A Role for Changes in Platelet Production in the Cause of Acute Coronary Syndromes

Bernd van der Loo, John F. Martin

Abstract—Platelets are heterogeneous with respect to their size, density, and reactivity. Large platelets are more active hemostatically, and platelet volume has been found to be increased both in patients with unstable angina and with myocardial infarction. Furthermore, platelet volume is a predictor of a further ischemic event and death when measured after myocardial infarction. Platelets which are anucleate cells with no DNA are derived from their precursor, the megakaryocyte. Therefore, it is suggested that changes in platelet size are determined at thrombopoiesis in the megakaryocyte and that those changes might precede acute cardiac events. Understanding of the signaling system that controls platelet production may also further elucidate the cascade of events leading to acute vascular occlusion in some patients. (Arterioscler Thromb Vasc Biol. 1999;19:672-679.)

Key Words: platelets ■ myocardial infarction ■ unstable angina ■ coronary heart disease ■ thrombosis

The biological events that occur in the coronary artery that immediately precede acute coronary syndromes are still not clear. However, platelets are involved, and changes in platelets may be a causal factor in producing a thrombus in the coronary artery.

Aspirin is the most widely used antiplatelet drug. As platelets have no nucleus and are therefore unable to synthesize protein de novo, an aspirin-induced functional defect lasts for the whole life span of the platelets (8 to 10 days).1 The results of large trials2–4 of the beneficial effect of aspirin treatment in patients with unstable angina are consistent with the hypothesis that platelet activity is causally related to acute coronary syndromes. Both the medium- (12 weeks)2 and long-term (2 years)3 risk of cardiac death and myocardial infarction (MI) in patients with unstable angina is reduced. More recently, the significant benefit of antiplatelet therapy with aspirin in protection against acute cardiovascular syndromes and death was further supported in an overview of 145 randomized trials by the Antiplatelet Trialists’ Collaboration.

Given the known effects of aspirin as an inhibitor of platelet function, these trials are strong evidence that platelets contribute to the pathophysiology of the acute complications of coronary artery disease. Aspirin is an inhibitor of only one of several specific pathways leading to platelet activation and aggregation.1 Inhibition of the glycoprotein (GP) IIb/IIIa receptor blocks the binding of fibrinogen, which is the final common pathway of platelet aggregation.5 Integrin, which is a GP IIb/IIIa receptor inhibitor, was evaluated in 227 patients with unstable angina and reduced significantly the number and duration of Holter-recorded ischemia compared with aspirin therapy.7 These recent data are further strong support for the pivotal role of platelets in patients with unstable angina.

Circulating platelets are heterogeneous in size, density, and reactivity.8,9 Changes in these variables may be causal in acute coronary syndromes.10 Initial plaque rupture in the coronary artery, and as a result of this exposure of thrombogenic components of the vessel wall to platelets,11 might be the precipitating event in thrombus formation,12 however, whatever changes in the plaque may be prothrombotic, the presence of larger, more reactive platelets,13 is also likely to contribute to thrombosis. Therefore, elucidating the causes of changes in platelet size and reactivity may help in understanding the origin of thrombosis in the coronary artery.

Animal studies using radiolabeled platelets have shown that platelet size does not change during their lifetime in the circulation,14 thus demonstrating that platelet size heterogeneity is not a consequence of the aging of platelets, but is determined during megakaryocytopoiesis and thrombopoiesis.

Despite the existence of several theories15–17 the mechanism of platelet production from the megakaryocyte is not understood, and the site of platelet production (either the bone marrow or the lungs) is still much debated. Martin and Levine18 favor the lungs, whereas evidence presented by groups led by Jackson19 and Levin20 supports the bone marrow as the site of production.

It has been suggested that an increase in the number of chromosomes in the nucleus of the megakaryocyte (DNA content, ploidy) might be associated, although not necessarily causally related, to the production of large, hyperreactive platelets.21 Here, we review the evidence for a role of platelet size as a key parameter in acute and chronic ischemic heart disease. We furthermore review the evidence suggesting that...
changes in the megakaryocyte may determine platelet size, and therefore reactivity. We also present a possible mechanism for the control of platelet production and size.

