

Anesthesiology  
79:255-261, 1993  
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## Perioperative Platelet Reactivity and the Effects of Clonidine

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**Background:** Increased postoperative platelet reactivity may contribute to arterial thrombotic complications following surgery.  $\alpha_2$  Agonists, which are being used increasingly to blunt the stress response of surgery, increase platelet aggregation *in vitro*. We compared perioperative changes in platelet reactivity in 21 patients receiving either clonidine or placebo.

**Methods:** Patients undergoing major abdominal surgery were randomized to receive oral and transdermal clonidine (n = 11) or placebo (n = 10). All patients received similar perioperative management, including preoperative sedation, general anesthesia without neuraxial opioids, or local anesthetics and postoperative patient-controlled intravenous morphine. Blood was obtained for measurement of clonidine level, fibrinogen concentration, platelet count, and platelet reactivity (impedance aggregometry and dense granule release) before induction and 24, 48, and 72 h postoperatively.

**Results:** Thirteen of the 21 patients had biopsy-proven cancer at surgery, 5 of 11 received clonidine and 8 of 10 received placebo (NS). Clonidine levels were therapeutic (1-2 ng/ml) throughout the study period. Clonidine administration had no effect on platelet count or platelet reactivity. Therefore, the groups were combined for further analysis. In this group (n = 21), compared to preoperative values, fibrinogen levels rose maximally (36%) at 72 h postoperatively and platelet counts decreased 22% at 48 h. Platelet reactivity (aggregation and degranulation) to collagen, adenosine diphosphate, arachidonic acid, and ristocetin, increased at 24, 48, and 72 h postoperatively. Thrombin-induced (supramaximal stimulus) dense granule release did not change from preoperative values.

**Conclusions:** These data indicate that major abdominal surgery causes increased platelet reactivity postoperatively but does not effect maximal degranulation. This increased platelet reactivity occurs within 48 h of surgery, coinciding with the peak incidence of postoperative arterial thrombotic complications. Clonidine administration has no effect on surgically induced changes in platelet reactivity. In this surgical patient population, the use of clonidine should not increase the risk of platelet-induced perioperative arterial thrombosis. (Key words: Blood, coagulation; degranulation; platelet aggregation. Sympathetic nervous system: catecholamines. Sympathetic nervous system,  $\alpha_2$  agonists: clonidine.)

INCREASES in blood hemostatic activity have been described following surgery suggesting a postoperative hypercoagulable state. These hemostatic changes include elevated circulating coagulation proteins,<sup>1</sup> decreased circulating coagulation inhibitors,<sup>2</sup> impaired *in vitro* fibrinolysis,<sup>3</sup> and increased *in vitro* platelet reactivity.<sup>4</sup> Following tissue trauma, these procoagulant changes can be viewed as teleologically adaptive but may place patients with underlying atherosclerotic vascular disease at risk for myocardial infarction, stroke, or limb occlusion. In nonoperative settings, increases in hemostatic activity are associated with the development of coronary ischemic syndromes (unstable angina and non-Q wave and Q wave myocardial infarction).<sup>5,6</sup> During the perioperative period, increased platelet-fibrinogen reactivity<sup>7</sup> is associated with the development of arterial thrombotic complications. Both inhalational<sup>8</sup> and local anesthetics<sup>9</sup> directly impair platelet function. However, data on postoperative platelet function are inconsistent, with some investigators reporting increased reactivity and others finding no change.<sup>10,11</sup> These discrepancies may be due to differences in anesthetic technique, level of surgical stimulation, or different methodologies used to assess platelet function.

The  $\alpha_2$  agonist clonidine is being used increasingly in the perioperative period for its sedative, analgesic, and antihypertensive effects.<sup>12</sup> Platelets contain surface  $\alpha_2$  receptors,<sup>13</sup> and stimulation of these receptors *in*

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Received from the Departments of Anesthesiology and Critical Care Medicine and Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland. Accepted for publication April 28, 1993.

