Platelet Function and Adrenoceptors during and after Induced Hypotension using Nitroprusside

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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, tympanoplasty, 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 ± 0.6 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 ± 168; B: 244 ± 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.)

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Received from the Department of Anesthesiology 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).

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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. 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. Accordingly, in vitro studies showed that incubation with nitroprusside decreases platelet aggregation.

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

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, blinded, non-cross-over 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 a control group (n = 20, no nitroprusside).

Premedication consisted of 7.5 mg midazolam given 45 min before patients arrived in the operating room. Anaesthesia 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 60% nitrous oxide in oxygen and isoflurane. Pressor support was only used in those patients who were not able to maintain their blood pressure within the normal range and were therefore treated with dopamine. Radial arterial blood pressure was measured on an instrument.

Venous access was established on the day of operation by insertion of an 8F catheter. Continuous infusion of nitroprusside was started after the surgical incision and stopped at 7:00 ("12 am"").

Density of α2-adrenoceptor binding sites was determined using [125I] 2β-hydroxy-3α-5α-cholestane-NH₂ (ED 198) as a radioligand and a binding assay method of the Scatchard analysis. Membranes (pH 7.5, 10 mmol/l TRIS buffer, 0.1 mmol/l EDTA, 2 mmol/l sodium azide, 2 mmol/l NaCl, 1 mmol/l MgCl₂, 0.5% Triton X-100) were prepared from the homogenate, and the equilibrium dissociation constant (Kd, nM) determined. Membranes were preincubated with different concentrations of α2-adrenoceptor agonists (Hyohimbine, Phentolamine, Dihydrophentolamine). Sedimentation was performed by centrifugation for 15 min at 20,000 rpm in a Spinco-type centrifuge (Beckman Instruments, Germanberg, Germany). Results were expressed as the specific binding expressed as the difference between the control and the test condition. The amount of bound radiolabeled hormone from the unbound ratio was then determined. (P-values were estimated after log-transforming the data.)

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and isoflurane. In the study group, nitroprusside (Ni- pruss; Schwarz Pharma, Monheim, Germany) was ad-
ministered 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 μg·kg⁻¹·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 induc-
tion 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 nitro-
prusside infusion in the study group, "intraoperative"),
and at 7:00 AM on the day after operation ("postopera-
tive").

Density and affinity of platelet α₂-adrenoceptors were
determined using 40 ml ethylenediamine tetraacetic
acid (EDTA)-anticoagulated blood according to the
method of Brodè and associates.⁷ Briefly, blood was
centrifuged at 17,000g for 5 min at 4°C. The cell pellets
were washed three times in 50 mm Tris-buffer (pH 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
(pH 7.35, 120 mm Tris-HCl, and 0.5 mm EDTA). The
membranes were incubated in duplicate with six con-
centrations ranging from 0.5 to 10 nm of the radioligand
‘Hyominine (Du Pont, Bad Homburg, Germany).
Phentolamine (10⁻³ M; Biotrend, Cologne, Germany)
was used to assess unspecific binding, which was de-
efined as radioactivity bound to the platelet membranes
that is not displaced by phentolamine. The specific
binding was calculated by subtracting unspecific bind-
ing from the total binding. To separate bound from
unbound radioactivity, the incubation mixture was vac-
um filtered (Whatman GF/C Filter; Whatman, Essen,
Germany). The filters were placed in 5 ml scintillation
fluid (Unisolve I; Zinszer, Frankfurt am Main, Germany).

Whole-blood aggregation was measured using a
ChromoLog¹ whole-blood aggregometer (model 540
VS; Chrono-Log Corp., Havertown, PA). Five minutes
after blood withdrawal, spontaneous platelet aggrega-
tion 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 measured as a difference after blood collection, and
platelet aggregation was induced simultaneously in
whole blood and platelet-rich plasma by adding aggreg-
gating solution. Platelet-rich plasma was obtained by
centrifuging a blood sample at 350g 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 con-
centration of 10 mg/l collagen, whereas in platelet-rich
plasma it was induced by 22 μg/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 (Cell-
trak®11; Nova, Frankfurt, Germany).

Epinephrine and norepinephrine plasma concentra-
tions were determined by high-performance liquid
chromatography and electrochemical detection, as de-
scribed 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 50 healthy persons and divided into five equal
courses. 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 aggrega-
tion was started after 5 min. The increase of impedance
was determined. After 1 h of incubation, turbidom-
metric 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 cali-
brated 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

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

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

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.

The density of a2 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 a2 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.

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

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

* P < 0.05 versus preoperative.
† P < 0.05 between groups.
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 15.5 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.

