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Short communication

Quantification of thrombus formation in malapposed coronary stents deployed *in vitro* through imaging analysis

Jonathan Brown [a,*], Caroline C. O'Brien [a], Augusto C. Lopes [a], Kumaran Kolandaivelu [a,b,1], Elazer R. Edelman [a,b,1]

[a] Institute of Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA
[b] Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Stent thrombosis is a major complication of coronary stent and scaffold intervention. While often unanticipated and lethal, its incidence is low making mechanistic examination difficult through clinical investigation alone. Thus, throughout the technological advancement of these devices, experimental models have been indispensable in furthering our understanding of device safety and efficacy. As we refine model systems to gain deeper insight into adverse events, it is equally important that we continue to refine our measurement methods. We used digital signal processing in an established flow loop model to investigate local flow effects due to geometric stent features and ultimately its relationship to thrombus formation. A new metric of clot distribution on each microCT slice termed normalized clot ratio was defined to quantify this distribution. Three under expanded coronary bare-metal stents were run in a flow loop model to induce clotting. Samples were then scanned in a MicroCT machine and digital signal processing methods applied to analyze geometric stent conformation and spatial clot formation. Results indicated that geometric stent features play a significant role in clotting patterns, specifically at a frequency of 0.6225 Hz corresponding to a geometric distance of 1.606 mm. The magnitude-squared coherence between geometric features and clot distribution was greater than 0.4 in all samples. In stents with poor wall apposition, ranging from 0.27 mm to 0.64 mm maximum malapposition (model of real-world heterogeneity), clots were found to have formed in between stent struts rather than directly adjacent to struts. This early work shows how the combination of tools in the areas of image processing and signal analysis can advance the resolution at which we are able to define thrombotic mechanisms in *in vitro* models, and ultimately, gain further insight into clinical performance.

1. Introduction

Each year over 500,000 coronary stents are implanted in the US as a treatment for the most common type of heart disease, coronary artery disease (Go et al., 2014). A significant shortcoming of stent implantation is stent thrombosis (ST), the formation of a thrombotic material, which can ultimately lead to post-intervention vessel occlusion. In the acute scenario, ST has been shown to occur in up to 1.4% of stent implantations (Aoki et al., 2009) and even as high as 5% in certain patient subpopulations such as ST-segment elevation myocardial infarction (Heestermans et al., 2010). Furthermore, ST has continued as an issue throughout the historical development of stents even in the newest class of biorebsorbable stents. These challenges are not only limited to stents but also extend into the newest class of stent-based heart valves used in transcatheter aortic valve replacements. (Capodanno et al., 2015; Makkar et al., 2015; Wykrzykowska et al., 2017) Historically benchtop flow systems (Kolandaivelu and Edelman, 2002) have been used to examine the formation of clot under hemodynamic conditions similar to those found in the coronary arteries. Such benchtop settings offer enhanced ability to investigate a wide range of variables such as device design, deployment, and environmental conditions that have the propensity to lead to acute stent thrombosis. Stent-vessel interaction of complex systems (Garasic et al., 2000; Gundert et al., 2012; Hara et al., 2006; Rogers and Edelman, 1995) such as these further complicates study. Often, numeric quantification of thrombosis within these benchtop setups are limited by global assays that represent integrated phenomenon (i.e. biochemical) rather than the local processes that define how clotting originates

* Corresponding author at: 77 Massachusetts Ave, E25-442, Cambridge, MA 02139, USA.
E-mail address: jbrown@mit.edu (J. Brown).
[1] Co-last authors.

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and progresses (Gunning et al., 2014; Sinn et al., 2011). To increase the specificity and resolution of benchtop models a poor stent-wall apposition model was used as a model system. While further factors, such as plaques and resulting vessel narrowing, can be considered, the controlled stent-wall apposition model was utilized as a way to increase heterogeneity among samples and better test the sensitivity of a new method of quantitative spatial clot quantification. Using this model as a platform, we propose a method of spatial quantification of clot in *in vitro* flow loops through image-analysis and signal processing. We report our early findings from this study on a sub-sample of three stents.