The Physiology of Platelet Size Heterogeneity and Its Biological Significance

The origin of platelet volume distribution is unique among cellular volume distributions in that it is log normal.22 There has been much debate about the origin of this platelet heterogeneity. Large platelets were thought to be young platelets because it had previously been suggested that platelets decrease in size as they age during their lifetime in the circulation.23,24 This served as an explanation for findings that platelets decrease in functional ability while aging in the circulation.25 Both Karpatkin9 and Corash et al26 have concluded that, at least in rabbit studies, the size and density of platelets change during their lifetime. However, in other studies it was shown that platelets do not change in size or density as they age. Thompson et al14 have shown that platelet volume heterogeneity is not related to aging in the circulation, but rather arises at thrombopoiesis. Furthermore, it was demonstrated that platelet age and size are independent determinants of platelet function.27 It was also shown in primates using validated methodology28 that platelets are produced in different densities at thrombopoiesis and then circulate with unchanging density. There is a linear relationship between platelet volume and density.29 Corash et al30 have shown in a mouse model that, under the condition of platelet antiserum-induced thrombocytopenia, an increase in Mean Platelet Volume (MPV) at the early stage (12 hours) was accompanied by a decrease in platelet density. Because Corash30 used discontinuous gradients in this study, factors other than platelet density may have influenced the separation of platelets. Studies29 in which platelet density was analyzed using continuous gradients support the view that platelet density is primarily determined during thrombopoiesis. Although most of these experiments were carried out on animal cells, the basic cell biology of platelets is similar in all mammals including humans.

During steady-state hematopoiesis in healthy volunteers, there is a significant inverse relationship between MPV (the most accurate measure of platelet size) and platelet count.13,31–34 This led to the suggestion that platelet production is regulated to maintain a constant functional platelet mass giving a constant hemostatic potential.35 The relationship between these two parameters appears to remain constant over a long period of time in steady-state platelet production.36 However, others37,38 have demonstrated that, during stimulated thrombopoiesis, there is an increase both in platelet count and in volume. Corash et al32 found an increase in the volume of circulating platelets 8 hours after induction of thrombocytopenia following antiserum. After induction of thrombocytosis by administration of vincristine to rats, an increase in platelet count could be observed without an increase in MPV.39 Taken together these findings suggest that platelet number and size are at least partly under independent control during platelet production.40 They can theoretically occur independently, but they occur together chronologically on most occasions.41 Platelets produced under conditions of stimulated platelet production, called “stress” platelets by

Penington et al38 show an increase in the MPV compared with normal circulating platelets.37,38,42-43 There is strong evidence indicating that MPV is an important biological variable14 and that large platelets have a higher thrombotic potential. Karpatkin et al45,46 and Corash et al47 have demonstrated that large platelets are metabolically and enzymatically more active than small platelets as assessed by ex vivo aggregometry. In a rabbit model of a sustained state of thrombocytopenia after IV injection of antiplatelet serum, the production of platelets with a larger MPV is accompanied by a decrease in bleeding time21 per unit volume of platelet (bleeding time is an indicator of in vivo platelet activity).48 Thromboxane B2 production per unit volume of platelet is also increased in large platelets after 24 hours of thrombocytopenia compared with platelets in normal steady-state production.21 However, Savage et al49 found no relationship between changes in volume and platelet destruction, after induction of acute thrombocytopenia in baboons by exposing flowing blood to spherical glass microbeads. The discrepancy between these results and those by Martin et al21 may be caused either by species-related differences or by the different method of inducing thrombocytopenia.

An increase in MPV similar to that seen in animals after platelet destruction can be observed in humans after cardiopulmonary bypass where platelets are destroyed in the extracorporeal circulation.50 A similar response to thrombocytopenia has also been seen by Levin and Bessman31 in patients recovering from idiopathic thrombocytopenic purpura. Eldor et al51 found that patients with hemorrhage and thrombocytopenia associated with a high MPV have a lower frequency of bleeding episodes than patients with both thrombocytopenia and a low MPV. Preferential aggregation of large platelets is observed after addition of ADP to platelet suspensions.52,53 Large platelets are denser,29,45,47 aggregate more rapidly on collagen challenge, have a higher capacity for thromboxane B2 production,21,54 release more serotonin and β-thromboglobulin,55,56 and express more GP Ib57 and GP IIb-IIIa receptors.58

Studies of the relationship of a distinct population of platelets and their function are technically limited as separation by size or density never yields a completely pure population. However, taken together there is a convincing body of evidence, much of it from studies in humans, suggesting that larger platelets have a greater hemostatic, and therefore thrombotic, potential, although data59 indicating the possibility of functional changes without alteration of size also have to be taken into account. Irrespective of some remaining controversies regarding the origin of platelet size heterogeneity, there is agreement that “stress” platelets are larger than steady-state platelets and have greater functional capacity than smaller platelets. This is the likely situation seen in acute coronary syndromes.