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*vitro* with clonidine causes increased platelet reactivity.<sup>14,15</sup> However, this effect has never been examined perioperatively *in vivo*. Concern about clonidine-induced platelet aggregability in the perioperative period has been raised,<sup>16</sup> since increased platelet reactivity could limit the usefulness of  $\alpha_2$  agonists in patients at risk for carotid, coronary, or peripheral vascular occlusion. These high-risk patients often are considered prime candidates for  $\alpha_2$ -agonist treatment to decrease the stress response of surgery. Accordingly, a major goal of this study was to define possible effects of  $\alpha_2$  agonists on perioperative platelet function by comparing perioperative platelet reactivity in patients receiving clonidine with that of a placebo group.

### Materials and Methods

Following institutional review and informed consent, patients scheduled for elective major upper abdominal surgery (Whipple procedure, biliary reconstruction, or cholangiocarcinoma resection) were enrolled the day before surgery. Patients were randomized to receive either clonidine or placebo on the night before surgery, at which time they were administered either 0.2 mg clonidine orally and a clonidine patch (TTS-3) or a placebo pill and placebo patch. Patients were excluded from the study if they had evidence of cardiovascular disease (coronary, carotid, or peripheral arterial symptoms), were taking clonidine or other centrally acting antihypertensives, or receiving aspirin or nonsteroidal antiinflammatory drugs. The morning of surgery, patients received an additional 0.3 mg-dose of clonidine or placebo orally. All patients were premedicated with intramuscular midazolam (up to 4 mg) and/or morphine sulfate (up to 0.1 mg/kg). Patients received only general anesthesia without neuraxial opioids or local anesthetics. Before induction, each patient had arterial and internal jugular venous catheters inserted. General anesthesia was induced with midazolam (up to 5 mg), fentanyl (up to 250  $\mu$ g), and thiamylal (4–6 mg/kg). Succinylcholine (1–2 mg/kg) was administered intravenously to facilitate tracheal intubation. Antibiotics (cefazolin, cefoxitin, or penicillin and gentamicin) were administered routinely before skin incision. Anesthesia was maintained using isoflurane or enflurane and nitrous oxide to maintain hemodynamic stability ( $\pm 20\%$  from baseline). Pancuronium and vecuronium were used for muscle relaxation. Incremental doses of morphine sulfate (up to 20 mg) were administered throughout surgery as needed. All patients were trans-

ferred to the intensive care unit postoperatively for at least 18–24 h, where they routinely received H<sub>2</sub> antagonists and antibiotics. Postoperative analgesia was achieved with patient-controlled intravenous morphine. Medical management was supervised initially by the intensive care unit team, then by the surgical team on the wards. No medications with platelet-inhibiting effects were administered.

Blood was obtained for measurement of clonidine level, fibrinogen concentration, platelet count, and platelet reactivity before induction and 24, 48, and 72 h postoperatively. All blood samples were obtained through the indwelling vascular catheters. Blood samples were collected at the same time each day to ensure that circadian variation had no effect on measured parameters. Blood for measurement of fibrinogen and clonidine was collected in 3.8% sodium-citrate and heparin-containing tubes, respectively, placed on ice, centrifuged at 3,000 RPM for 20 min, and stored at  $-70^\circ$  C for later testing. Fibrinogen was assayed by the vonClaus method,<sup>17</sup> and results are reported in grams/liter. Clonidine levels were shipped frozen to TSI Mason Laboratories (Worcester, MA), where they were analyzed by radioimmunoassay.<sup>18</sup>