2. Methods

2.1. Experimental set-up

We constructed *in vitro* flow loops mounted in parallel (Fig. 2), using an established flow loop model (Kolandaivelu et al., 2011). Three closed-cell, commercially available coronary bare metal stents (BMS; 3.0 × 18 mm) were used. An under-expansion model of the stents was induced via the fitting of Polyethylene tubing around the middle portion of angioplasty balloon catheter prior to mounting of the stent onto the balloon. Each stent was crimped (Machine Solutions, Inc., AZ) onto a modified balloon catheter delivery system setup previously employed (O'Brien et al., 2016) and deployed into silicone tubing. This setup created ranges of malapposition that reflect clinically reported ranges (Gutiérrez-Chico et al., 2012). A modified balloon catheter system was used to create artificial lack of stent wall-apposition or malapposition of the stent in a "dog-bone" shape (Fig. 1B). Flow loop/stent and blood draw sample preparation is described in detail in Appendix A. Loops were then filled with ~2.5 ml of blood collected from healthy human subjects under established IRB protocols, rotor mounted and run for 5 min at 37C to allow adequate time for formation of thrombosis. After each run was completed, samples were washed with a tyrode solution and infused with a 4%

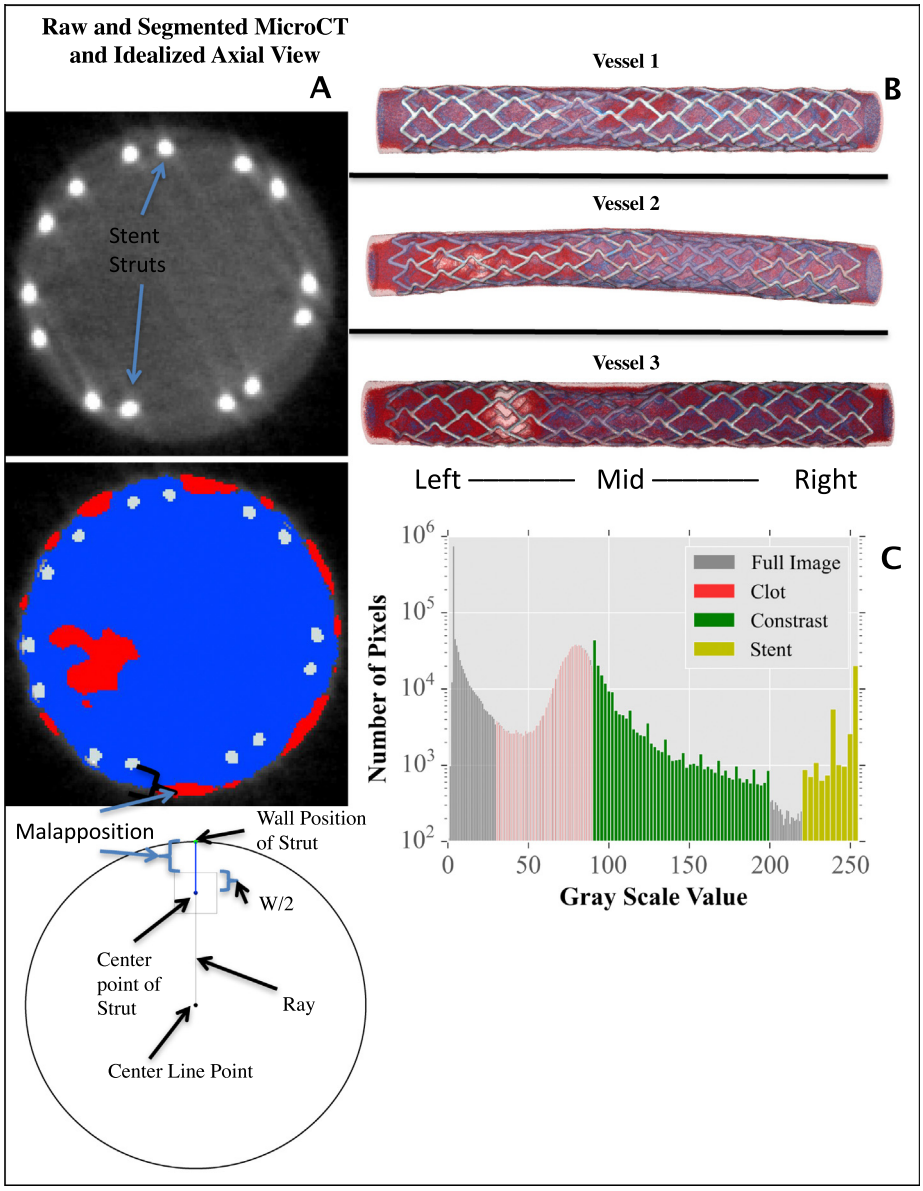

Fig. 1. MicroCT slice of malapposed stent and corresponding slice segmentation with red, blue, and silver representing clot, contrast and stent struts. A schematic diagram is shown displaying how malapposition of each stent struts was computed (A), a 3D reconstruction of each sample is shown (B). Calibration scan histogram (C) used to determine ranges of Hounsfield units used for segmentation of MicroCT slices into the masks of clot, contrast, and stent. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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