The Relationship Between Megakaryocytes and Platelet Volume

Platelets are produced from megakaryocytes and are biologically unique among all mammalian cells in that they can reduplicate their chromosomes, measured as the amount of DNA content, without undergoing mitosis. This process is called endomitosis. Recent studies59 suggest that this process
is due to a unique regulatory mechanism in anaphase. Penington et al.\textsuperscript{60} originally proposed that platelet heterogeneity was established during thrombopoiesis in the megakaryocyte and was not a consequence of aging in the circulation. This has been extended by Martin et al.\textsuperscript{21,61} and by Bessman\textsuperscript{62} to suggest a relationship between changes in megakaryocyte ploidy distribution and megakaryocyte cytoplasmic volume on one hand and MPV on the other. To date, however, a direct observation of platelet production by megakaryocyte of different ploidy and/or size has not been performed. Based on these studies, it is assumed that the relationship is probably chronological and not causal.

Several experiments have been conducted to elucidate a possible control mechanism linking platelet production from megakaryocytes and the need for circulating platelets. Corash et al.\textsuperscript{63} found that 8 hours after induction of thrombocytopenia in the mouse, there was a rapid increase in MPV of circulating platelets without any change in megakaryocyte nuclear DNA content. Other studies done by Corash and Levin\textsuperscript{64} underlined that, during steady-state thrombopoiesis, a shift toward higher ploidy megakaryocytes does not necessarily alter peripheral platelet volume nor count. Furthermore, in a series of studies done by Stenberg et al.\textsuperscript{33,34,64} evidence is given to suggest the hypothesis that platelet formation and release of large platelets do not depend on the ploidy of the producing megakaryocytes. In patients recovering from idiopathic thrombocytopenic purpura an increase in MPV has been demonstrated\textsuperscript{31} as well as a shift to a higher megakaryocyte mean ploidy.\textsuperscript{65} A causal relationship between megakaryocyte ploidy and MPV in those patients has not yet been demonstrated. Furthermore, after administration of recombinant thrombopoietin (c-mpl ligand) (TPO) to normal animals both Harker et al.\textsuperscript{66} and Ulich et al.\textsuperscript{67} have demonstrated a decrease in MPV accompanied by an increase in megakaryocyte number and modal ploidy.

Others, however, have shown that when platelet destruction is induced by injection of anti-platelet-serum to animals for a prolonged time,\textsuperscript{68} both MPV and megakaryocyte ploidy are increased. If vincristine is administered to rats, thrombocytosis occurs together with an increase in megakaryocyte ploidy but without any change in MPV.\textsuperscript{69,66} From these experimental results it has been postulated\textsuperscript{40} that MPV and megakaryocyte ploidy are under separate hormonal control such that they may be stimulated independently or together. Changes in platelet volume would occur only after an alteration in the rate of platelet destruction, whereas changes in megakaryocyte ploidy would be associated with a change in the rate of platelet production. In acute states of platelet destruction, increase in platelet volume might be a result of a change in the fragmentation pattern of megakaryocyte cytoplasm. In chronic states, when platelet destruction and production are stimulated together, an increase in platelet size may be associated with a gradual increase in megakaryocyte ploidy. The larger ploidy megakaryocytes contain more cytoplasm, and therefore can produce more platelets. On the other hand the recent studies by Harker et al.\textsuperscript{66} and Ulich et al.\textsuperscript{67} conclude that increased MPV only occurs after induction of thrombocytopenia, whereas stimulation of platelet production in the presence of secondary thrombocytopenia (eg, secondary to bone marrow damage) is not associated with an increased MPV. This is supported by studies of thrombocytopenia in humans.\textsuperscript{69,70}