Blood for determination of platelet count and platelet reactivity was collected in EDTA and 3.8% sodium-citrate tubes, respectively, kept at room temperature, and analyzed within 3 h of drawing. Platelet count was determined by a Coulter counter (Hialeah, FL). Platelet reactivity in whole blood was assessed by quantifying agonist-stimulated platelet aggregation and dense granule secretion (release of adenosine triphosphate [ATP]) using a model 500 Chrono-Log Lumi-Aggregometer (Havertown, PA).<sup>19</sup> Briefly, aliquots of whole blood diluted with isotonic saline (0.5 ml of blood and 0.45 ml of isotonic saline) were placed in plastic cuvettes and warmed to  $37^\circ$  C. Luciferin-luciferase reagent (50  $\mu$ l, Chrono-Log) was added, and the sample was stirred at 1,200 RPMs using Teflon-coated magnetic bars. Platelet reactivity was studied using five platelet agonists: (1) collagen (1  $\mu$ g/ml), (2) adenosine diphosphate (ADP; 5  $\mu$ M), (3) arachidonic acid (AA; 0.5 mM), (4) ristocetin (0.37 mg/ml), and (5) thrombin (1 unit/ml).<sup>1</sup> Agonists were added to the sample during stirring, and the resultant aggregation and ATP release were measured until a maximal response was attained or for 10 min. Peak response is reported for aggregation in ohms of impedance and for ATP release in picomoles of ATP (luminescence). An internal impedance standard (20 ohms) was measured before the addition of

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**Table 1. Clinical Characteristics of the Study Subjects**

	Clonidine (n = 11)	Placebo (n = 10)	P
Age (yr)	52 ± 3.2	55 ± 2.4	NS
Male:female	6:5	5:5	NS
ASA physical status			
4	—	1	NS
3	5	5	NS
2	6	4	NS
Cancer	5 (45%)	8 (80%)	0.10
EBL (ml)	723 ± 161	455 ± 87	0.09
PRBC transfusions	2 (18%)	2 (20%)	NS

Results are mean ± SD.

ASA = American Society of Anesthesiologists; EBL = estimated blood loss; PRBC = packed red blood cells.

each agonist, and ATP release was calculated by measuring an ATP standard added to the patient's blood. Platelet reactivity is reported on a per-platelet basis.

**Statistical Analysis**

Discrete variables were analyzed using chi-square analysis and *t* tests were used to compare preoperative values in patients receiving clonidine and placebo. Differences between clonidine- and placebo- treated groups were analyzed by two-way analysis of variance (ANOVA) for repeated measures. Combined changes in measured parameters were analyzed using one-way ANOVA for repeated measures. Duncan's *post hoc* test was performed on significant ANOVA changes. All results are presented as mean ± SEM and considered significant at the *P* < 0.05 level.

**Results**

Demographic and relevant treatment data for the 21 patients studied are shown in table 1. There were no differences in age, gender, or ASA classification between clonidine and placebo patients. Thirteen of 21 (62%) patients had biopsy-proven cancer (either pancreatic or biliary adenocarcinoma) at operation and 8 had nonmalignant disease. The type of surgery performed, included 10 Whipple procedures, 5 biliary reconstructions, 1 distal pancreatectomy, 1 cholangiocarcinoma resection, and 4 double-bypass procedures (gastrojejunostomy and choledochojejunostomy) for metastatic disease discovered at surgery. There were no differences in the surgical procedures performed between groups. Blood loss in the clonidine group (722 ± 161 ml) did not differ significantly from placebo group (455 ± 87 ml), and there was no difference in the number of patients receiving transfusion or the volume of erythrocytes transfused. Throughout the study period, no patient received fresh frozen plasma or platelet transfusions. Eleven patients were treated with clonidine and 10 with placebo. Plasma clonidine levels were 1.9 ± 0.2 ng/ml immediately before induction and 1.0 ± 0.4 ng/ml, 1.3 ± 0.2 ng/ml, and 1.4 ± 0.2 ng/ml at 24, 48, and 72 h, respectively. Platelet aggregation (table 2) and ATP release (table 3) were not different at baseline and behaved similarly over time in the clonidine and placebo groups. Platelet counts (table 2) were also no different at baseline and behaved similarly over time. Fibrinogen levels increased in both groups postoperatively and were statistically higher at 72 h in the placebo group compared

