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Research Article

Wound-Healing in the Saphenous Vein Coronary Bypass Graft in the Canine Model: Endothelial Cell Loss, Platelet Thrombus Formation, its Inhibition with Aspirin-Persantine Therapy and Cholesterol Influx in the Acute and Chronic Phase

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Abstract

Radiolabeling of the platelets with Indium-111 tropolone and the LDL-C and HDL-C lipoproteins with Iodine-131 and Iodine-125 provided us a with a quantitative method of measurement of platelet deposition and uptake of Iodine-131and C-14 labeled cholesterol, LDL-C and HDL-C on all segments of coronary artery bypass graft in the acute and chronic phase in the canine model. We sampled the thrombogenicity and cholesterol uptake for a 24-hours exposure/interaction time of tracers after intravenous injection, post-CABG implantation at 1, 3, 7, 30, 90 and 365 days. Most of the reactivities of components of CABG or components of cardiovascular prostheses are passivated after absorption of albumin, and coverage with fibroblasts and/or partially with endothelial cells. Although we calculated the percent of injected dose on CABG segments, the algebraic equation for the calculation of Regional Platelet Density (RPD) revolutionized our measurement methods. RPD was higher at the proximal and distal anastomoses than the mid-section of CABG. We also evaluated the role of endothelial cell loss by SEM technique during the harvesting and post-suturing of saphenous vein graft on the platelet deposition on the injured intima in the acute and chronic phase and their inhibition using Persantine before CABG and Aspirin after surgery. As the SEM studies demonstrated the complete endothelialization of the CABG at 90 days, there was no difference in regional platelet density between the treated and control animals. Platelet consumption on the components of the heart-lung machine and platelet fragmentation by the roller or centrifugal pump along with the hollow-fiber oxygenator perturb the functional platelet pool during the cardiopulmonary bypass procedure. Using several control animals and separate cardiopulmonary bypass experiments, we also measured the number of platelets consumed in the wound-healing process, about 15-20% of injected dose and components of the heart-lung machine, which declined significantly during two decades of our measurements from 25% to 0.25%. These clinically relevant issues that transform the CABG into venosclerosis were reviewed by critical analysis of all segments of CABG in a comprehensive manner.

Keywords: Coronary artery bypass graft; Dual-antiplatelet therapy; Endothelial cell loss from saphenous vein; Quantitation of regional platelet thrombus; Thrombus inhibition with aspirin-Persantine therapy; Uptake of C-14 and I-131 cholesterol and LDL-C and HDL-C on CABG

Introduction

After I joined Mayo Clinic as a staff consultant and Director of Radioactive Drug Laboratory in Nuclear Medicine Division, I had a surprise visit from a young cardiologist, Dr. Valentin Fuster. Valentin congratulated me for my synthesis of Technetium-99m tetracyclines and their evaluation in the "Dead Cell model" and noninvasive imaging of myocardial infarct in canine model and Boston patients [1-3]. Valentin mentioned that there is no such method available for the measurement of platelet thrombus in the coronary artery-the culprit for inducing MI. He offered me his million-dollar grant, if I wanted to work on the thrombus imaging and measurements. In mid-1970, (25-30) % of distal anastomosis of CABG was occluded with limited choice for the patients for recuperation with another vessel. We wanted to maintain CABG patency in the canine model with dual platelet-inhibitors: aspirin post CABG and Persantine, before surgery.

After three years of measurements using radioactivity ratios of control saphenous vein and CABG segments and percent of injected dose, I wanted to quantitate the regional platelet density, a universal and an absolute parameter for the measurement of thrombogenicity in 1979 and made the simple Algebraic equation [4-7] from three unknown variable parameters and three equations. I also kept my promise to my visiting mother from Kolkata, India, to solve the thrombus puzzle and use minimal number of cows for evaluation of the calcification of platelet thrombus in the tissue heart valves [8-15]. Last year, 2019, was the 40th anniversary and I decided to write a comprehensive book on the number one killer, measuring and imaging the platelet thrombi and emboli [16]. With the assistance from Dr. JS Robertson, we did the estimate of human dosimetry study [17,18]

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and I wrote an IND to FDA for clinical investigations on the thrombogenicity of synthetic vascular grafts [13,19-22] and mechanical heart valves and the effect of multiple platelet-inhibitors, used today in clinical practice.

