Anesthesiology
72:443–449, 1990

Ibuprofen Pretreatment Inhibits Prostacyclin Release during Abdominal Exploration in Aortic Surgery

Joanne C. Hudson, M.D., W. Heinrich Wurm, M.D.,* Thomas F. O'Donnell, Jr., M.D.,† Francis R. Kane, Ph.D.,* William C. Mackey, M.D.,‡ Ying-Fu Su, Ph.D.,§ W. David Watkins, M.D., Ph.D.¶*

Mesenteric traction during aortic surgery produces facial flushing, reduced mean arterial pressure (MAP), and systemic vascular resistance (SVR) with increased heart rate (HR) and cardiac index (CI). Elevated 6-keto-prostaglandin-$F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) suggests prostacyclin is the mediator. To test this hypothesis, the cyclooxygenase inhibitor, ibuprofen (n = 14), or placebo (n = 13) was administered to patients electively scheduled for aortic reconstruction. The hemodynamic measurements and plasma concentrations of prostanoids between groups were compared immediately before (0), and 5, 10, 15, 30, and 45 min following mesenteric traction. Following mesenteric traction significant differences ($P < 0.05$) were observed between the ibuprofen pretreatment and placebo group over time in SVR, MAP, HR, CI, 6-keto-$PGF_{1\alpha}$, and thromboxane B_2 (TXB_2). Significant differences between groups at individual times were found in SVR, HR, CI, 6-keto-$PGF_{1\alpha}$, and TXB_2. In the placebo group flushing was accompanied by reduced SVR and MAP and increased HR and CI. The greatest effect was seen at 10 min and resolved over 30 min. Plasma concentration of 6-keto-$PGF_{1\alpha}$ increased from 159 ± 103 (mean ± SEM) pg/ml to a peak value of 3,765 ± 803 at 10 min. A late increase in TXB_2 occurred with a peak value of 1,970 ± 891 (mean ± SEM) pg/ml at 30 min. In the ibuprofen pretreated group no significant changes occurred in hemodynamic measurements or concentrations of prostanoids. The inhibition of 6-keto-$PGF_{1\alpha}$ and its associated hemodynamic changes in the treatment group, but not in the placebo group, confirms the hypothesis that prostacyclin is the mediator of the mesenteric traction response in abdominal aortic surgery. (Key words: Anesthesia, general. Antagonists: prostaglandin. Hormones: prostaglandin. Surgery, abdominal: aortic.)

AS A CONSEQUENCE of traction on the mesentery and eventration of the bowel during aortic surgery, patients experience facial flushing with reduced systemic vascular resistance (SVR), reduced mean arterial pressure (MAP), increased heart rate (HR), and increased cardiac index (CI).[1–3] These events are associated in magnitude and time course with increased concentrations of the prostacyclin metabolite 6-keto-prostaglandin-$F_{1\alpha}$.[4,5] It is likely that local production of prostacyclin is causative because endothelial cells lining blood vessels[6] and the intestinal mucosa contain enzymes capable of synthesizing prostaglandins.[7–10] In addition, prostacyclin production from the intestines may be enhanced with endothelial injury, such as atherosclerosis or tissue hypoxia.[11] That prostacyclin is released from the intestines and/or its mesentery is supported by our previous study in which we compared hemodynamic parameters and blood concentration of 6-keto-$PGF_{1\alpha}$ in patients having the retroperitoneal approach with those having the transabdominal approach to aortic surgery.[3] Only those patients having the transabdominal approach experienced the profound reduction in SVR coincident with elevation in blood concentrations of 6-keto-$PGF_{1\alpha}$. This phenomenon was temporally related to exploration of the bowel. The absence of hemodynamic changes and unchanged blood concentration of 6-keto-$PGF_{1\alpha}$ in patients undergoing the retroperitoneal surgery indicated that the intestines was the likely source.

To further test this hypothesis, we performed a double-blind placebo-controlled study to determine if pretreatment with the cyclooxygenase inhibitor ibuprofen would prevent the hemodynamic consequences of this syndrome by inhibiting prostacyclin release.