**Table 2. Perioperative Platelet Aggregation, Platelet Count, and Fibrinogen Concentration: Aggregation (ohms)**

Agonist	Condition	Preoperative	24 h	48 h	72 h
Collagen	Placebo	16.6 ± 4.6	45.4 ± 5.6	39.4 ± 8.5	43.4 ± 12.9
	Clonidine	15.8 ± 4.2	28.1 ± 5.4	45.7 ± 7.3	32.7 ± 3.0
ADP	Placebo	25.7 ± 4.8	35.5 ± 5.4	53.2 ± 12.6	38.7 ± 10.7
	Clonidine	29.6 ± 6.2	28.2 ± 4.1	36.3 ± 5.6	30.2 ± 4.5
Arachidonic acid	Placebo	18.8 ± 4.7	29.8 ± 6.4	49.4 ± 13.7	38.4 ± 10.5
	Clonidine	25.9 ± 4.4	27.8 ± 3.6	35.7 ± 6.5	32.6 ± 4.0
Ristocetin	Placebo	30.1 ± 8.4	42.2 ± 5.3	70.5 ± 13.0	50.5 ± 8.5
	Clonidine	21.5 ± 5.9	30.9 ± 7.0	46.2 ± 9.9	32.3 ± 3.3
Platelets (1,000/mm <sup>3</sup> )	Placebo	366 ± 49	331 ± 54	263 ± 41	296 ± 42
	Clonidine	326 ± 26	326 ± 14	277 ± 18	293 ± 25
Fibrinogen (g/L)	Placebo	4.88 ± 0.40	6.31 ± 0.65	7.29 ± 0.58	7.93 ± 0.62*
	Clonidine	3.95 ± 0.36	4.93 ± 0.67	5.41 ± 0.51	5.80 ± 0.50

Results are mean ± SEM. ADP = adenosine diphosphate.

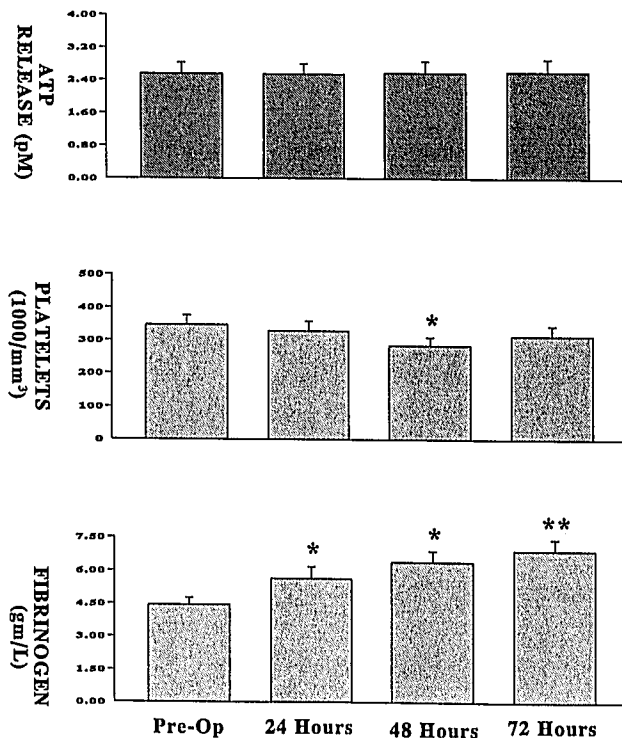
\* *P* < 0.05 versus clonidine.

**Table 3. Perioperative Platelet Degranulation: ATP Release (picomoles/10,000 platelets)**

Agonist	Condition	Preoperation	24 h	48 h	72 h
Collagen	Placebo	1.4 ± 0.5	2.3 ± 0.5	2.8 ± 0.5	2.4 ± 0.4
	Clonidine	1.4 ± 0.5	3.0 ± 0.5	2.0 ± 0.6	2.5 ± 0.7
ADP	Placebo	2.1 ± 0.5	2.4 ± 0.5	2.3 ± 0.6	1.5 ± 0.3
	Clonidine	1.9 ± 0.5	2.6 ± 0.5	2.1 ± 0.5	1.8 ± 0.5
Arachidonic acid	Placebo	2.3 ± 0.5	2.8 ± 0.4	3.2 ± 0.7	2.7 ± 0.3
	Clonidine	2.6 ± 0.7	2.5 ± 0.5	2.7 ± 0.6	2.4 ± 0.8
Ristocetin	Placebo	1.1 ± 0.3	1.6 ± 0.4	2.1 ± 0.5	1.8 ± 0.4
	Clonidine	1.6 ± 0.6	2.8 ± 0.6	1.9 ± 0.4	1.8 ± 0.5
Thrombin	Placebo	5.5 ± 0.8	4.6 ± 0.8	5.3 ± 0.8	5.2 ± 1.0
	Clonidine	4.6 ± 0.5	5.6 ± 0.5	5.0 ± 0.8	5.3 ± 0.6