Since the original clinical study in 1968 by Dr. Rene Favaloro at Cleveland Clinic, the saphenous vein Coronary Artery Bypass Graft (CABG) provides a unique conduit for a second chance of coronary circulation [23] after diffuse plaque occlusion and myocardial infarction. Unlike the focal occlusion, where the angioplasty followed by stenting played a predominant role, for the patients suffering from the multivessel diffuse coronary occlusions, CABG is now perfected and is an acceptable procedure with low risk of bleeding, thrombosis and infection [9]. I summarized the critical steps of rapid interventions by the radiologists or cardiologists as dictated by the 5-hour narrow window of myocardial preservation after coronary plaque rupture that results in coronary occlusion or focal occlusion and their recanalization by angioplasty/stenting or CABG for multi-vessel diffuse occlusions (Figure 1).

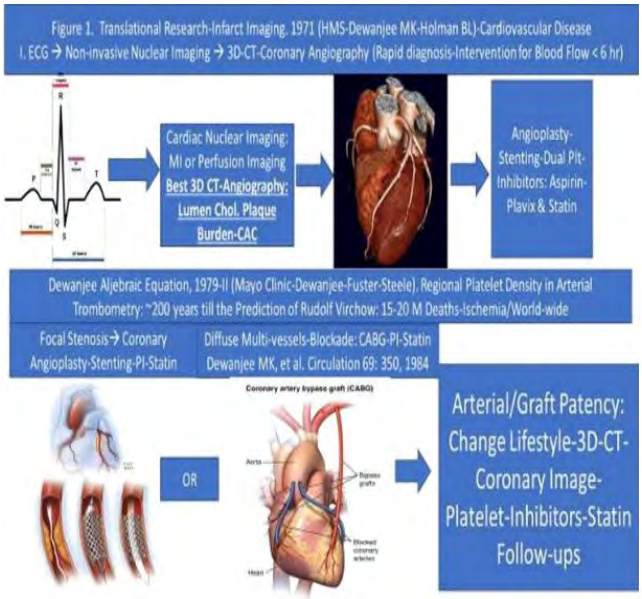

Figure 1: Translation research-infarct imaging.

The cardiopulmonary bypass procedure perturbs the platelet-kinetics and thrombosis on CABG segments. We carried out separate control experiments on the status of platelet consumption and thrombus formation on the components of the heart-lung machine [14,15,19,24-30]. In addition, the hollow-fiber oxygenator also induces platelet fragmentation reducing their potential for additional thrombus formation. However, as new generation of platelets pour out of the bone marrow, these activated platelets form thrombi on all wound surfaces of major vessels and the sites of thoracic incisions. We also estimated that ~15-20% of platelets were consumed by the wound-healing process in the canine model [5,6,24,25].

The alternative Synthetic blood Vessels (SVGs) are thrombogenic and smaller vessels (<4 mm ID) occlude rapidly [11,13,19]. The larger SVGs also formed thrombus at a higher level in the acute phase. However, they also form low-level thrombus even after15 years of grafting in a patient implanted with Dacron graft for aortic aneurysm [5,30]. The aspirin-Persantine therapy reduced the thrombus level about 10-20% on the graft segments mainly in the mid-sections of the graft.

Methods

Aortocoronary bypass grafting in the canine model

An autologous segment of reversed femoral vein was implanted as a bypass-graft from the aorta to the left anterior descending coronary artery in 50 mongrel dogs weighing 18 to 26 kg, using the cardiopulmonary bypass procedure [6,24].

Oral medication with dipyridamole and aspirin

25 dogs were used as control and they were treated only with systemic antibiotics during surgery (Untreated group); the other 25 were given dipyridamole, 55 mg orally, on 2 days preceding surgery and then were given 55 mg of dipyridamole and 325 mg of aspirin at 1 hr after surgery and daily thereafter until they were euthanized with Nembutal.

Autologous platelet labeling with indium-111 tropolone

Autologous platelets of the dogs were labeled with In-111 (tropolone) 3 according to the method of Dewanjee et al., and injected intravenously with 300-400 microcuries [4-6]. The platelet-rich plasma was separated from blood anticoagulated with acid citrate dextrose solution and ACD-saline washed platelets were labeled with the procedure as shown in figure 2.