Methods

In a prospective randomized, double-blind protocol approved by the Human Investigation Review Board at New England Medical Center, 29 patients who gave written informed consent and were scheduled for elective transabdominal aortic surgery were entered in the study. The patients were studied consecutively between September 1986 and March 1988. All electively scheduled patients agreed to participate. In cooperation with our pharmacy, the patients were assigned to receive either placebo or ibuprofen 800 mg po in three doses, 6 h apart, before surgery. The last dose was given at 6 A.M. All investigators were blinded as to treatment until after data analysis. At least 7 days prior to the operation, aspirin was discontinued. No patient was taking any nonsteroidal anti-inflammatory drugs that could influence the production of cycloxygenase.

* Associate Professor, Department of Anesthesiology.
† Professor and Chairman, Department of Surgery.
‡ Assistant Professor, Department of Surgery.
§ Assistant Medical Research Professor, Department of Anesthesiology.
¶ Professor and Chairman, Department of Anesthesiology.

Received from the Departments of Anesthesiology and Surgery, New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts (where the patients were studied), the Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina (where the samples were assayed), and the Department of Anesthesiology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia (where statistics were prepared). Accepted for publication October 11, 1989. Presented in part in abstract form in ANESTHESIOLOGY 69:A131, 1988.

Address reprint requests to Dr. Hudson: Department of Anesthesiology, MCV Station, Box 695, Richmond, Virginia 23298-0695.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/72/3/443/636092/0000542-199003000-00009.pdf by guest on 09 April 2024

All patients received intravenous (iv) fluids overnight at a rate of 70–80 ml/h and were denied food overnight. Patients customarily receiving β-adrenergic blocking drugs, long-acting nitrates, and calcium channel blocking drugs were given these medicines the morning of surgery. All patients received 0.1 mg/kg morphine and 0.05 mg/kg lorazepam intramuscularly (im) and their last po dose of either ibuprofen or placebo at 6 A.M. Additional sedation with iv diazepam in 2.5-mg increments was permitted as needed. Two iv catheters, a 20-G radial artery and a 7-Fr triple-lumen pulmonary artery thermodilution catheter, were inserted. Prior to time 0, 10–15 ml/kg of 5% dextrose in lactated Ringer's solution was infused until the pulmonary capillary wedge pressure (PCWP) was at least 10 mmHg but no greater than 15 mmHg.

Electrocardiographic leads II and V_5, along with the pulmonary artery pressure (PAP), central venous pressure (CVP), and arterial pressure, were recorded on a Hewlett-Packard multichannel recorder. Temperature and cardiac output (CO), determined in duplicate by injection of 10 ml room temperature saline at end expiration, were measured by a CO computer (Model 9520A, American Edwards Laboratory). Anesthesia consisted of 1–2 mg/kg thiopental or 0.3–0.5 mg/kg diazepam followed by 20 μg/kg fentanyl, oxygen 35–40% in nitrous oxide. Ventilation was controlled. Relaxation was obtained with 0.1 mg/kg pancuronium or pancuronium combined with metocurine iodide. Upon skin incision, if the systolic blood pressure reached 150 mmHg, isoflurane 1.5% was added to reduce the pressure below 150 mmHg. As soon as this was achieved, the isoflurane was reduced. Once the study began, the isoflurane concentration remained constant between 0.5% and 0.8%. Following mesenteric traction a reduction in systolic blood pressure was initially treated with an iv fluid bolus of 500 ml. If the reduction in systolic pressure was greater than 25% of the preinduction value or if the systolic pressure was reduced to 100 mmHg and fluids alone were unable to restore the blood pressure, a phenylephrine infusion was used. Arterial blood gases verified the adequacy of ventilation and oxygenation.

Hemodynamic measurements were taken at the following times: before induction, during the surgical preparation, at the time 0, and 5, 10, 15, 30, and 45 min thereafter. Time 0 was taken after the incision of the peritoneum but before any abdominal contents were handled. The surgeons paused to allow data collection at time 0, after which the operation proceeded without interruption; the surgeon explored the peritoneal cavity and retracted the small bowel, protecting it with wet Mikulicz pads. The posterior parietal peritoneum and ligament of Treitz were incised. The duodenum was separated from the aorta, and the preaortic sheath was opened. The aorta was not cross-clamped in any patient during data collection. Data at each time point included HR, systolic, diastolic, and mean arterial pressure (MAP), PAP, CVP, PCWP, and CO. Cardiac index (CI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated from standard formulas.[12] The change in facial color was observed and assigned a value: 0 if no change, 1^+ if mild, and 2^+ if marked flushing occurred. We recorded estimated blood loss and fluid replacement for each group. In each patient hemoglobin, hematocrit, BUN, and creatinine were measured daily for the first 2 postoperative days.