Results are mean ± SEM. ADP = adenosine diphosphate.

to the clonidine group ( $P = 0.03$ ). Power analysis performed on the platelet reactivity data demonstrates confidence in these results at the  $\beta < 0.2$  level for every analysis except ristocetin aggregation. We concluded



**Fig. 1. (Top)** Perioperative thrombin-induced ATP release in pm/10,000 platelets (mean ± SEM). **(Middle)** Perioperative platelet count (mean ± SEM). \* $P < 0.05$  versus preoperative value. **(Lower)** Perioperative plasma fibrinogen level (mean ± SEM). \* $P < 0.01$  versus preoperative values. \*\* $P < 0.01$  versus preoperative and 24 h postoperative values. All results are for the combined study group ( $n = 21$ ).

that there was no difference in perioperative platelet reactivity between clonidine and placebo groups, and data from all 21 patients were combined to define perioperative changes in platelet function. Comparing patients with cancer ( $n = 13$ ) to those without ( $n = 8$ ), there were no differences in platelet count, fibrinogen level, or platelet reactivity at any time point (data not shown).

In the combined group ( $n = 21$ ; fig. 1) platelet counts decreased 22% at 48 h from preinduction levels ( $347,000 \pm 28,000/\text{mm}^3$  to  $270,000 \pm 22,000/\text{mm}^3$ ). Fibrinogen levels (fig. 1) were  $4.54 \pm 0.3$  g/l preoperatively,  $5.66 \pm 0.5$  g/l at 24 h,  $6.41 \pm 0.5$  g/l at 48 h, and  $6.93 \pm 0.5$  g/l at 72 h postoperatively. These represented a 21%, 31%, and 36% change from preoperative values, respectively. Thrombin-induced ATP release (fig. 1) was  $2.59 \pm 0.3$  pm/10,000 platelets before induction and did not change postoperatively. Platelet aggregation and degranulation (ATP release) in response to collagen, ADP, AA, and ristocetin are shown in figure 2. All four agonists follow a similar pattern of increased postoperative platelet reactivity. Thrombin at the concentration used (1 unit/ml) is a supramaximal stimulus and should cause complete degranulation of available dense granule contents (ATP). Therefore, peak ATP release in response to collagen, ADP, AA, and ristocetin in this study was approximately half the maximal response ( $1.1$ – $1.4$  pm/10,000 platelets vs.  $2.6$  pm/10,000 platelets).

## Discussion

Results of this study indicate that platelet reactivity and fibrinogen levels increase postoperatively in patients undergoing major upper abdominal surgery. Dif-