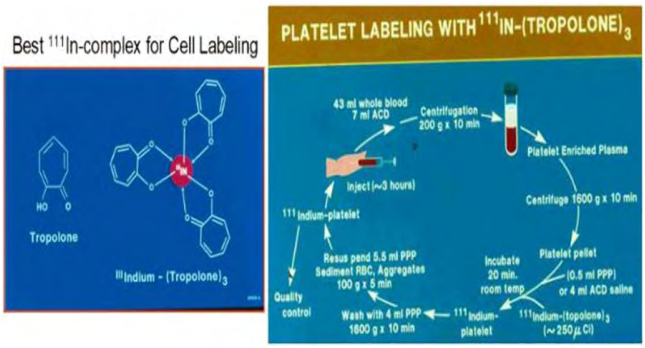

Figure 2: Platelet labeling with the charge-neutral and water soluble in-111 tropolone complex and the optimal method of platelet labeling in ACD-saline or ACD-plasma media. Only purified platelet fraction separated from other cells in whole blood must be incubated with in-tropolone complex.

Radioiodination of canine LDL-C with I-131 and LDL-C with I-125 radionuclide using the IodoGen transfer method

Canine LDL-C and HDL-C particles were separated using the cesium-chloride density-gradient method with an ultracentrifuge (Beckman, Inc.). Stock solutions separated lipoproteins were radiolabeled in a chemical hood using the IodoGen-transfer method and the free radioiodide was separated from radiolabeled lipoproteins by gel-filtration. They were filtered for sterilization and aliquots were kept frozen. After thawing and filtering to remove sediments, they were injected intravenously with C-14 and I-131 tagged cholesterol along with radioiodine-tagged lipoproteins after the CABG procedure. After 24 hours, the dogs were heparinized and euthanized [31-36].

The CABG segments were cut into five segments, weighed and radioactivity was measured in a calibrated gamma-ray spectrometer (Beckman, Inc.). Control saphenous vein were isolated and radioactivity per unit weight was calculated. The ratio of CABG segments was compared to that of control radioactivity. Unlike In-111 tagged platelets, where anastomoses retained higher level of radioactivity, the distribution of I-125 and I-131 tagged lipoproteins on CABG segments were uniform. We plotted the radioactivity ratios of CABG segments to control vein during (Figures 3 and 4) our follow-up period of 1-365 days post CABG [32].

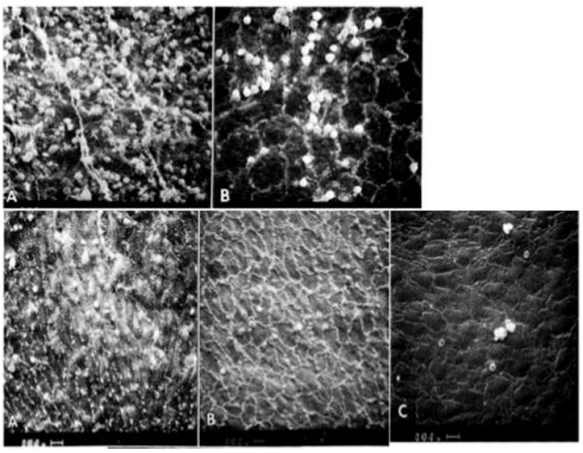

Figure 3: Chronological SEM evaluation to correlate the changes of endothelial loss in the saphenous vein segments of CABG and platelet aggregates from day 1 to and 7 days after grafting and reendothelialization at 30 and 90 days.

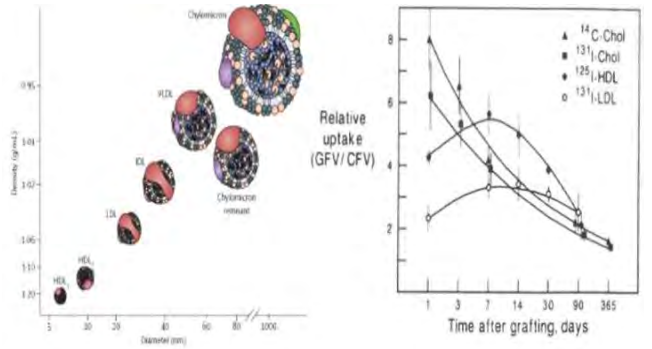

Figure 4: Rapid uniform deposition of iodine-131 and C-14 labeled cholesterol, HDL-C and LD-CL on CABG segments from EC-loss with respect to control saphenous vein graft at 24 hours after IV injection. Statin therapy is essential after CABG due to patchy EC loss and rapid cholesterol, LDL-C and HDL-C influx.