Blood samples for prostanoid analysis were collected with the hemodynamic data at time 0 and at 5-, 10-, 15-, 30-, and 45-min time periods. After the first 10 ml was discarded, 5 ml of blood was collected from the arterial catheter. Samples were slowly drawn into sterile disposable plastic syringes and transferred into heparinized polypropylene test tubes. They were placed on ice immediately, and plasma was isolated and stored at −80° C in preparation for prostanoid assay. Plasma concentration of prostacyclin and thromboxane A_2 (TXA_2) were measured by radioimmunoassay of the stable metabolites 6-keto-$PGF_{1\alpha}$ and thromboxane B_2 (TXB_2). The details of this double-antibody assay have been described previously.[13] The binding and inhibition curves were constructed with a four-parameter logistic method described by Rodbard.[14] Absolute lower level of detection is 50 pg/ml plasma with our system. All plasma samples were analyzed in duplicate, and standard curve samples were analyzed in triplicate. Radiolabeled tritiated 6-keto-$PGF_{1\alpha}$ was purchased from New England Nuclear, standard 6-keto-$PGF_{1\alpha}$ from the Upjohn Company, specific antiserum to 6-keto-$PGF_{1\alpha}$ from Biotex Company, and normal and goat antirabbit serum from Pel-Freez.

Five milliliters of arterial blood was drawn into a heparinized syringe, placed in polypropylene tubes, centrifuged at 2,000 × *g* for 20 min, and then the plasma was frozen at −80° C. The plasma ibuprofen concentrations were analyzed by high-performance liquid chromatography (HPLC) by the Hazelton Laboratories America, Inc. (Madison, Wisconsin).[15] The lower limit of quantification is 0.5 μg/ml. The intraassay and interassay coefficient of variation were both 10%. Blank human plasma was used for the standard curve and was obtained from volunteers and checked for assay interference before use.

Data are expressed as mean ± SE. Demographic data were analyzed by unpaired Student's *t* test or Fisher's exact test. To test for treatment effects using a repeated measures analysis of variance (ANOVA) with random patient effects, we first determined if the effect of treatment varied over time between the ibuprofen and placebo group in each of the hemodynamic variables. A *P* value of less than 0.05 was considered significant. The patients were considered random effects, implying that our conclusions will be applicable to all patients and not just those

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/72/3/443/636092/0000542-199003000-00009.pdf by guest on 09 April 2024

observed in this study. If it was found that there was an interaction that varies over time, we then examined the effect of treatment *versus* placebo at each of the time periods using the Bonferroni correction.[16] To maintain a $P < 0.05$ for the overall test, we adjusted this level for each of the separate six tests, so that the P level of less than $0.05/6 = 0.0083$ was considered significant. The Spearman correlation coefficient was used to test for rank correlations between hemodynamic variables.

Results

Twenty-seven patients completed the study; two patients were eliminated because either the data or blood sampling were incomplete. The ibuprofen (n = 14) treated group consisted of nine males, five females, mean age 56 ± 11 yr (mean ± SD), and mean body surface area (BSA) of 1.90 ± 0.21. The placebo (n = 13) group consisted of ten males, three females, mean age 66 ± 7 yr, and mean body surface area of 1.95 ± 0.23. The groups were not statistically different in age, height, weight, body surface area, history of previous myocardial infarction, congestive heart failure, history of angina, hypertension, diabetes mellitus, smoking, or medication with β-adrenergic or calcium channel blocking drugs, nitrates, digitalis, diuretics, or antiarrhythmics.