### Changes in the Volume of Platelets in Acute Coronary Syndromes

Platelet volume has been found to be increased in patients at the time of MI.\textsuperscript{71–73} In the study performed by Martin et al.\textsuperscript{72} the increase in volume also was accompanied by a significant increase in density when measured in the first 12 hours after MI. Therefore, these platelets contained more secretory granules and mitochondria. Because the life span of the platelet is about 10 days, >90% of the measured platelet population was circulating before the occlusion of the coronary artery occurred, which strongly suggests that MPV is increased before MI. This increase in MPV persisted 6 weeks after discharge from the hospital, which supports the fact that MPV was larger in the infarct group, at least for a period of several weeks. Log normality of the distribution of platelet volume was preserved in the MI group. (Platelets are unique in that their volume distribution is log normal compared with all other cells where volume distribution is normal, probably as a consequence of mitotic division.) In MI the whole distribution curve of volume is shifted to higher values\textsuperscript{74} suggesting that the change arose at thrombopoiesis in the megakaryocyte. (There was no new peak of large platelets independent of the log normal volume distribution.) (Figure) One explanation might be that the increased platelet size was secondary to a compensated state of platelet destruction in that increased platelet turnover may be due to decreased endothelial cell function which preceeded the thrombotic event. In this situation secondary increased platelet volume may be part of the causal link between systemic endothelial cell change and coronary artery occlusion. The definitive way to test this hypothesis would be to decrease circulating platelet volume...
and observe the effect on coronary artery occlusion. However, the tools do not exist to perform such a study.

In patients with MI, bleeding time, as an in vivo measure of platelet behavior, was shortened.75,76 After aspirin administration, bleeding time (measured as an absolute increase in seconds) significantly increased in the MI group compared with controls, but still remained significantly shorter. These findings imply greater activity of cyclooxygenase in patients with MI. Because platelets have no nuclei, the cyclooxygenase concerned must have been produced in the megakaryocyte before the platelets entered the circulation. This is further circumstantial evidence that platelet reactivity may be increased before MI.

Several reports have suggested that platelet behavior, when measured after MI, might predict outcome. An increased platelet release reaction after MI is associated with death.77 Trip et al78 measured spontaneous platelet aggregation (SPA) in 149 survivors of MI after 3 months and followed up for 5 years. A positive SPA was associated with a greater risk of death than a negative SPA. Martin et al80 measured MPV in 1716 men 6 months after MI. Deaths and recurrent ischemic events were then assessed at 2 years. MPV, measured 6 months after MI, was significantly greater in those who had a further fatal or nonfatal MI than in those who had not. Furthermore, MPV was larger in men who died than in those who did not. MPV was a significant predictor of both death and second infarct. As MPV did not correlate with other known risk factors for ischemic heart disease, large platelets seem to be an independent risk factor for MI. When analyzed by quartiles, consistent trends of increasing relative odds of death and recurrent ischemic events were noted for MPV, such that patients with an MPV in the upper quartile had a >2-fold increased risk of a recurrent MI and of death than those with an MPV in the lower quartile. Therefore, a group of post-MI patients exists who are at risk of death or recurrent MI, and who can be identified by a positive SPA test, an increased platelet release reaction and an increased MPV. The properties of large platelets may explain these observed changes in platelet reactivity. The same changes in platelets might not only precede the second, but also the first MI.

Further evidence that an increase in MPV contributes to the prethrombotic state in acute coronary syndromes was found in a recent study of 981 patients performed by Pizzulli et al.79 They found a significant increase in MPV in patients with unstable angina compared with stable angina and noncardiac chest pain. This increase in platelet size was accompanied by a decrease in platelet count. Patients with unstable angina that required immediate angioplasty had an even higher MPV than the rest of the population with unstable angina. It is therefore likely that in unstable angina, these larger platelets contribute to thrombus formation in the coronary artery. The presence of larger platelets in patients with unstable angina may in part be interpreted as a consequence of platelet consumption at the site of the coronary lesion or may be secondary to altered endothelium. The increased MPV would then be secondary to the drop in platelet count. However, because changes in platelet size arise at thrombopoiesis in the mother cell, the megakaryocyte, and because platelets circulate for 10 days, it is reasonable to assume that those larger platelets were circulating at the initiation of chest pain in patients with unstable angina.

Megakaryocyte cytoplasmic volume has been found to be increased both after an MI and at the time of sudden cardiac death.80 Because there is a positive relationship between megakaryocyte size and ploidy,81 an increase in megakaryocyte ploidy might precede the cardiac event. Taken together, the increase in platelet size in unstable angina and before second MI indicate that megakaryocyte changes may take place before unstable angina or MI. However, the changes in MPV seen in patients with unstable angina and MI may not necessarily reflect alterations in megakaryocyte ploidy.

