Anesthesiology
1996; 85:1334-40

Platelet Function and Adrenoceptors during and after Induced Hypotension using Nitroprusside

Gerald V. Dietrich, M.D., Michael Heesen, M.D.,† Joachim Boldt, M.D.,‡ Gunter Hempelmann, M.D.‡*

Background: **Hypotension induced by sodium nitroprusside can minimize intraoperative blood loss. The release of endogenous catecholamines can influence adrenoceptors of platelets and thus might change the ability of platelets to aggregate.**

Methods: **Forty patients undergoing nasal septum, tympanoplastic, or sphenoid sinus surgery were randomly divided into two groups, those having controlled hypotension (A) and those serving as controls (B). Blood samples were drawn before the operation, after induction of anesthesia, 1 h after the start of the operation, and on the day after surgery.**

Results: **Epinephrine-induced platelet aggregation only increased in the controls on the day after surgery (A: from 49 ± 25% to 47 ± 29%; B: from 53 ± 24% to 72 ± 14%; mean ± SD; $P < 0.01$). Spontaneous platelet aggregation increased in the controls from a median of 1.2 Ω/h to 2.4 during the operation and 2.9 on the day after surgery but not after hypotension. On the day after surgery, α2 receptors reached their maximum (A: 238 ± 164; B: 234 ± 80 per platelet). During the operation, the norepinephrine concentrations were significantly greater in group A (median, 419 pg/ml) than in group B (median, 217 pg/ml; $P < 0.05$). Blood loss was greater in the controls (A: 180 ± 75; B: 379 ± 120 ml; $P < 0.05$).**

Conclusions: **Controlled hypotension using sodium nitroprusside reduces epinephrine-induced and spontaneous platelet aggregation. Even on the day after hypotension, the usual postoperative reactive increase in platelet aggregation did not occur. These results may be explained by the direct effect of nitroprusside on platelets, the augmented stress response, lower shear stress on platelets due to the lower blood pressure, or the decreased blood loss compared with the controls. (Key words: Blood, platelets: human. Hemostasis: platelet aggregation. Hypotension, controlled: nitroprusside. Receptors, adrenergic: alpha-2.)**

* Consultant Anesthetist.

† Resident.

‡ Professor of Anesthesiology.

Received from the Department of Anaesthesiology and Intensive Care Medicine, Justus-Liebig-University, Giessen, Germany. Submitted for publication August 15, 1995. Accepted for publication August 28, 1996. Supported by the German Research Association (Deutsche Forschungsgemeinschaft).

Address reprint request to Dr. Dietrich: Department of Anaesthesiology and Intensive Care Medicine, Justus-Liebig-University, Rudolf-Buchheim-Str. 7, D-35385 Giessen, GERMANY.

SODIUM nitroprusside is a vasodilator that predominantly affects arterial vessels. Nitroprusside and nitric oxide, which is generated after degradation of the nitroprusside molecule by contact with hemoglobin, activate the enzyme guanylate cyclase and cause a concomitant increase in the intracellular concentration of cyclic guanosine monophosphate.[1] This effect is not limited to blood vessels, but it has also been shown in platelets, where high cyclic guanosine monophosphate concentrations inhibit platelet aggregation.[2] Accordingly, *in vitro* studies showed that incubation with nitroprusside decreases platelet aggregation.[3]

Platelets contain 100 to 300 α2-adrenoceptors per cell.[4] Platelet α2-adrenoceptors are involved in regulating aggregation because the stimulation of these receptors by catecholamines enhances platelet aggregation.[5,6]

We examined the influence of nitroprusside administration on platelet aggregation during and on the first day after operation. A further aim was to determine whether increases of adrenergic hormone concentrations during nitroprusside application influence platelet aggregation and platelet α2-adrenoceptor density.

Materials and Methods

After receiving approval from the local ethics committee and informed written consent, we enrolled 40 patients in this prospective, randomized, unblinded, noncrossover study. They were classified as American Society of Anesthesiologists (ASA) physical status 1 and 2 and were scheduled for otorhinolaryngologic operations. The patients were randomly allocated to a study group (n = 20, receiving nitroprusside) or the control group (n = 20, no nitroprusside).