There were significant differences, as determined by the two-way ANOVA, between the treatment group and placebo group over time in SVR, MAP, HR, CI, 6-keto-$PGF_{1\alpha}$, and TXB_2. Significant differences between groups at individual times were found in SVR, HR, and CI (fig. 1) and 6-keto-$PGF_{1\alpha}$ and TXB_2 (fig. 2). There was no difference between groups in any hemodynamic variable, 6-keto-$PGF_{1\alpha}$ or TXB_2 at time 0. The mean ibuprofen concentration was 20.6 ± 2.31 (mean ± SEM) μg/ml in the ibuprofen-treated group and 0.51 ± 0.01 μg/ml in the placebo group. In the treatment group the range was 9.65 to 35.9 μg/ml. In the placebo group 12 patients had

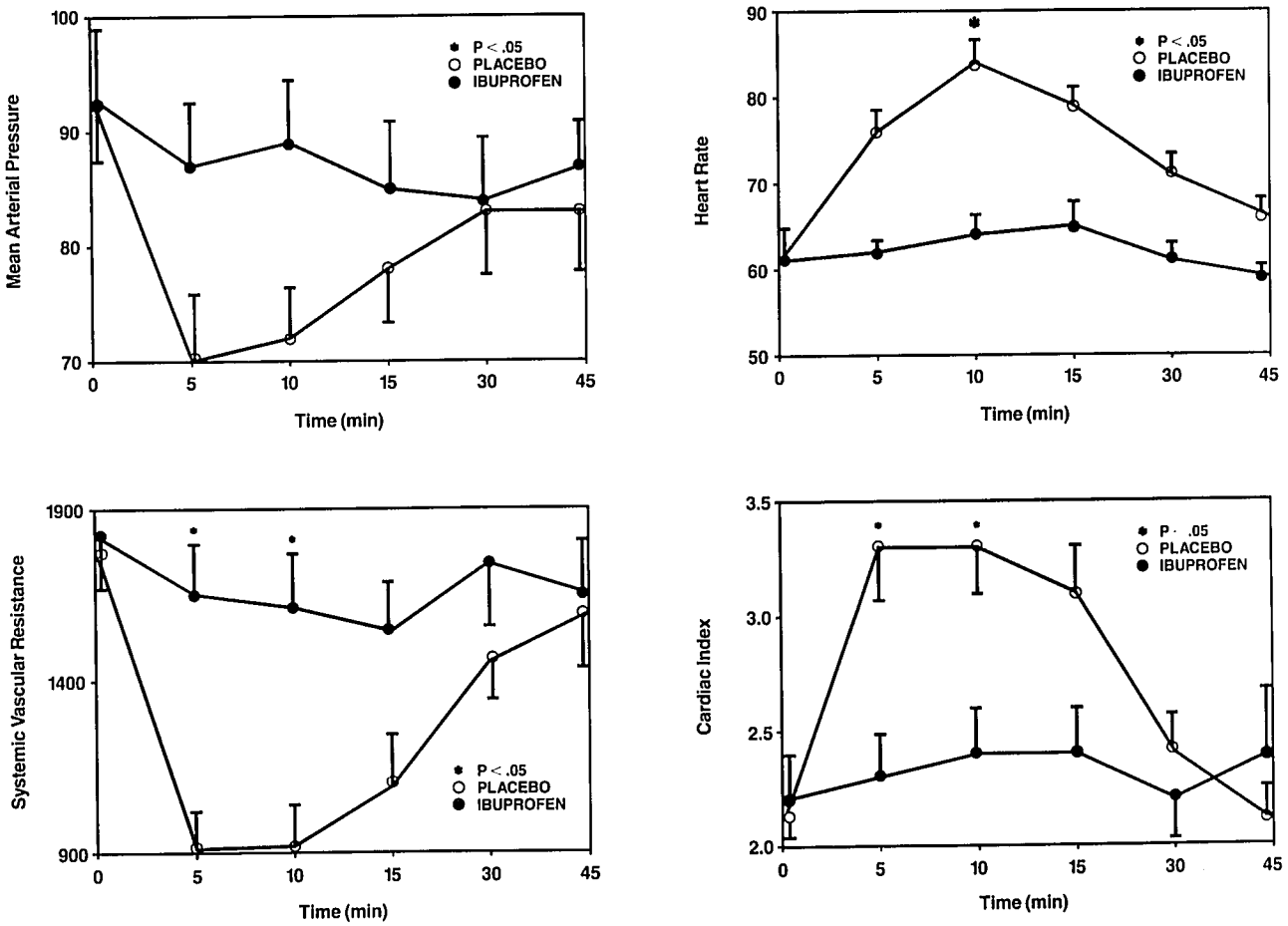

FIG. 1. Differences in hemodynamic variables during abdominal exploration between the placebo group (n = 13) and the ibuprofen-pretreated group (n = 14) of patients having aortic surgery. Time zero is immediately preceding exploration. MAP is measured in mmHg, SVR in dynes · s · cm^5, CI in $l \cdot min^{-1} \cdot BSA^{-1}$, and HR in beats/min. Values are mean ± SEM. P values were determined using the two-way ANOVA and applying the Bonferroni correction.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/72/3/443/636092/0000542-199003000-00009.pdf by guest on 09 April 2024

