OCT image acquisition, a 749 Cole Parmer series dual infusion pump is used to pump blood-saline mixtures through a system of flow cells at a constant flow rate of 2 mL/min ($2000\text{ mm}^3/\text{minute}$). The geometry of a flow-cell and the way it is integrated into the flow system, is shown in figure 2. The flow-through cell system is set horizontally with the OCT probe beam coming from the top. This setting prevents any gravitational-induced changes in the flow rate.

In the following analysis the term “*cell width*” will be equated with the thickness of the blood-saline slab passing through a cell. This quantity is marked with “*t*” in figure 2. Flow cells of two different widths, 2-mm and 0.2-mm, with corresponding volumes of 640 mm^3 and 64 mm^3 respectively, are used in this experiment. This arrangement is used in order to characterize the blood-saline mixtures and their corresponding OCT signal acquired during flow through channels with various dimensions. The inlet-outlet distance for both cells (i.e. the length of the flow channel) is 40 mm. The height of each cell (i.e. the dimension that is perpendicular on the page plane as seen from figure 2) is 8 mm. The cells are connected in series so that the blood-saline mixtures can pass from one to the other. Taking into account the geometrical dimensions of the cells together with the set flow rate, the average flow velocities can be calculated to attain the values of 2 mm/s and 20mm/s across the sections of the 2-mm and the 0.2-mm wide cells.

As also shown in figure 2, the OCT beam was tilted at a small, $\sim 5^\circ$, angle relative to the cell surface to ensure that only light scattered or reflected by blood constituents is detected and the bright specular reflections that occur at the interfaces with glass are eliminated from detection. Eliminating these intense specular reflections avoids detector saturation and allows for higher intensities of the source to be used resulting in a detection with higher signal-to-noise ratio. During image acquisition, the OCT probe beam is positioned so that it has roughly the same diameter along the entire depth being probed, ~ 1.5 mm. The maximum depth probed along an A-scan within the turbid fluid is considered to be the location where the magnitude of the recorded signal is 20% higher than the noise floor. Bracketing this depth within the depth of focus and centering it at the beam waist minimizes the impact of beam divergence on the intensity of the detected OCT signal.

Fig. 2. Flow cell at the end of the sample arm of the OCT system. Tilting the cell eliminates specular reflections from the glass/fluid interfaces from being recorded. Only light scattered by blood cells (marked with grey) is detected.

A computer-controlled mechanical stage ensures the displacement of the probing beam from one cell to the other at the end of each image acquisition process. This ensures that the probing beam is always brought back at the same positions where previous images have been collected. A computer controlled mechanical stage delivers high precision in repositioning the beam from one cell to the other. In this way experimental artifacts that could appear in the OCT images due to possible non-uniformities existent in the glass material or due to cell tilting are avoided.

Examples of OCT images of a blood-saline mixture flowing through both cells are provided elsewhere ⁵. As the flux of probing light penetrates deeper inside the blood-saline mixture, the light is reflected, scattered and absorbed by various cellular aggregates and fluidic components. It has been widely reported in the literature that the effect of optical absorption due to blood components is negligible compared to scattering in the near-infrared spectral domain ⁶⁻⁸. Therefore the only process affecting the recorded OCT signal taken into consideration in this study is the scattering of light by blood cells.

OCT images of turbid environments present themselves with a spotted appearance due to coherent speckle, an unavoidable feature of imaging methods based on the interference of coherent waves. A portion of the speckle is constituted from the signal-carrying speckle generated by light un-deviated from its ballistic path that undergoes only a single back-reflecting event that also guides it toward detection. This signal is directly related to the morphology of the studied sample. Another part of the speckle recorded in an OCT image is generated by light flux detected after multiple interactions with scattering centers. The latter speckle has the effect of reducing the correspondence between the intensity variations recorded across OCT images and the physical distribution of scattering centers. There is no method to separate or distinguish “good” speckle from “bad” one. All that can be done is to use various techniques to alleviate the effect that speckle detected after multiple interactions has on the OCT signal. An efficient method to diminish

speckle noise is to compound (add) OCT images of the same sample with coherent speckle that is uncorrelated from one image to another. Uncorrelated speckle is obtained by modifying the acquisition conditions from image to image. Some procedures used to decrease the correlation between the multiple-scattered components of the speckle from image to image are described in other publications^{9, 10}. Compounding independent speckle patterns in order to quench the coherent noise is a method that works not only for whole OCT images but also for A-scans^{5, 11, 12}.

4. RESULTS AND DISCUSSION

Smooth profiles like the ones shown on a logarithmic scale in figure 3 are obtained by compounding a high number (one thousand in this case) of A-scans that are part from the same OCT image. Compounded profiles corresponding to blood-saline mixtures with blood concentrations of 100%, 60% and 25% are shown in the figure. With the speckle noise strongly quenched by compounding, the profiles reveal the general characteristics of OCT signal propagating through blood-saline mixtures. The x-axis represents the physical distance traveled.