Premedication consisted of 7.5 mg midazolam given 45 min before patients arrived in the operating room. Anesthesia was induced with 0.1 mg fentanyl, 2 mg vecuronium bromide, 0.3 mg/kg etomidate, and 1 mg/kg succinyl choline. After orotracheal intubation, anesthesia was maintained with 66% nitrous oxide in oxygen

and isoflurane. In the study group, nitroprusside (Nipruss; Schwarz Pharma, Monheim, Germany) was administered *via* a central venous catheter by an infusion pump for exactly 60 min. The infused dosages were within the permitted range of 0.5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and were adjusted to decrease the mean arterial blood pressure to 50 mmHg. In the nitroprusside group, a radial artery was cannulated for direct blood pressure measurement.

Venous blood samples were taken at 7:00 AM on the day of operation ("preoperative"), 15 min after induction of anesthesia (before the start of the nitroprusside infusion in the study group, "postinduction"), 60 min after the start of the operation (at the end of the nitroprusside infusion in the study group, "intraoperative"), and at 7:00 AM on the day after operation ("postoperative").

Density and affinity of platelet α2-adrenoceptors were determined using 40 ml ethylenediamine tetraacetic acid (EDTA)-anticoagulated blood according to the method of Brodde and associates.[7] Briefly, blood was centrifuged at 17,000*g* for 5 min at 4°C. The cell pellets were washed three times in 50 mM Tris-buffer (*p*H 7.35, 120 mM NaCl, and 20 mM EDTA). After mechanical homogenization followed by centrifugation, the platelet membranes were resuspended in ice-cold lysis buffer (*p*H 7.35, 120 mM Tris-HCl, and 0.5 mM EDTA). The membranes were incubated in duplicate with six concentrations ranging from 0.5 to 10 nM of the radioligand ^{3}H-yohimbine (Du Pont, Bad Homburg, Germany). Phentolamine (10^{-5} M; Biotrend, Cologne, Germany) was used to assess unspecific binding, which was defined as radioactivity bound to the platelet membranes that is not displaced by phentolamine. The specific binding was calculated by subtracting unspecific binding from the total binding. To separate bound from unbound radioactivity, the incubation mixture was vacuum filtrated (Whatman GF/C Filter; Whatman, Essen, Germany). The filters were placed in 5 ml scintillation fluid (Unisolve I; Zinsser, Frankfurt am Main, Germany), and the radioactivity was measured in a scintillation counter (Beckman LS 9000; Beckman Instruments, Munich, Germany). Data were analyzed according to the method of Scatchard.[8]

Whole-blood aggregation was measured using a Chrono-Log® whole-blood aggregometer (model 540 VS; Chrono-Log Corp., Havertown, PA). Five minutes after blood withdrawal, spontaneous platelet aggregation was performed by stirring each sample for 30 min without adding any aggregating agent. The increase of impedance (Ω/h) between two wires of the electrode was determined 40 min after blood collection, and platelet aggregation was induced simultaneously in whole blood and platelet-rich plasma by adding aggregating solution. Platelet-rich plasma was obtained by centrifuging a blood sample at 350*g* for 15 min at 25°C and adjusted to a platelet concentration of 150,000/μl by adding platelet-poor plasma. In the turbidometric method, the light transmission through platelet-rich plasma represents 0% aggregation; through platelet-poor plasma it represents 100% aggregation. In whole blood, platelet aggregation was induced by a final concentration of 10 mg/l collagen, whereas in platelet-rich plasma it was induced by 22 mg/l collagen or 22 μM epinephrine. All aggregation tests were performed twice.

Platelet counts were determined in EDTA whole blood and in EDTA platelet-rich plasma before analyzing α2 receptors, and in citrated platelet-rich plasma before induction of platelet aggregation. Platelet counts, mean platelet volumes, and hemoglobin concentrations were obtained using an automated electronic counter (Celltrak®11; Nova, Frankfurt, Germany).