Others82 found no significant difference in MPV when studying 426 patients with coronary heart disease waiting for cardiac surgery compared with healthy volunteers. However, these were chronic stable patients, and one might argue that only the transition from the stable to the unstable form of coronary artery disease is accompanied by activation of thrombopoiesis and production of larger platelets. Furthermore the study by Pizzulli et al did find an increase in MPV in a similar group of patients.79 A study83 of diabetic and nondiabetic patients, with and without atherosclerosis, found that diabetic patients with vascular disease had a significant increase both in megakaryocyte ploidy and in MPV, as well as increased levels of interleukin-6 (IL-6), a proinflammatory cytokine. Together with data in animals showing that IL-6 is capable of increasing platelet volume and the number of high ploidy megakaryocytes in the bone marrow,84 this study suggests that IL-6 may be one of the key factors involved in promoting changes during thrombopoiesis that lead to a thrombotic tendency in inflammatory conditions. It is suggested that IL-6 is capable of progressively augmenting platelet size by acting on megakaryocytes and modifying their maturation.

Recently, evidence for inflammatory cells being involved in acute coronary syndromes has been shown in at least one study that found increased neutrophil and monocyte adhesion receptors in patients with unstable angina.85 Furthermore, the inflammatory response, as measured as increased levels of C-reactive protein in the plasma, has been linked with an adverse prognosis in patients with unstable angina.86 Also, elevated levels of IL-6 have been found in patients with unstable angina.87 IL-6 is both a potent mediator of inflammatory responses and an inducer of platelet changes.

Although the histologic, angiographic, and angiographic data to support a pathophysiological role for plaque rupture are observational, there is certainly a strong qualitative evidence for plaque rupture being involved in unstable angina.11,12,88–90 However, the possibility that changes in platelets are causally involved in acute coronary syndromes should also be considered. The events in the blood or vessel wall leading to acute coronary syndromes are not yet known. There are three possibilities. (1) Unstable angina and MI are two discrete diseases each with a distinct pathophysiology. (2) Unstable angina and MI may be differing manifestations of a shared pathophysiology (or of a shared combination of pathophysiological processes). Whether a patient develops unstable angina or MI would then depend on the way in which any of the pathophysiological processes combine. (3) Unstable angina and MI are part of a single disease process in which unstable angina would be a transitional
stage to MI. Thus platelet changes alone, plaque rupture alone, or a combination of both might be involved to varying degrees in determining the final picture of the acute coronary syndrome in an individual.

A Proposed Mechanism for the Control of Platelet Production and Platelet Volume

The recent discovery of thrombopoietin (TPO) has been an advance in the understanding of the control of platelet production.\textsuperscript{91–94} The TPO receptor is found in all cells of the megakaryocytic lineage, including platelets.\textsuperscript{95} TPO regulates platelet number, and its serum level increases when platelet count decreases.\textsuperscript{66,96–98} It acts primarily on the bone marrow to stimulate the production of megakaryocytes.\textsuperscript{99,100} TPO serum levels do not seem to be regulated at the mRNA level,\textsuperscript{67,101,102} and current evidence suggests that the megakaryocyte-platelet system itself, especially the number of circulating platelets, regulates TPO concentration in the plasma.\textsuperscript{102} However, the actual mechanism by which TPO controls platelet production is not yet known. There has been no evidence so far for the existence of a negative feedback system between the cell originally producing TPO, although de Sauvage et al\textsuperscript{92} have demonstrated c-mpl ligand mRNA in the liver, kidney, and megakaryocyte. There is no obvious sensor that determines the concentration of TPO produced from the cell of origin and therefore modulates the concentration reaching the megakaryocyte.