Fig.3. Three profiles (corresponding to blood concentrations of 100%, 60% and 20%) obtained after compounding 1000 A-scans. Regions with different attenuation rates of the OCT signal with respect to the travel distance are easily identified along the profiles corresponding to blood concentrations of 100% and 60%. The profile corresponding to the 25% blood concentration does not show a change of its slope. Beyond a travel distance of 0.6 mm the tail of the signal intensity corresponding to 100% blood is located between the other two profiles.

A comprehensive characterization of profiles like the ones shown in figure 3 has been done somewhere else¹³. Briefly, changes in the attenuation rate of the OCT signal with depth (i.e. in the profile slope) can be observed for all studied profiles starting from a blood concentration of 25% up to 100%. The exception is the profile corresponding to the 20% blood concentration, which can be fit with an exponential all the way to the noise floor. There are two regions separated by a transition zone that can be identified along the profiles. In the first region, starting from the peak of the recorded OCT signal, all profiles decrease with roughly similar attenuation coefficients. It is obvious in figure 3 that the attenuation coefficients for the 100%, 60% and 20% profiles are roughly similar up to a depth of ~0.6 mm. This fact was

also verified by numerically fitting the profiles with exponential functions up to the transition zone in the manner indicated also in figure 3. The weak dependence on blood concentration of the attenuation coefficients in this region suggests that the recorded signal is a balanced mixture between light that was back-reflected only once before detection and light that was detected after undergoing multiple interactions with the probed environment.

A transition zone is signaled by an inflexion point occurring around a depth of 0.6 mm in all profiles. A second region with different properties starts behind the transition zone. Along this region, the attenuation with depth occurs slower than in the first region. OCT profiles with similar characteristics, attributable to a dominant presence of multiple scattered components of the signal, have been also generated using the extended Huygens-Fresnel principle^{14, 15}. In addition, Monte Carlo simulations of OCT scans from turbid environments show the transition zone followed by a similar decrease in attenuation along segments that correspond to longer travel distances^{13, 16}.

This variation of the attenuation coefficient along the compounded profiles in second region of the compounded profiles is related to the presence of signal that is detected after undergoing multiple scattering within the blood-saline mixture. Figure 3 is an indication that the amount of recorded multiple scattered signal from the segment located behind the inflexion point is dependent on blood concentration in a rather complex manner. An analysis of all compounded profiles reveals that as blood concentration increases from 20% to 60%, the OCT signal attenuation with depth in this region decreases. This indicates an increase in the detection of multiple scattered OCT signal as blood concentration increases. A qualitative explanation could be provided by observing that for lower blood concentrations the interactions with scattering centers become scarcer and scattered light has to travel longer distances between two consecutive interactions. Therefore a greater portion from the multiple-scattered flux accrues longer travel distances, distances that could fall beyond the limitations imposed by either the field of view or by the coherence gate of the OCT system, and end up not being recorded by the interference-based detection.

A higher degree of randomization in the propagation direction of the light flux leads to the detection of a diminished multiple-scattered contribution at blood concentrations higher than 60%. This translates into a subsequent increase in the attenuation of the signal beyond the transition zone at blood concentrations higher than 60%. In these cases, the high concentration of blood cells generates an intensive scattering process that impedes part of the flux with too much scattering history from reaching the OCT detection. For example, this is the reason why in figure 3, after the transition zone, the profile corresponding to 100% blood declines faster than the one generated from the mixture with 60% blood.

To better understand the relation between the flow properties of blood-saline mixtures and their corresponding OCT profiles, the analysis is switched on data collected from the cell with the width of 0.2 mm. Compounded profiles corresponding to OCT images of several blood-saline mixtures flowing through the 0.2 mm cell are shown in figure 4. Detailed in this figure are profiles corresponding to blood concentrations ranging from 100%, 90%, 80%, 70%, 60% and 45%. The x-axis represents the optical distance of propagation for the recorded OCT signal and the conversion factor is 1000 pixels for an equivalent distance of 0.16 mm.

A general characteristic of the profiles in figure 4 is that they all increase reaching a maximum within about 100 μm from the glass/mixture interface (i.e. the point where the probing beam enters the mixture). This happens for all the studied blood-saline mixtures, including the ones that for the sake of plot clarity are not contained in figure 4. Worth noticing is the fact that the maximum intensity recorded is directly proportional to blood concentration. Meanwhile the location of the maximum intensity is independent of blood concentration. Although the ascending region of the profiles extends for only several tens of micrometers the recorded signal increase is very gradual and can be explained by the migration of blood cells away from the interfaces and toward the axis of the flow channel. This redistribution of blood cells has been attributed to flow-induced shear stress¹⁷. Therefore, along the ascending part of the profile, the light flux encounters more and more scattering centers as it propagates deeper into the solution, the number of interaction events with the cellular ensemble increases and so does the amount of signal detected by the OCT system. In addition, this portion of the profile should be dominated by OCT signal generated by ballistic backscattered light.

Fig.4. Profiles obtained after compounding 1000 A-scans from OCT images acquired from blood-saline mixtures flowing in the 0.2-mm wide cell. The local minimum of the compounded OCT signal observed in the center of the flow channel is a consequence of the flow-induced redistribution of blood cells. This local minimum vanishes in mixtures with blood concentrations lower than 50%. The following conversion rule applies for the units along the abscissa: 1000 pixels = 0.16 mm.