Epinephrine and norepinephrine plasma concentrations were determined by high-performance liquid chromatography and electrochemical detection, as described earlier.[9] Normal values are 30 to 85 pg/ml for epinephrine and 180 to 285 pg/ml for norepinephrine.

In vitro tests were performed to determine the direct effect of nitroprusside on the test results. Because of the short half-life of the drug in whole blood, platelet-rich plasma was used here. Citrated blood was drawn from 30 healthy persons and divided into five equal parts. Platelet-rich plasma was centrifuged. Four parts were mixed with nitroprusside in concentrations of 1, 10, 100, and 1,000 nmol/ml, respectively. The fifth part served as a control. Measurement of spontaneous aggregation was started after 5 min. The increase of impedance was determined. After 1 h of incubation, turbidometric platelet aggregation tests were performed in a separate sample, as described previously.

Blood loss was defined as volume of blood collected in the suction canister. It was determined using a calibrated scale in 50-ml intervals. Sponges were rarely used in the observed operations.

Statistics

After analyzing the data for normal distribution using the Bartlett test, the two-way analysis of variance for repeated measurements and then the Scheffé test were

Table 1. Biometric, Operative, and Anesthetic Data: Mean ± SD or Median (and Range)

	NP Group	Controls
Age (yr)	29 ± 8	30 ± 17
Height (cm)	177 ± 10	175 ± 7
Weight (kg)	75 ± 15	69 ± 9
Surgery		
Nasal septum	8	11
Sphenoid sinus	5	5
Tympanoplastic	2	1
Osteosynthesis	4	2
Others	1	1
Duration of anesthesia (min)	151 ± 51	151 ± 54
Mean dosage		
Isoflurane (vol %)	1.2 ± 0.3	0.9 ± 0.2
Nitroprusside (mg)	10.3 ± 6.4	—

used. Catecholamine plasma concentrations and the values of spontaneous platelet aggregation were not normally distributed. For these parameters, Friedman's test followed by Miller's test with Bonferroni correction were used to analyze differences between the time points within one group. The Wilcoxon-Mann-Whitney test evaluated differences between the two groups.

Results

Biometric Data

The groups did not differ in mean age, sex, body weight, height, or mean duration of surgery (table 1). Intraoperative blood loss was significantly greater in the control group (379 ± 120 ml; mean ± standard deviation; $P < 0.05$) than in the nitroprusside group (180 ± 75 ml).

Catecholamines

In the nitroprusside group, we found a peak norepinephrine concentration after the end of the controlled hypotension with a significant difference ($P < 0.05$) compared with the controls (table 2). In the nitroprusside group, epinephrine increased significantly ($P < 0.05$) after anesthesia was induced but did not differ from the controls.

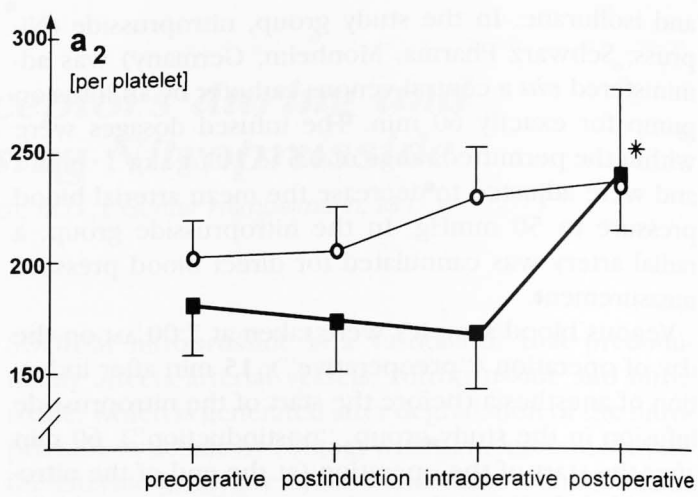

Fig. 1. Average number of $\alpha 2$ receptors per platelet. Mean ± SEM. Squares = nitroprusside; circles = controls (n = 200; *$P \geq 0.05$ compared with preoperative values in the nitroprusside group).