One possibility for a control mechanism is that TPO is constantly produced in an unregulated fashion by its cell of origin, possibly the liver.\textsuperscript{92} TPO receptors on platelets would bind ligand in the circulation such that changes in platelet count would determine the concentration of TPO reaching megakaryocytes. When less platelet production is needed, more platelets in the circulation would bind more TPO, thus allowing less ligand to reach megakaryocytes. Conversely, when few platelets are circulating and more platelet production is needed, less ligand will bind to platelets, allowing more to reach the megakaryocyte to signal increased platelet production.\textsuperscript{103} There is a similarity to the control of circulating monocytes in that this is also controlled by binding of the hormone cytokine, in this case M-CSF, to the monocyte.\textsuperscript{104} Such a control system also would take into account changes in platelet size. Large platelets are more reactive, which means fewer platelets will need to be produced from megakaryocytes to maintain constant hemostatic potential if those larger platelets circulate. If it may be assumed that larger platelets have more TPO receptors as they have more GP Ib and GP Ib/IIa receptors,\textsuperscript{57,58} larger platelets would then bind more ligand than smaller ones. Thus, larger platelets would allow less ligand to reach megakaryocytes than an equal number of smaller ones. This would also explain the inverse relationship between platelet count and size in steady-state platelet production. Platelet production is unique in mammalian biology in that one cell (the megakaryocyte) gives rise to between 2000 to 3000 daughter cells (the platelets).\textsuperscript{105} It is therefore appropriate to invoke a unique control system.

TPO levels do not seem to be regulated only by circulating levels of platelets. Markedly elevated TPO levels were found by Emmons et al\textsuperscript{106} in patients with aplastic anemia, whereas in patients with platelet destructive disorders, TPO levels were undetectably low. Therefore, the megakaryocyte also could be a regulator of TPO levels.

Although it is now clear that TPO is the major controller of platelet number, the evidence for what controls platelet volume is scant. Current experimental evidence\textsuperscript{99,107} suggests that TPO is a potent promotor of polyploidy. Circumstantial evidence suggests that IL-6\textsuperscript{108} might play a role in controlling platelet size through its effects on megakaryocyte differentiation. Also, consistent with a potential role in vivo, both IL-6 and leukemia inhibitory factor (LIF), when injected into c-mpl-deficient mice, were shown recently to increase the number of megakaryocytes, megakaryocyte progenitor cells, and circulating platelets.\textsuperscript{109} This is evidence for the contribution of cytokines to the control of thrombopoiesis independent of TPO signaling. Recently, Chang et al\textsuperscript{110} found increased levels of IL-11, but not of TPO or IL-6, in patients recovering from idiopathic thrombocytopenic purpura. They suggested that IL-11 may regulate thrombopoiesis in states of acute platelet destruction. Indeed, because in idiopathic thrombocytopenic purpura the MPV is increased,\textsuperscript{37} these findings raise the possibility that IL-11 is a factor that regulates platelet volume. The involvement of other cytokines such as stem cell factor\textsuperscript{111} in the production of platelets of a particular size and function is also possible.

If acute coronary syndromes are preceded by changes in platelets and megakaryocytes, then those changes probably arise from changes in circulating cytokines that control platelet production. If IL-6 is involved, this may be a link between inflammation and coronary artery occlusion. If systemic platelet destruction, eg, caused by endothelial changes, is involved by switching on the bone marrow production of platelets before acute coronary syndromes, then this will probably be mediated by TPO. However, studies that show direct cytokine alteration of platelet function ex vivo\textsuperscript{112} raise the possibility that some determinants of platelet function are established after thrombopoiesis.

A fruitful way of understanding the events leading to coronary artery occlusion may include the study of the signaling system involved in platelet production, the effects of systemic changes (particularly proinflammatory) on those signals and how they may be controlled.

Acknowledgment

J.F. Martin is British Heart Foundation Professor of Cardiovascular Science.