**Discussion**

According to Born, a 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 50% 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 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.

Hines and Barash 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-

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

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postinduction</th>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP group</td>
<td>1.1 (-0.8–9.8)</td>
<td>2.4 (-0.8–12.9)</td>
<td>1.3 (-0.3–7.8)</td>
<td>1.4 (-0.2–15.0)</td>
</tr>
<tr>
<td>Controls</td>
<td>1.2 (-1.6–5.1)</td>
<td>2.0 (0.0–9.7)</td>
<td>2.4* (0.0–7.0)</td>
<td>2.9* (0.0–8.6)</td>
</tr>
</tbody>
</table>

* $P < 0.01$ versus preoperative values.
Table 4. Platelet Aggregation in Platelet-rich Plasma Incubated with Different Concentrations of Nitroprusside

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>1 nmol/ml</th>
<th>10 nmol/ml</th>
<th>100 nmol/ml</th>
<th>1000 nmol/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen-I (%)</td>
<td>26.9 ± 7.8</td>
<td>19.1 ± 8.6*</td>
<td>19.0 ± 8.9*</td>
<td>17.5 ± 6.8*</td>
<td>15.6 ± 5.7*</td>
</tr>
<tr>
<td>(mean ± SD)</td>
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<td></td>
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<tr>
<td>Epinephrine-T (%)</td>
<td>44.9 ± 28.5</td>
<td>15.6 ± 14.5*</td>
<td>12.3 ± 11.2*</td>
<td>13.5 ± 11.2*</td>
<td>11.9 ± 9.6*</td>
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<tr>
<td>(mean ± SD)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Collagen-T (%)</td>
<td>83.3 ± 11.3</td>
<td>67.3 ± 16.2*</td>
<td>64.7 ± 19.3 (NS)</td>
<td>66.1 ± 17.7*</td>
<td>71.3 ± 17.2*</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous (f1/h)</td>
<td>0.0</td>
<td>0.0 (NS)</td>
<td>0.0 (NS)</td>
<td>0.0 (NS)</td>
<td>−0.7 (NS)</td>
</tr>
<tr>
<td>Median</td>
<td>(−1.7−1.3)</td>
<td>(−1.2−0.6)</td>
<td>(−1.8−1.7)</td>
<td>(−1.3−4.6)</td>
<td>(−15.0−24.5)</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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/Shelffe).

The 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. Decreased blood flow resulted in decreased platelet activation. Diodati and colleagues 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 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.

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 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 α2 receptors per cell. This corresponds to our preoperative values. The increase of catecholamines did not result in a pronounced downregulation of α2 receptors on platelets. In contrast, the density of α2 receptors on platelets increased on the day after the operation in the nitropusside group. A similar phenomenon has been described for β2 receptors on lymphocytes: After in vitro exposure to high concentrations of catecholamines, the number of β2 receptors per cell increased. 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. Zucker and Amory even found a slight increase in the receptor density. In contrast, Michel and coworkers described a decrease of α receptors associated with long-term antihypertensive therapy with nifedipine.

Rosenfeld and colleagues showed that platelet reactivity increased in volunteers who received stress hormones intravenously. Although norepinephrine concentrations in plasma increased after nitropusside 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 α2 receptors may induce different intracellular mechanisms, such as inhibition of adenylate cyclase. If the stimulation is triggered by epinephrine alone, supraphysiologic concentrations are required to induce platelet aggregation. Therefore, its role in the in vitro activation of platelets must involve cooperative effects. The activation of α2 receptors promotes the expression of latent fibrinogen receptors on the cell surface dependent on the adenosine diphosphate concentration.

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, who described wide interindividual differences in both parameters. On the other hand, Mehta and coworkers showed this correlation.

In our study, a positive correlation between the spontaneous platelet aggregation and the receptor density was found in the nitropusside-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 α2-adrenergic receptor regulates the adhesive function of the glycoprotein Iib-I1la complex, which is the most abundant glycoprotein on the platelet surface. Therefore platelets containing many α2 receptors might have adhered and consequently have been consumed for hemostasis during the operation in the control group. Only platelets with either fewer α2 receptors or less ability to aggregate would have remained. Nitropusside specifically inhibits the glycoprotein Iib-I1la complex. Therefore platelets with a high density of 2α receptors could have remained here afterward, even with elevated spontaneous aggregation in the absence of nitropusside.

Nitropusside-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 nitropusside impair platelet function. Our data do not permit us to determine whether the hypotension or the drug itself caused the in vitro effects on platelet aggregation. A reduction in shear stress or in blood loss in the hypotension group might be important. α2 Receptors increased in the nitropusside 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.

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