Along some of the compounded profiles shown in figure 4 there is a local minimum that is positioned approximately at the center of the 0.2-mm flow channel. These local minima appear along the profiles of blood-saline mixtures with a concentration of blood greater than 45%. The depth of these dips decreases with blood concentration. Similar local minima along OCT recorded depth-scans have been also observed when flowing blood-saline mixtures have been investigated with Doppler OCT. The decrease of the OCT signal in the middle of the flow channel at certain blood concentrations and average flow velocities have been also attributed to the redistribution of blood cells due to flow-induced shear stress¹⁷. Under the effect of shear stress, starting at an average flow velocity of 20 mm/s and for blood concentrations higher than 45%, a region with a low density of blood cells forms at the center of a narrow flow channel. In this case, the OCT beam is scattered less because fewer scattering centers are present and this translates into less OCT signal recorded near the center of the flow channel. Once the blood concentration decreases below 50%, the compounded profiles exhibit the expected behavior with the intensity decreasing monotonically with depth and lacking any local minimum. At low concentrations the shear stress-induced effects diminish and, with the exception of the zones found within several tens of μm 's from the glass/mixture interfaces, the blood cells are uniformly distributed across the flow channel.

Meanwhile, the data collected from the 2-mm flow cell does not show a local minimum along any of the profiles investigated. As the cells are connected, an average flow velocity of 20 mm/s in the narrower cell becomes ten times smaller in the wider cell thus insufficient to generate enough shear-stress capable to redistribute the blood cell ensemble.

The magnitude of the flow-induced shear-stress determines if a fluid flow can be characterized as laminar or turbulent. In the context of blood circulation, the difference between laminar and turbulent flow impacts the dynamics of blood cells. When shear stress is present it generates laminar friction and the red blood cells tend to align themselves with the biconcave surfaces on average parallel to the direction of flow. This situation is conceptually described by the left side of figure 5. From the perspective of OCT analysis, the cells are facing the incoming probing beam with a certain degree of spatial order therefore increasing the anisotropy of the scattering process and introducing a preferential direction of scatter. At lower blood cell concentrations shear stress decreases and flow becomes less laminar, process that randomizes the spatial orientation of individual blood cells as conceptually represented on the right side of figure 5. In this case blood cells cease to collectively align along an average direction and no longer preferentially expose their biconcave surfaces toward the probing light beam.

Fig.5. Orientation of the blood cell ensemble for two types of flow. At higher blood concentrations, the increase in the shear stress induces laminar flow and the spatial alignment of blood cells with the bi-concave sections oriented on average in a direction favorable to efficient backscattering of light toward detection (left side). As the shear stress decreases with blood cell concentration, the flow becomes turbulent, the spatial orientation of cells is randomized and the coherent back-scattering toward the OCT detection system becomes less efficient (right side).

Being able to determine the flow regime is important because it is a state of the system that is directly determined by the flow-induced shear stress. It has been established already that shear stress plays an important role in vascular physiological and pathophysiological responses by acting on the endothelial layer. Its role is to trigger signals responsible for vessel dilatation and for the production of vasoactive substances: nitric oxide and prostacyclin^{18, 19}. In addition, it has been shown that plaque accumulation occurs in regions of turbulent flow and its presence perturbs the flow-induced shear stress on the surrounding vessel walls^{20, 21}. Therefore, determining the type of flow in arteries through time-domain OCT and relating it to the shear stress could provide a marker for various clinical conditions that develop along the arteries.

CONCLUSIONS

A study of the scattering properties in flowing blood-saline solutions with blood concentrations ranging from 20% to 100% is presented in this paper. The flow occurs through an interconnected system of cells with the flow channel in one cell being 2 mm wide while the channel width in the second cell is 0.2 mm. The experimental data is acquired by OCT imaging at a wavelength of 1300 nm. A compounded profile showing the dependence on the distance traveled within the mixtures of the recorded signal intensity is obtained for each blood-saline mixture by compounding one thousand A-scans from the corresponding OCT image. The attenuation coefficient with depth of the OCT signal in the first 0.6 mm along the compounded profiles starting from the point of maximum signal is independent of blood concentration. This property indicates a balanced mixture between single- and multiple-scattered OCT signals. Meanwhile, OCT signal recorded from depths greater than 0.6 mm is dominated by multiple-scattered light flux. Interestingly, the amount of multiple scattered signal recorded for the blood-saline mixture with a 20% blood concentration is similar to the one recorded in the case of the mixture containing 100% blood. The dependence on blood concentration of the amount of multiple scattered signal recorded resembles a parabola with its maximum located at 60% blood concentration.

The analysis of a narrow region, located within the first 200 μm from the point where the probing beam enters the fluid is also performed by using compounded profiles corresponding to OCT images acquired from the flow through the 0.2-mm channel. Here the signal is dominated by the ballistic single-scattered component. Multiple scattering is minimal so the recorded OCT signal originates from light interactions with individual blood cells. Information about the flow regime, i.e. laminar or turbulent, is imbedded in this region of the compounded OCT profiles.

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