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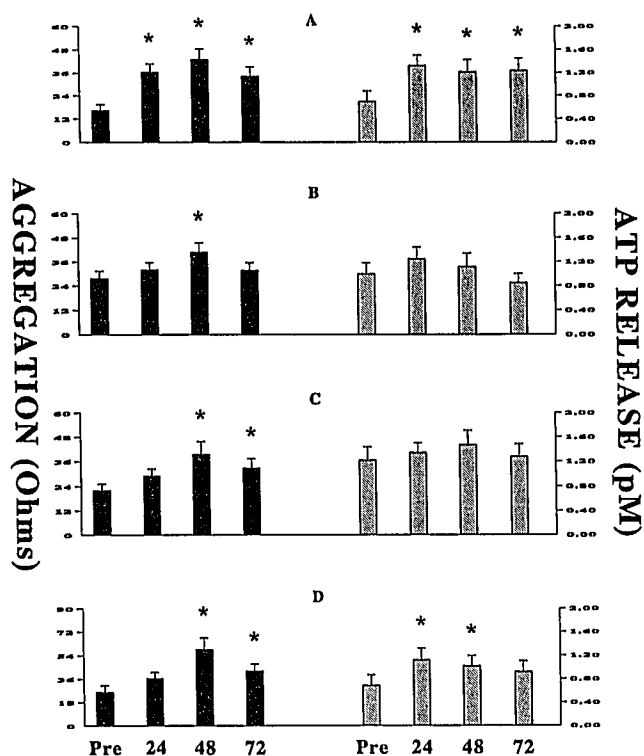


Fig. 2. Perioperative agonist-induced aggregation in ohms of impedance and ATP release in pM/10,000 platelets (mean  $\pm$  SEM). (A) collagen (1  $\mu$ g/ml), (B) adenosine diphosphate (ADP; 5  $\mu$ M), (C) arachidonic acid (AA; 0.5 mM), and (D) ristocetin (0.37 mg/ml). \* $P < 0.01$  versus preoperative values by analysis of variance. All results are for the combined study group ( $n = 21$ ).

ferences in the time course of platelet reactivity and fibrinogen level suggest possibly different mechanisms responsible for these increases. The different time course also suggests that increased postoperative platelet reactivity is not wholly dependent upon elevated fibrinogen level. The  $\alpha_2$  agonist clonidine and the presence of pancreatic and biliary adenocarcinoma had no effect on perioperative platelet reactivity.

The initial hypothesis to be tested was that  $\alpha_2$  agonists increase perioperative platelet reactivity. This hypothesis was based on *in vitro* data demonstrating that platelet  $\alpha_2$  receptors bind clonidine, and this leads to increased aggregation.<sup>14,15</sup> The dosing paradigm we used in this study achieved therapeutic clonidine levels throughout the perioperative period (1–2 ng/ml).<sup>20</sup> The initial preinduction peak and subsequent decline at 24 h in mean clonidine plasma levels likely reflects a rapid rise and fall due to the oral loading dose, with a more gradual increase from the transdermal prepa-

ration. Clonidine administration significantly lowered norepinephrine levels but had no effect on epinephrine levels throughout the perioperative period compared to controls. This effect on perioperative norepinephrine levels was reported previously.<sup>21</sup> Platelet reactivity was not different in the placebo and clonidine groups preoperatively and throughout the postoperative period. The likely explanation for this observation is that the direct  $\alpha_2$  platelet-stimulating properties of clonidine are counterbalanced by the reduced endogenous catecholamine levels in this group.<sup>22</sup> Another possible explanation is that *in vitro* effects of clonidine are not representative of the *in vivo* situation and circulating catecholamines have no effect on platelet reactivity. Clonidine does not appear to increase platelet reactivity perioperatively when patients undergo abdominal operations, suggesting that this agent also might be used safely in patients at risk for vascular occlusion.

Whole blood impedance platelet aggregometry compares favorably with the traditional technique of optical aggregation using platelet-rich plasma<sup>23</sup> and has additional advantages. Whole blood aggregometry does not require platelet preparation (centrifugation), which can activate platelets while retaining erythrocytes, leukocytes, and macroplatelets. With these cellular elements present, whole blood analysis more closely mimics the *in vivo* situation, and recent data suggests that these other cell lines may be important modulators of platelet function.<sup>24</sup> ATP release and aggregation data were expressed on a per-platelet basis to more accurately compare perioperative effects on platelet function. Dense granule release is proportional to platelet number, and *in vitro* aggregation depends upon platelet-platelet interactions, which can be affected by the absolute platelet count. Analysis of uncorrected values (not shown) demonstrated similar changes in platelet function over time and the absence of any clonidine effect.