Figure 5 the coronary artery bypass graft model (A). The saphenous vein was harvested and anastomosed to aorta at the proximal end and to coronary artery at the distal end (likely site of occlusion) beyond the ligated site. For mapping the adherent regional thrombi, the graft was carefully dissected from the heparinized and euthanized dog. It was cut into five segments and surface area was measured by placing them on a graph paper. Platelet density was calculated from the Dewanjee equation (B). Level of thrombi was highest at both anastomoses and lower in the midsection of graft [30]. However, the platelet density decreased in both and control and Aspirin-Persantine treated groups always lower in the treated group. During harvesting, patchy areas of vein graft loses endothelial cells as shown by the SEM study. As the patches of injured vein-wall were re-endothelialized, there was no difference of platelet density at 90 days (D). Initially, we also compared radioactivity of the walls of CABG graft and control artery or vein (C). This the first study of long-term follow-up of CABG thrombi and their sequential reduction as the wound-healing progresses on graft intimal surface with and without platelet-inhibitors. Dr. Rene Favaloro, the first surgeon of Argentine, who did the CABG surgery at Cleveland Clinic on November 30, 1967, will be delighted at the high acceptance level of his life-saving intervention all over the world.

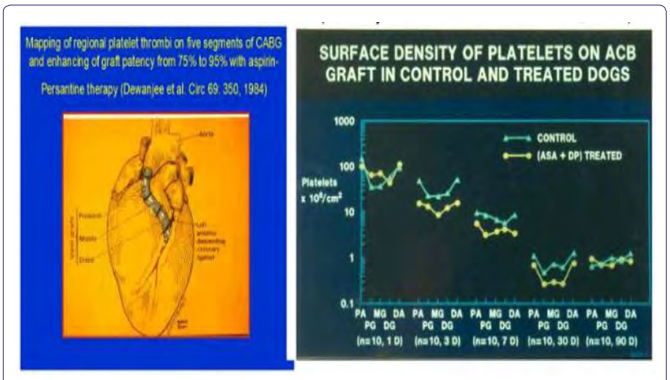

Figure 5: Chronological quantitation of the Regional Platelet Density (RPD: Platelets/cm2), an absolute value derived from the segment-adherent platelet radioactivity in the thrombus from day1 to day 90, highest RPD was always at the proximal and distal anastomoses than the mid-section of CABG. After EC-coverage, there is no difference in RPD value.

Figure 3 SEM of gold-coated CABG segments at day 1, 7, 30 and 90 (Left). Note complete Endothelial Cell (EC) coverage of CABG at day 90. Platelet agonist-induced aggregation (Right). Was reduced was minimized with Aspirin-Persantine administration. After complete EC coverage, no drugs were necessary [10].

Consumption of platelets for surgical repair and wound-healing, Interaction time of blood-device interactions for in vitro and animal studies

Most of the clinicians and surgeons do not have access to data about many issues related to complex cardiovascular surgery, e.g. how much platelets are consumed for Surgical Repair and Wound Healing (SRWH). What biomaterials are less thrombogenic for making a functional device? What is the right dose and when they must be administered not to enhance bleeding complications? Open-heart surgery alone with a heart-lung machine makes it difficult to sort out the issues of surgery vs.

Prosthesis we limited the post-clamping surgical time or hemodialysis time to 90-180 minutes in three animal models in dogs, cows and cows [6,14,24,26]. We also measured the platelet emboli in the cortex of brain and kidneys by measuring the tissue/blood radioactivity ratios. They increased twofold to fourfold after implantation of the mechanical heart valve in the canine model [5,8]. By injecting In-111 tagged platelets before and after this surgery, we measured that (15-20) % of total platelets are consumed for SRWH in the canine model, which are not easily extrapolated to patients due to higher platelet thrombogenicity. In most of the studies, we try to simulate the

experimental studies to mimic the clinical parameters with similar drug-regimen [5,14].

