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Research Communication

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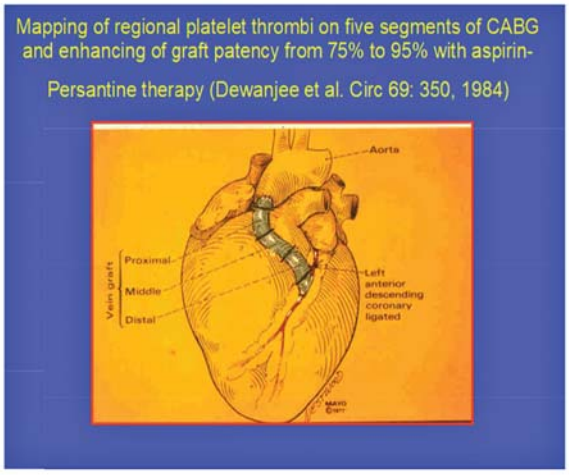
Multiple Phases of the Platelet Recruitment after Interventional Injury in Angioplasty and Coronary Artery bypass Graft Surgery

***Abstract*: In the absence of any critical parameter of thrombogenicity after a thrombotic heart attack and stroke, we developed the first parameter of regional platelet density (RPD) in the adherent platelet thrombus (APT) in 1978. From the platelet counts per ml of radioactive blood and area of injury and APT radioactivity, we developed an algebraic equation for converting the APT into number of platelets and normalized this value per unit area, an ideal universal parameter. The rate of reduction of platelet recruitment (RPR) is an index of progression of wound healing after an interventional injury and effectiveness of antiplatelet drug therapy in the animal models. After the analysis of regional platelet density (RPD: millions of platelets/cm^2) in an adherent thrombus after coronary artery bypass surgery (CABG) and angioplasty for myocardial reperfusion, we observed that the RPR occurs in two to three phases with definite half-life values. The areas of injury from angioplasty and the anastomosis in CABG surgery are the specific sites for platelet recruitments. The regional platelet density (RPD) at proximal and distal anastomoses (DA, PA) showed three values of declining radioactivity with half-lives of (30 ± 5), (50 ± 10) and (500 ± 50) hours, a tri-exponential curve. The mid-graft showed a bi-exponential curves with half-life values of (15 ± 5) and (150 ± 15) hours. Due to invasive nature of direct sampling for radioactivity and area, these measurements could not be repeated in human patients.**

Keywords: Thrombotic Closure, Angioplasty and CABG Surgery, Regional Platelet Density, Dual and Triple Phase of PR Vascular Wound Healing (WH)

One of our concerns was the retention of platelet aggregates of different sizes and the process of continuous embolization of radioactive thrombi[1,5,6]. However, I focused on the thrombus-directed dissection of a 2-3 mm segments of proximal and distal anastomoses, which was much lower than the midsection of CABG segments. For angioplasty, we cut the central single segment of highest level of injury and highest level of radioactivity. We observed that at 24 hours, there was some degree of equilibrium, where the retained thrombus-adherent radioactivity had lower values of standard deviation. In vitro flow chamber studies suggested that the SD values were much lower at later periods. Hence, we euthanized the animals for both CABG and angioplasty at 24 hours after injection of 300-400 microcuries of ^{111}In-tagged platelets. Autologous platelets of the dogs were labeled with ^{111}In-(tropolone)$_3$ according to the method of Dewanjee et al.[1,2]. Five animals were included in each group at 24 hours, 3-, 7-, 30- and 90 days for the CABG group. Before euthanasia with intravenous barbiturate solution, we heparinized the animals at 4 mg/kg for the reduction of post-mortem thrombus formation. The harvested CABG angioplasty segment was rinsed with saline from loosely bound radioactivity. The area of five segments was measured by spreading the segments on the graph paper (Keuffel & Esser Co.) with 2-dimensional linear grids. The number of squares and total area were evaluated with a microscope. The gamma counter was adjusted to cover both the 174-keV and 247-keV peaks of the ^{111}In radioisotope. After measuring the radioactivity with a calibrated gamma counter (Beckman Inc. CA), we calculated the radioactivity (counts/min). Using the algebraic equation, we converted the radioactivity into the number of platelets. This value was normalized per unit area (cm^2). The details of these measurements are described by Dewanjee et al.[3-5]

Platelet recruitment on the arterial wall of exposed collagen surface after the interventional injury, mainly the loss of protective endothelial cells in the intima and tear of medial wall, is a statistically random process. Although Rene Favaloro on May 9 in 1967 at Cleveland Clinic, rejuvenated the ischemic myocardium with rapid access to oxygenated blood, fatty acids and glucose via bypassing the occluded longer segment of the coronary artery with the reversed saphenous vein graft (CABG) surgery, the platelet thrombus occluded the grafts (30-40)% in 6 months. Similar fate of early closure at a level of (30-45)% at 3 months, occurred after angioplasty for opening the focal segment first by Andreas Gruentzig at 1978. At Mayo