Platelets form the primary hemostatic plug, which occludes sites of vascular injury. Therefore, surgical trauma with its direct vascular injury is probably responsible for declining postoperative circulating platelet counts.<sup>4,25,26</sup> This utilization for vascular hemostasis also may correlate with the type and magnitude of surgery.<sup>4,25,26</sup> We observed a postoperative decrease in mean platelet count at 48 h postoperatively. The higher mean platelet count at 72 h may represent a decrease in platelet utilization and/or increased platelet release from the bone marrow. With the overall trend in platelet reactivity decreasing at 72 h postop-

eratively (fig. 2), it is attractive to hypothesize the release of unstimulated platelets (those not exposed to the operative stimulus) from the bone marrow into the circulation.

Platelet activation is an ordered sequence of events that begins with binding of an agonist to its receptor and ends with shape change, aggregation, and degranulation. Previous studies examining perioperative platelet reactivity have demonstrated mixed results. Both increased platelet release<sup>27</sup> and aggregation to specific agonists<sup>10</sup> have been reported, whereas other studies find no change in these parameters.<sup>11,28</sup> Different surgeries, type of anesthesia, and methods to assess platelet reactivity were used in these studies. We limited surgery to major upper abdominal procedures, attempting to standardize the stress response. We also controlled the anesthetic management by protocol and evaluated platelet reactivity at the same time each day, avoiding possible circadian variations. Our results demonstrate increased postoperative platelet reactivity to collagen, ADP, AA, and ristocetin. During the perioperative period, circulating platelets may be exposed directly to some of these agonists, potentially "priming" them to be more reactive. Collagen located in the subendothelial matrix is exposed with vascular injury<sup>29</sup>; ristocetin acts through von Willebrand factor, which increases postoperatively<sup>30</sup>; and thrombin levels increase from activation of the coagulation cascade.<sup>31</sup> Elevated levels of circulating catecholamines also act as agonists to increase platelet reactivity.<sup>22</sup> Whether perioperative exposure to these particular agonists or other platelet stimulants, or both, is responsible for our results is not apparent. The similar response to thrombin at all time points demonstrates that maximal dense granule release is unaffected by surgical stimulation and suggests that postoperative depletion of dense granule contents (platelet exhaustion) probably does not occur.

Fibrinogen is a glycoprotein that has multiple effects on hemostasis, including direct effects on platelet aggregation.<sup>32</sup> Fibrinogen is also an acute phase protein and levels increase postoperatively.<sup>31</sup> Fibrinogen is necessary for platelet aggregation to occur, acting as a ligand for platelet-platelet binding at the activated glycoprotein IIb/IIIa receptor. Therefore, rising fibrinogen levels could be responsible for postoperative increases in platelet aggregation.<sup>33</sup> In support of this, Tuman *et al.* demonstrated postoperative increases in fibrinogen-platelet interaction that correlated with vascular thrombotic events.<sup>7</sup> We observed continued elevation

of fibrinogen at 72 h despite decreasing platelet reactivity. This argues against circulating fibrinogen levels being directly responsible for postoperative platelet reactivity. Furthermore, fibrinogen levels increased more in the placebo group without a comparable increase in platelet reactivity. Further investigation to elucidate the mechanisms involved in postoperative fibrinogen elevation and its interaction with platelet reactivity is needed.

In summary, changes in platelet aggregation and degranulation in patients undergoing major abdominal surgery indicate increased postoperative platelet reactivity, which is unaffected by clonidine administration. Therefore, clonidine should not be withheld perioperatively in this patient population for concern about increased platelet reactivity. The large percentage of patients in our study with cancer may have affected the results found, and whether these observations can be extended to other patient groups requires further study. The postoperative increase in platelet aggregation and dense granule secretion to all four agonists follows a similar time course, peaking within 24–48 h postoperatively. This temporal response closely follows the peak in postoperative myocardial infarction, unstable angina, and vascular graft occlusion observed in vascular surgery patients.<sup>7,34</sup> If a causal relationship can be demonstrated, this would suggest that patients at risk for vascular thrombotic events might benefit from antiplatelet therapy during this time period.

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