Short blood-biomaterial interaction time (less than 24 hours) does not provide reproducible data with acceptable standard deviations [11-13]. We limited the duration of in vitro experiments using the flow-loop to one to three hours [26]. Longer over-night run resulted in the buildup of pressure and rupture of circuit and splashing of radioactive precious human blood! For the patients, we only could gather semi-quantitative platelet-deposition data due to slower clearance of in-111 platelet radioactivity [13,29] except in the splenomegaly patient, which showed of acquisition of platelet pool of 68% in the spleen [37]. Measurements before and after surgery with a calibrated gamma camera provided the best data for the attenuation correction of the 171- and 247-keV gamma-ray photons [17,37].

Kinetics of thrombosis and healing are two to three times faster in the dog model as we studied the platelet reactivity with a hemodialyzer in the flow-loop with both platelet and fibrinogen tracers respectively [5]. Canine platelets are three-times more thrombogenic than human platelets. Porcine platelets are slightly more thrombogenic than human platelets and a lot of other cardiovascular functions and platelet pharmacology is closer to that of human health. However, no such difference was found for the deposition of fibrinogen for all three species we measured. From the I-125 tagged fibrinogen, we could estimate the mixed amount of fibrinogen along with the corresponding fibrin fragments (Figure 6). For the healing of human saphenous vein-coronary bypass graft, it might take four to six months, while it is two-to-three months in the canine model. The vascular surgeons also learned a lesson of vein harvesting in a gentle manner and the preservation in human serum or plasma to preserve the endothelial cells so that graft-healing on all segments would occur, including the wound-healing of complex area of anastomoses could be accelerated.

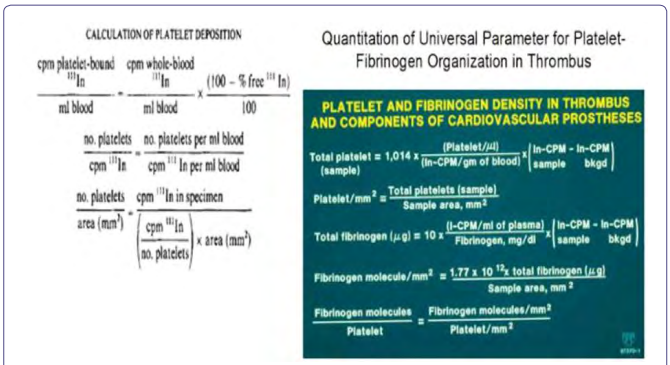

Figure 6: Quantitation of the universal parameter of the regional platelet density (Platelets/cm2), an absolute value derived from the segment-adherent platelet radioactivity and platelet/fibrinogen organization in the stable and unstable thrombus. There is always a 10-15 times excess fibrinogen than the fibrinogen receptor for each platelet.

Results

This is an integrated review article from our previous scattered publications in Circulation, Journal of Nuclear Medicine, radiolabeling of autologous platelets with freshly prepared In-111 tropolone, separation and labeling of canine and lipoproteins with the radionuclides of Iodine-125 and Iodine-131 and Thrombosis Research. But we never covered the EC loss, thrombosis and lipid uptake simultaneously that modified vein-graft transformation in an arterial high-pressure environment. We carried out the SEM studies for the evaluation of EC-repair for the reduction of platelet-thrombus with the platelet-inhibitors before and after CABG surgery. We also carried the SEM and TEM studies after pressure-perfusion of CABG. They showed us the sparse SMC proliferation and their scattered distribution in the media. The repair in the mid-section of CABG is much simpler. There was no area of intimal proliferation in the intima. The CABG thickened in all segments including the area of distal narrow anastomoses. About 4-6% of graft was occluded with platelet thrombus and with proliferation of smooth muscle cells and occasional fibroblasts. However, there was a narrower channel for blood flow in the patented anastomoses [38]. Figure 7 demonstrated the dynamics of platelet thrombus on synthetic vascular graft at 4 hours, day 3 and day 5 after the implantation of Dacron graft in pediatric patients born with pulmonary atresia.