The density of $\alpha 2$ receptors on platelets did not change in the controls during the study period (fig. 1). After operation the receptor density increased significantly ($P < 0.05$) in the nitroprusside group compared with preoperative values. The affinity of $\alpha 2$ receptors was assessed by the dissociation constant. No alterations were seen.

Spontaneous platelet aggregation increased during the operation in the control group only (table 3) and remained increased until the day after operation ($P < 0.01$).

Collagen-induced aggregation determined by the change of impedance did not change significantly. The

Table 2. Plasma Concentrations of Epinephrine and Norepinephrine (pg/ml): Median (and Range)

	Preoperative	Postinduction	Intraoperative	Postoperative
Norepinephrine				
NP group	290 (87–922)	289 (29–898)	419 (43–898)	279 (34–786)
Controls	199 (17–744)	184 (20–985)	217† (46–872)	267* (130–1204)
Epinephrine				
NP group	77 (8–129)	130* (14–343)	67 (18–186)	87 (8–143)
Controls	56 (9–129)	75 (47–302)	67 (33–320)	65 (26–160)

* $P < 0.05$ *versus* preoperative.

† $P < 0.05$ between groups.

Table 3. Spontaneous Platelets Aggregation in Whole Blood (Ω/h): Median (and Range)

	Preoperative	Postinduction	Intraoperative	Postoperative
NP group	1.1 (−0.8–9.8)	2.4 (−0.8–12.9)	1.3 (−0.3–7.8)	1.4 (−0.2–15.0)
Controls	1.2 (−1.6–5.1)	2.0 (0.0–9.7)	2.4* (0.0–7.0)	2.9* (0.0–8.6)

* $P < 0.01$ *versus* preoperative values.

same was true for the collagen-induced aggregation determined in Born's optical system (fig. 2).

After anesthesia was induced, epinephrine-induced platelet aggregation was reduced in the nitroprusside group (fig. 2). But there was no difference from the controls. On the day after surgery it increased only in the controls but not in the patients receiving nitroprusside ($P < 0.001$).

Hemoglobin concentration significantly ($P < 0.001$) decreased from 15.1 g/dl before operation to 13.7 g/dl after operation in the nitroprusside group. In the controls it decreased from 15.8 g/dl to 13.5 g/dl ($P < 0.001$). We observed no differences between both groups at any time. Platelet concentration and platelet volume did not change.

The density of $\alpha 2$ receptors on platelets did not correlate with epinephrine or with norepinephrine plasma concentrations, and neither did the receptors' density correlate with the epinephrine-induced aggregation. On the day after operation, a positive correlation between spontaneous platelet aggregation and density of $\alpha 2$ receptors was found (Spearman's rank coefficient: r = +0.49) after nitroprusside was given, whereas the correlation in the controls was inverse (r = −0.39, difference between both groups: $P < 0.01$).

In the *in vitro* part of the study, nitroprusside was added to platelet-rich plasma of healthy volunteers. Chemically induced platelet aggregation decreased significantly compared with the controls (table 4). The decrease was not dose dependent in the range of 1 to 1,000 nmol/ml. Spontaneous aggregation was hardly seen in any of the samples. Aggregation phenomena and disaggregation were more pronounced in platelet-rich plasma containing high concentrations of nitroprusside.

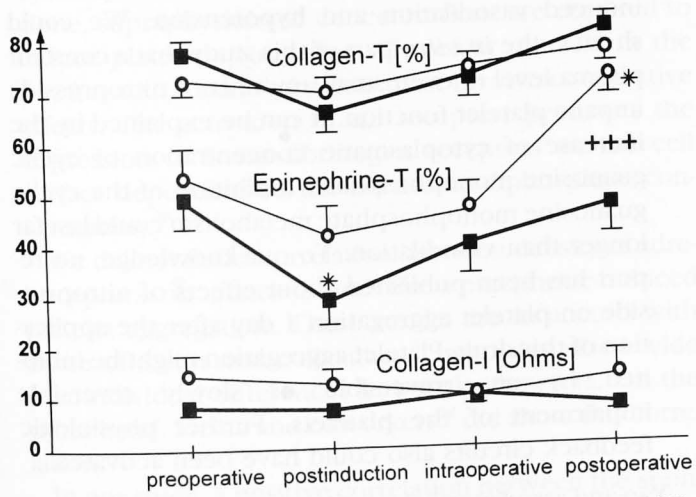

Fig. 2. Platelet aggregation. Methods: Impedance aggregometry, collagen induced (Collagen I); turbidometry, epinephrine (Epinephrine T); and collagen induced (Collagen T). Mean ± SEM. Squares = nitroprusside; circles = controls (n = 20, +++$P \geq 0.001$; nitroprusside *vs.* control group, *$P \geq 0.05$ compared with preoperative values).