References


Platelet Production and Acute Coronary Syndromes

60. Penington DG, Lee NYL, Roxburgh AE, McGready JR. Platelet density
68. Harris RA, Penington DG. The effects of low dose vincristine on
63. Corash L, Levin J. The relationship between megakaryocyte ploidy and
70. Pfueller SL, Chesterman C, Illes J, Hussein S, Martin JF. Relationship
69. Illes J, Pfueller SL, Hussein S, Chesterman CN, Martin JF. Platelets in
66. Harker LA, Hunt P, Marzec UM, Kelly AB, Tomer A, Hanson SR, Stead
71. Kishk YT, Trowbridge EA, Martin JF. Platelet volume subpopulations
75. Kristensen SD, Bath PMW, Martin JF. Differences in bleeding time,
82. Halbmayer WM, Haushofer A, Radek J, Schon R, Deutsch M, Fischer
81. Penington DG, Olsen TE. Megakaryocytes in states of altered platelet
80. Trowbridge EA, Slater DN, Kishk YT, Woodcock BW, Martin JF. Platelets in
79. Pizzulli L, Yang A, Martin JF, Lu¨deritz B. Changes in platelet size and
78. Trip MD, Cats VM, van Capelle FJL, Vreeken J. Platelet hyperreactivity
84. Brown AS, Hong Y, de Belder A, Beacon H, Beesco J, Sherwood R,
83. Brown AS, Hong Y, de Belder A, Beacon H, Beesco J, Sherwood R,
55. Tschoepe D, Roesen P, Kaumann L, Schanzeil S, Kehrel B, Ostermann
51. Martin JF, Trowbridge EA, Salmon GL, Slater DN. The relationship
48. Bessman JD. The relation of megakaryocyte ploidy to platelet density.
47. Giles H, Smith REA, Martin JF. Platelet glycoprotein IIb-IIIa and size
58. Giles H, Smith REA, Martin JF. Platelet glycoprotein IIb-IIIa and size
49. Brown AS, Hong Y, de Belder A, Beacon H, Beesco J, Sherwood R,
52. Epstein RB, Savage K. Thrombopoiesis in normal and sublethally
53. Wendling F, Maraskovsky E, Debili N, Caliguri G, Monaco C, Rezvi
56. Harker LA, Mukerjee S, Hunt P, Marzec UM, Kelly AB, Tomer A, Hanson SR, Stead
59. Epstein RB, Savage K. Thrombopoiesis in normal and sublethally
40. Brown AS, Hong Y, de Belder A, Beacon H, Beesco J, Sherwood R,
46. Harker LA, Mukerjee S, Hunt P, Marzec UM, Kelly AB, Tomer A, Hanson SR, Stead
44. Brown AS, Hong Y, de Belder A, Beacon H, Beesco J, Sherwood R,
42. Halbmayer WM, Haushofer A, Radek J, Schon R, Deutsch M, Fischer
41. Brown AS, Hong Y, de Belder A, Beacon H, Beesco J, Sherwood R,
45. Kristensen SD, Bath PMW, Martin JF. Differences in bleeding time,
39. Pizzulli L, Yang A, Martin JF, Lu¨deritz B. Changes in platelet size and
38. Trip MD, Cats VM, van Capelle FJL, Vreeken J. Platelet hyperreactivity
37. Cameron HA, Philips R, Ibbotson RM, Carson PHM. Platelet size in
36. Harker LA, Mukerjee S, Hunt P, Marzec UM, Kelly AB, Tomer A, Hanson SR, Stead
35. Trowbridge EA, Slater DN, Kishk YT, Woodcock BW, Martin JF. Platelets in
34. Harris RA, Penington DG. The effects of low dose vincristine on
33. Illes J, Pfueller SL, Hussein S, Chesterman CN, Martin JF. Platelets in
32. Pizzulli L, Yang A, Martin JF, Lu¨deritz B. Changes in platelet size and
31. Kristensen SD, Bath PMW, Martin JF. Differences in bleeding time,
aspirin sensitivity and adrenaline between acute myocardial infarction
29. Heptonstall S, Mulley GP, Taylor PM, Mitchell JRA. Platelet release
28. Trip MD, Cats VM, van Capelle EFL, Vreeken J. Platelet hyperreactivity
27. Pizzulli L, Yang A, Martin JF, Lu¨deritz B. Changes in platelet size and
count in unstable angina compared to stable angina or non cardiac chest
26. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
25. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
24. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
23. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
22. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
21. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
20. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
19. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
18. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
17. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
16. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
15. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
14. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
13. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
12. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
11. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
10. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
8. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
7. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
6. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
5. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
4. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
3. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
2. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.
1. Trowbridge EA, Saffran DN, Kishik YT, Woodcock BW, Martin JF.


106. Emmons RV, Reid DM, Cohen RL, Meng G, Young NS, Dunbar CE, Shulman NR. Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction. Blood. 1996;87:4068–4071.


A Role for Changes in Platelet Production in the Cause of Acute Coronary Syndromes

Bernd van der Loo and John F. Martin

*Arterioscler Thromb Vasc Biol.* 1999;19:672-679
doi: 10.1161/01.ATV.19.3.672

*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/19/3/672