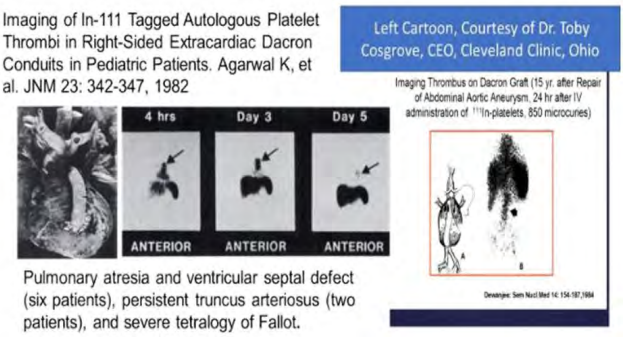

Figure 7: Thrombus dynamics on a Dacron conduit at 4 hours, day 3 and day 5 after intravenous injection in-111 labeled platelets in a pediatric patient at Mayo Clinic (Left). Platelet deposition after 15 years of implanted a Dacron graft for the repair of abdominal aortic aneurysm (Right).

Discussion

Therapeutic mechanisms of aspirin and dipyridamole Aspirin inhibit the formation of the aggregating agents, e.g. prostaglandins G2 and H2 and thromboxane A2 from arachidonic acid, by acetylation of platelet cyclooxygenase. Its inhibition of platelet cyclooxygenase persists about three times longer than the inhibition of endothelial cyclooxygenase. Prostacyclin synthesis by the endothelial cell is less affected by aspirin. The prostacyclin production in the vascular endothelium is compromised by the partial de-endothelialization of the edematous vessel wall. Dipyridamole, an inhibitor of cyclic AMP phosphodiesterase, increases cyclic AMP in platelets and suppresses platelet activation [5,9,13,30,39-41].

Study methods

Higher platelet deposition at the anastomotic sites was observed by light microscopic and electron microscopic techniques. However, it is inadequate for the calculation of the number of platelets per unit of surface area. We also estimated that about (20-30) % of the platelets are consumed in the bubble oxygenator and another (15-20) % are consumed in repair of blood vessels [6,24-26]. With the novel design of the hollow-fiber oxygenators, the adherent thrombus decreased to less than 0.25% [25].

Electron microscopic techniques are useful in demonstrating the patchy de-endothelialization and the adherence of single and multi-platelet aggregates to deendothelialized surface. However,

multiple manipulations during specimen preparation, e.g. pressure-perfusion, fixation, gold-coating, resulted in the loss of surface-adherent platelets and underestimation of platelet thrombosis. The radioactivity-measurement method is ideal for studying platelet thrombosis in the arterial system as well as for evaluation of platelet-inhibitors in models of bilateral femoral-graft implants [5]. Considering the restrictions on the use of radionuclides in large animals, these procedures will not be repeated [5,7,30] for the clarification of the role of EC loss, platelet thrombus formation, cholesterol buildup and calcification of platelet thrombus.

Since thrombosis with the platelet-fibrin mesh occurs on the injured surface or surfaces of thrombogenic biomaterials, the normalized value of regional platelet density, expressed as number of adherent platelets per unit surface area, is the best method of measurement. We carried out these measurements in a large numbers of animals and more than 200 human subjects implanted with thrombogenic Dacron polyester (polyethylene terephthalate) and GoreTex (Teflon) grafts. The tracer technique is five to 100 times more sensitive [11,14,15,29].

Clinical implications of the quantitative measurements

In managing the CABG patients, it is essential to prevent thrombotic graft occlusion without inducing excessive postoperative bleeding. Multiple parameters, e.g. side effects of drugs, variability of intolerance, drug cost and compliance of patients to drug therapy, complicate decisions as to how long the treatment should be continued. Our animal studies suggest a relatively short therapy-period for CABG is necessary. However, their healthy coronary arteries and healthy veins might benefit less from prolonged inhibition of platelet deposition than do the diseased veins and coronary arteries of man [9,28]. In patient pool having an atherogenic diet, adverse lipoprotein profile, rate of slower reendothelialization or recurrent endothelial damage, prolonged platelet-inhibitor therapy is justified. Considering the small lumen at the distal anastomoses, the inhibitors of platelet adhesion must be present in this critical early period [7,32].

The advantage of the tracer technique is that we estimated the total platelet deposition over a wider surface area [5,14,15], whereas the electron microscope reveals only the superficial layer of platelets on a smaller selected area and underestimates the total number of platelets adhering. In addition, we used the platelet swiping method to study the effect of stenotic versus aneurysm configuration without destroying the well-designed plexiglass tube [42].

Acknowledgements

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