Discussion

According to Born,[10] turbidometric determination of chemically induced platelet aggregation in platelet-rich plasma is a well-established method to uncover deficits in platelet function. To obtain platelet-rich plasma, centrifugation is necessary in which as many as 30% of the platelets, especially large ones, are lost. The impedance technique has the advantage that it is performed in citrated whole blood without further processing. Thus it assesses the actual function of platelet. In contrast to methods of chemically induced aggregation, spontaneous platelet aggregation[11] does not show the hemostatic potential but rather the actual function of platelets. It can be determined in whole blood by measuring electrical impedance according to the method of Flower and Cardinal.[12]

Hines and Barash[13] previously reported that nitroprusside caused a dose-dependent impairment of platelet aggregation in patients scheduled for heart operations. However, in their study, nitroprusside was administered before cardiopulmonary bypass was started and measurements were taken only until 90 min after induction of anesthesia. Our results suggest that controlled hypotension induced by nitroprusside also inhibits the post-

Table 4. Platelet Aggregation in Platelet-rich Plasma Incubated with Different Concentrations of Nitroprusside

		Concentration of Nitroprusside in the Samples			
	Controls	1 nmol/ml	10 nmol/ml	100 nmol/ml	1000 nmol/ml
Collagen-I (Ω)					
(mean ± SD)	26.9 ± 7.8	19.1 ± 8.6*	19.0 ± 8.9*	17.5 ± 6.8*	15.6 ± 5.7*
Epinephrine-T (%)					
(mean ± SD)	44.9 ± 28.5	15.6 ± 14.5*	12.3 ± 11.2*	13.5 ± 11.2*	11.9 ± 9.6*
Collagen-T (%)					
(mean ± SD)	83.3 ± 11.3	67.3 ± 16.2*	64.7 ± 19.3 (NS)	66.1 ± 17.7*	71.3 ± 17.2*
Spontaneous (Ω/h)					
Median	0.0	0.0 (ns)	0.0 (ns)	0.0 (ns)	−0.7 (ns)
Range	(−1.7–1.3)	(−1.2–0.6)	(−1.8–1.7)	(−1.3–4.6)	(−15.0–24.5)

Methods: Impedance-aggregometry: spontaneous, collagen-induced (Collagen-I). Turbidometry: epinephrine-(epinephrine-T) and collagen-induced (collagen-T). mean ± SD or median (and range); n = 30.

ns = not significant (Friedman's test); NS = not significant (ANOVA).

* $P < 0.001$ *versus* controls (ANOVA/Sheffe).

operative increase in platelet aggregation. These changes last far longer than the pharmacodynamic activity of the drug. They were still visible on the day after the operation. Because of the design of our study, we could not distinguish between the effects of hypotension and those of the drug itself.

The following hypotheses could explain our findings:

1. Vasodilation: The vasodilatory properties of nitroprusside and the lower blood pressure reduced shear stress on platelets. The wall shear rate greatly influences platelet adhesion on the endothelium or subendothelium.[14] Decreased blood flow resulted in decreased platelet activation. Diodati and colleagues[15] reported that platelet activation in coronary arteries induced by high-frequency atrial pacing could be suppressed by nitroprusside.
2. Blood loss: Intraoperative bleeding was less in the nitroprusside group, and no patients or controls experienced postoperative bleeding. Decreased ability of platelets to aggregate after controlled hypotension compared with that in the control group does not seem to have any relevant adverse effect. However, we found increased epinephrine-induced and spontaneous aggregation in the controls, whereas there was no difference compared with the preoperative value after controlled hypotension. Perhaps the greater blood loss in the control patients caused a liberation of active platelets[16] that did not occur in the control group.
3. Stress response: Controlled hypotension is a stress factor even under anesthesia. This can be clearly demonstrated by the increase in norepinephrine. We can presume that other stress reactions, such as the liberation of corticosteroids or glycolysis, were also activated. Those "secondary" stress responses could have influenced platelets. There are only a few systematic reports of the long-term influence of perioperative stress.[17]
4. Direct drug-effect: Nitroprusside increases the cytoplasmatic concentrations of cyclic guanosine monophosphate, which induces vasodilation and inhibits platelet aggregation. The effect of nitroprusside on platelets could have lasted longer than nitroprusside-induced vasodilation and hypotension. We could show in the *in vitro* part of this study that a constant plasma level of even small amounts of nitroprusside impairs platelet function. It can be explained by the increase of cytoplasmatic concentration of cyclic guanosine monophosphate. Inhibition of the cyclic guanosine monophosphate metabolism could last far longer than vasodilation. To our knowledge, no report has been published about effects of nitroprusside on platelet aggregation 1 day after the application of this drug. Platelet aggregation might be inhibited by an irreversible or slowly reversible impairment of the platelets. Further physiologic feedback circuits also could have been activated.

Yao and associates[18] showed that nitroprusside administration protected dogs against intracoronary thrombosis. Our findings suggest that nitroprusside might also influence the incidence of thromboembolic complications during the perioperative period in humans.

Platelets possess 200 to 300 $\alpha 2$ receptors per cell.[19] This corresponds to our preoperative values. The increase of catecholamines did not result in a pronounced downregulation of $\alpha 2$ receptors on platelets. In contrast, the density of $\alpha 2$ receptors on platelets increased on the day after the operation in the nitroprusside group. A similar phenomenon has been described for $\beta 2$ receptors on lymphocytes: After *in vivo* exposure to high concentrations of catecholamines, the number of $\beta 2$ receptors per cell increased.[20,21] Until now this phenomenon has not been described for α receptors of platelets. Our results are confirmed by other reports that could not show downregulation of α receptors.[22,23] Zucker and Amory[24] even found a slight increase in the receptor density. In contrast, Michel and coworkers[25] described a decrease of α receptors associated with long-term antihypertensive therapy with nifedipine.

Rosenfeld and colleagues[26] showed that platelet reactivity increased in volunteers who received stress hormones intravenously. Although norepinephrine concentrations in plasma increased after nitroprusside administration in our study, platelet aggregation did not. The intravenous application of catecholamines may have a different effect than the endogenous liberation of norepinephrine in a complex of stress reactions. Furthermore, we must consider that plasma norepinephrine levels do not contain catecholamines liberated into tissues.

Stimulation of $\alpha 2$ receptors may induce different intracellular mechanisms, such as inhibition of adenylate cyclase.[27] If the stimulation is triggered by epinephrine alone, supraphysiologic concentrations are required to induce platelet aggregation. Therefore, its role in the *in vivo* activation of platelets must involve cooperative effects. The activation of $\alpha 2$ receptors promotes the expression of latent fibrinogen receptors on the cell surface dependent on the adenosine diphosphate concentration.[28-30]

We did not find a correlation between density of adrenoceptors on platelets and the epinephrine-induced platelet aggregation. These results are in accord with those of Swart and colleagues,[31] who described wide interindividual differences in both parameters. On the other hand, Mehta and coworkers[32] did show this correlation.

In our study, a positive correlation between the spontaneous platelet aggregation and the receptor density was found in the nitroprusside-treated patients on the day after the operation. For the control group, an inverse correlation was observed. The relation between the density of receptors and spontaneous aggregation has not been analyzed in clinical studies before. We know, however, that the $\alpha 2$-adrenergic receptor regulates the adhesive function of the glycoprotein IIb-IIIa complex,[33,34] which is the most abundant glycoprotein on the platelet surface. Therefore platelets containing many $\alpha 2$ receptors might have adhered and consequently have been consumed for hemostasis during the operation in the control group. Only platelets with either fewer $\alpha 2$ receptors or less ability to aggregate would have remained. Nitroprusside specifically inhibits the glycoprotein IIb-IIIa complex.[35] Therefore platelets with a high density of 2α receptors could have remained here afterward, even with elevated spontaneous aggregation in the absence of nitroprusside.