CALCULATION OF PLATELET DEPOSITION

$$\frac{\text{cpm platelet-bound } {}^{111}\text{In}}{\text{ml blood}} = \frac{\text{cpm whole-blood } {}^{111}\text{In}}{\text{ml blood}} \times \frac{(100 - \%\ \text{free } {}^{111}\text{In})}{100}$$

$$\frac{\text{no. platelets}}{\text{cpm } {}^{111}\text{In}} = \frac{\text{no. platelets per ml blood}}{\text{cpm } {}^{111}\text{In per ml blood}}$$

$$\frac{\text{no. platelets}}{\text{area (mm}^2\text{)}} = \frac{\text{cpm } {}^{111}\text{In in specimen}}{\left(\frac{\text{cpm } {}^{111}\text{In}}{\text{no. platelets}}\right) \times \text{area (mm}^2\text{)}}$$

CABG Patency by Platelet-inhibitors
(Dewanjee et al. Circulation 69:350, 1984)

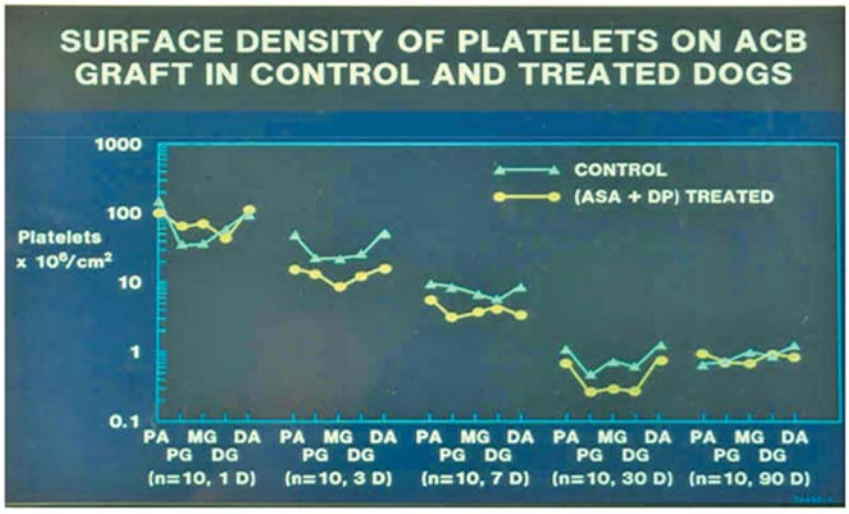


Fig. 1. The CABG surgery model, the Algebraic equations for the calculation of regional platelet density and the chronological loss of platelet recruitment with time after intervention.

Clinic, we developed the technique of arterial patency with the powerful combination of dual anti-platelet therapy: Aspirin-Persantine for CABG and Aspirin-Plavix for angioplasty[7-9]. In 1978, the Dewanjee equation of regional platelet density provided the ranking and potency of Aspirin, Persantine, Clopidogril, the precursor of Plavix, Ibuprofen, Prostacyclin. With dual-drugs, we increased the patency of repaired vessels from (60-70)% to (90-95)%. Out of 60,000 miles of highways arteries, veins and capillaries supplying nutrients for 40 trillion cells in an adult human body, the most vulnerable segments are the four branches of coronary artery segments, ~25 cm, are susceptible to atherosclerosis from the deposition of cholesterol due to smaller diameter, 2-5 mm internal diameter, branchings and twistings inducing high shear.

Exponential decline of platelet recruitment during wound healing after arterial injury for revascularization from angioplasty and bypass surgery

For all random pathological events, e.g. the deposition of cholesterol and hydroxyapatite on the walls of smaller arteries, like the decay of natural and synthetic radionuclides, the relationship of growth or decline of platelet recruitment could be expressed by the exponential equations. After publishing my personal book with several databases in several books with my colleagues, I realized that I was sitting on the goldmine of absolute values of recruited platelets that occluded the repaired vessels.