Nitroprusside-induced hypotension prevented an increase in platelet aggregation, because it was seen in the control group on the morning after operation. *In vitro* results provide evidence that even low concentrations of nitroprusside impair platelet function. Our data do not permit us to determine whether the hypotension or the drug itself caused the *in vivo* effects on platelet aggregation. A reduction in shear stress or in blood loss in the hypotension group might be important. $\alpha 2$ Receptors increased in the nitroprusside group but not in the controls. Therefore they are unlikely to account for the changes in platelet aggregation.

The authors thank Professor Brodde, Department of Pharmacology, University of Halle, Halle, Germany, for his help.

References

1. Katsuki S, Arnold W, Mittal C, Murad F: Stimulation of guanylate cyclase by sodium nitroprusside, nitroglycerin and nitric oxide in various tissue preparations and comparison to the effects of sodium azide and hydroxylamine. J Cyclic Nucl Protein Phosphor Res 1977; 3:23-35

2. Brodde OE, Hardung A, Ebel H, Bock KD: GTP regulates binding of agonists to alpha-2-adrenergic receptors in human platelets. Arch Int Pharmacodyn Ther 1982; 258:193-207

3. Gerzer R, Karrenbrock B, Seiss W, Haim JM: Direct comparison of the effects of nitroprusside, SIN 1 and various nitrates on platelet aggregation and soluble guanylate cyclase activity. Thromb Res 1988; 52:11-21

4. Motulsky HJ, Insel PA: Adrenergic receptors in man. N Engl J Med 1982; 307:18-29

5. Hsu CY, Knapp DR, Halushka PV: The effects of alpha adrenergic agents on human platelet aggregation. J Pharmacol Exp Ther 1979; 208:366-70

6. Grant JA, Scrutton MC: Novel alpha2-adrenoceptors primarily responsible for inducing human platelet aggregation. Nature 1979; 277:659-61

7. Brodde OE, Anlauf M, Graben N, Bock KD: In vitro and in-vivo down-regulation of human platelet a2-adrenoreceptors by clonidine. Eur J Clin Pharmacol 1982; 23:403-9

8. Scatchard G: The attractions of proteins for small molecules and ions. Ann N Y Acad Sci 1949; 51:660-72

9. Adams HA, Allerkamp S, Borgmann A, Hempelmann G: Sympatho-adrenerge Reaktionen bei medikamentös induzierter Hypotension. Eine vergleichende Studie an Probanden. Anaesthesist 1990; 39:158-65

10. Born GVR: Quantitative investigation into the aggregation of blood platelets. J Physiol 1962; 162:67-8

11. Abbate R, Boddi M, Prisco D, Gensini GF: Ability of whole blood aggregometer to detect platelet hyperaggregability. Am J Clin Pathol 1989; 91:159-64

12. Flower RJ, Cardinal DC: The electronic aggregometer: A novel device for assessing platelet behaviour in blood. J Pharmacol Methods 1980; 3:135-58

13. Hines R, Barash PG: Infusion of sodium nitroprusside induces platelet dysfunction in vitro. ANESTHESIOLOGY 1989; 70:611-15

14. Baumgartner HR: The role of blood flow in platelet adhesion, fibrin deposition and formation of mural thrombi. Microvasc Res 1973; 5:167-79

15. Diodati JG, Cannon RO III, Hussain N, Quyyumi AA: Inhibitory effect of nitroglycerin and sodium nitroprusside on platelet activation across the coronary circulation in stable angina pectoris. Am J Cardiol 1995; 75:443-8

16. Yamazyki H, Motomiya T, Watanabe C: Consumption of larger platelets with decrease in adenine phosphate content in thrombosis, disseminated intravascular coagulation, and postoperative state. Thromb Res 1980; 18:77-88