Hence, I developed the following exponential equations for the calculation of multiple phases of declining rate of

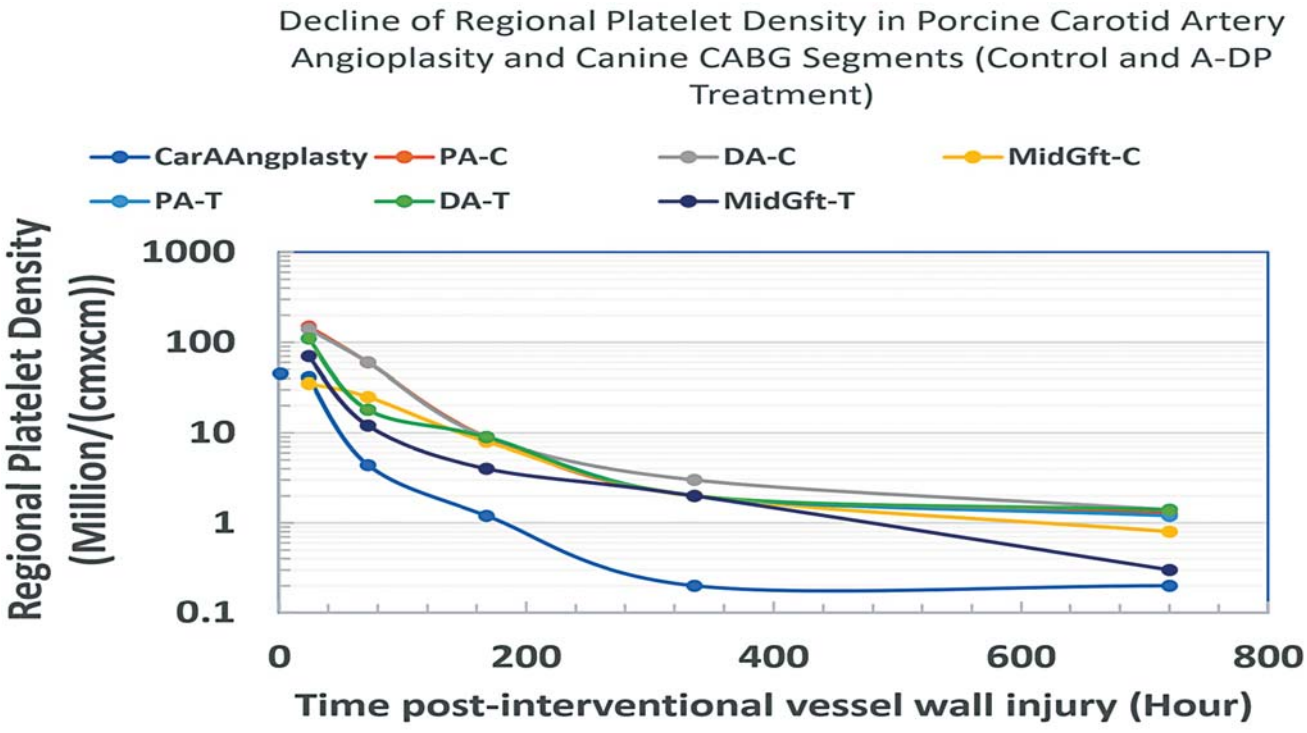


Fig. 2. The curve-stripping method for the estimation of half-life of reduction of platelet recruitment at the sites of interventional injury

average platelet recruitments and $RP_{...}$ is initial net value of recruited platelets at post-surgery time t_0,

$$-d(RP)n/dt = (\lambda n)x(RP)n, \quad \text{Equation (1)}$$

$$(RP)_t = (RP)_0 x e^{-\lambda t} \text{ and} \quad \text{Equation (2)}$$

$$(t_{1/2})n = 0.693/\lambda n \quad \text{Equation (3)}$$

where λn is the slope of decline-constant for each phase of PR declining rate for the half-life values $(t_{1/2})n$ of declines of platelet recruitments.

In the multi-radionuclide decays, we use the curve-stripping method for the estimation of half-life of their decays. In the reanalysis of the platelet recruitment data, I replotted the logarithm of platelet density in the ordinate Y-axis and the time after injury in the X-axis. I was gratified to find the dual and triple phase of platelet retention (PR) in the superficial injury and triple phase of PR in the deep-wall injury of anastomosis in both proximal and distal anastomoses or medial tear in DA. These RPD values for focal segment angioplasty are similar to that of PA and DA sites with a triexponential curve.

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Dr. Dwight McGoon, editor of the Journal of Thoracic and Cardiovascular Surgery, the medical and surgical staff believed in my equations and principle of *in vivo* qualitative and *in vitro* quantitative measurements. Dr. McGoon, the pioneer cardiac surgeon, stopped surgery at a young age of 42 years after the development of Parkinson's disease and became a mentor for the younger generations of surgeons. He asked for my autograph on the article, I shared for his comments, including the algebraic equations for the conversion of thrombus-adherent radioactivity into the number of platelets and made me a reviewer of his critical Journal [3,7].

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