17. O'Brien JR, Etherington MD, Shuttleworth RD, Davison S: Platelets and other tests followed sequentially for 14 days after operation. Clin Lab Haemat 1984; 6:239-45

18. Yao SK, Akhtar S, Scott-Burden T, Oberr JC, Golino P, Buja LM, Casscells W, Willerson JT: Endogenous and exogenous nitric oxide protect against intracoronary thrombosis and reocclusion after thrombolysis. Circulation 1995; 92:1005-10

19. Kerry R, Scrutton MC: Platelet adrenoceptors, The Platelets: Physiology and Pharmacology. Edited by Longenecker GL. Orlando, Academic Press, 1985, p 113

20. Tohmeh JF, Cryer PE: Biphasic adrenergic modulation of β-adrenergic receptors in man. Agonist induced early increment and late decrement in β-adrenergic receptor number. J Clin Invest 1980; 65:836-840

21. FitzGerald GA, Robertson D, Wood AJ: Biphasic regulation of β-adrenoceptor density by epinephrine and norepinephrine infusions in man. Clin Pharmacol 1982; 31:225

22. Pfeifer MA, Ward K, Malpass T, Stratton J, Halter J, Evans M, Beiter H, Harker LA, Porte Jr D: Variations in circulating catecholamines fail to alter human platelet alpha-2-adrenergic receptor number or affinity for 3H-Yohimbine or 3H-Dihydroergocryptine. J Clin Invest 1984; 74:1063-72

23. Villeneuve A, Berlan M, Lafontan M, Montastruc JL: Characterization of dog platelet alpha-adrenergic receptor: Lack of in vivo down regulation by adrenergic agonist treatments. Comp Biochem Physiol 1985; 81C:181-187

24. Zucker JR, Amory DW: Platelet alpha-adrenergic receptors are not down-regulated during cardiopulmonary bypass. ANESTHESIOLOGY 1985; 63:449-51

25. Michel MC, Mindermann G, Daul A, Brodde OE: Effects of antihypertensive therapy on human alpha- and beta-adrenoceptors. J Hypertens 1991; 9:1-6

26. Rosenfeld BA, Faraday N, Campbell D, Dise K, Bell W, Goldschmidt P: Hemostatic effect of stress hormone infusion. ANESTHESIOLOGY 1994; 81:1116-26

27. Gilman AG: Guanine nucleotide binding regulatory proteins and dual control of adenylate cyclase. J Clin Invest 1984; 76:1-8

28. Bennett JS, Vilaire G: Exposure of fibrinogen receptors by ADP and epinephrine. J Clin Invest 1979; 64:1993

29. Gachet C, Cazenave JP: ADP-induced blood platelet activation: A review. Nouv Rev Fr Hematol 1991; 33:347-358

30. Plow EF, Marguerie G: Induction of fibrinogen receptor on human platelets by epinephrine and ADP. J Biol Chem 1980; 255:10971

31. Swart SS, Pearson D, Wood JK, Barnett DB: Human platelet a2-adrenoreceptors: Relationship between radioligand binding studies and adrenaline-induced aggregation in normal individuals. Eur J Pharmacol 1984; 103:25

32. Mehta J, Mehta P, Krop I, Lawson D: The primary wave of epinephrine-induced platelet aggregation represent a2-adrenoceptor status. Thromb Res 1984; 49:531

33. Shattil SJ, Budzynski A, Scrutton MC: Epinephrine induces fibrinogen receptor expression, fibrinogen binding and aggregation in whole blood in absence of other excitatory agonists. Blood 1989; 73:150-8

34. Banga HS, Simons ER, Brass LF, Rittenhouse SE: Activation of phospholipases A and C in human platelets exposed to epinephrine: Role of glycoproteins IIb/IIIa and dual role of epinephrine. Proc Natl Acad Sci USA 1986; 83:9197-9201

35. Shahbazi T, Jones N, Radomski MW, Moro MA, Gingell D: Nitric oxide donors inhibit platelet spreading on surfaces coated with fibrinogen but not with fibronectin. Thromb Res 1994; 75:631-42