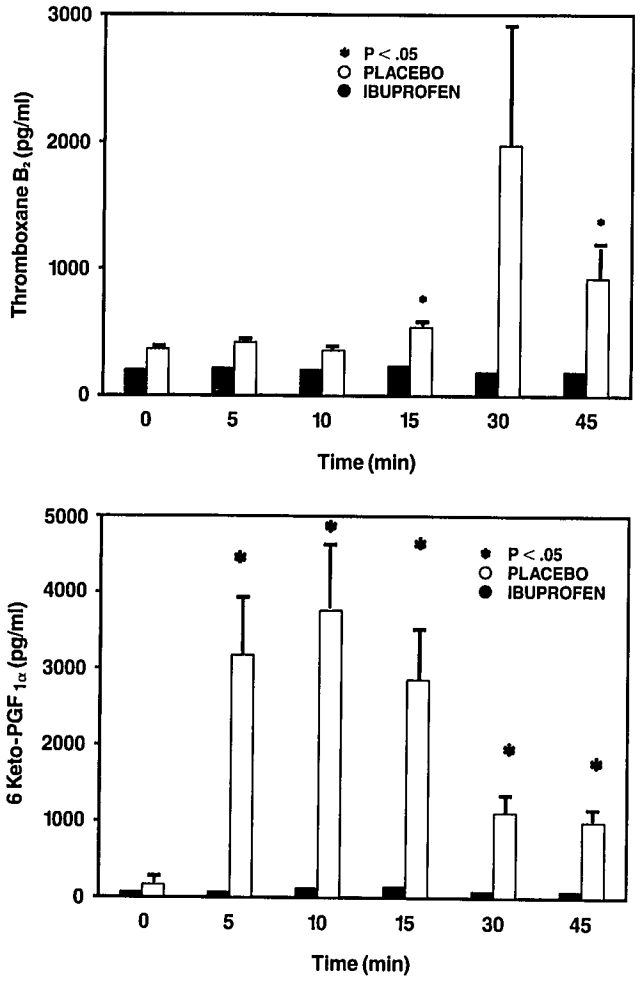

FIG. 2. Plasma concentrations of 6-keto-$PGF_{1\alpha}$ (pg/ml) and TXB_2 (pg/ml) of the placebo group (n = 13) and the ibuprofen-pretreated group (n = 14) during abdominal exploration in patients having aortic surgery. Values are mean ± SEM. *P* values were determined using the two-way ANOVA and applying the Bonferroni correction.

a concentration < 0.5 μg/ml, and in one patient the ibuprofen concentration was 0.62 μg/ml.

With exploration of the abdomen, the placebo group showed a decrease in SVR and MAP and an increase in CI and HR (fig. 1). These changes peaked at 10 min and resolved over 30 min. The changes in prostanoids are seen in figure 2. A significant ($P < 0.05$) increase in 6-keto-$PGF_{1\alpha}$ occurs in the placebo group, which peaks at 10 min and declines over the data collection period. In addition, an increase occurred in TXB_2 starting at 15 min, and peaking at 30 min with possible resolution beginning at 45 min (fig. 2). In the ibuprofen-treated group these changes were absent, and the 6-keto-$PGF_{1\alpha}$ and TXB_2 concentration remained at preexploration values (time 0).

No differences were seen between ibuprofen treatment and placebo groups in PAP, PCWP, CVP, or PVR (table 1). Each patient received between 500 and 1,000 ml to achieve a PCWP between 10 and 15 mmHg prior to the time 0. No patient required a vasodilator to achieve this. In the ibuprofen group a score of 0 flushing was observed in ten patients, a score of 1 in three patients, and a score of 2 in one patient. The mean flush score was 0.36 ± 0.17 (mean ± SEM). In patients who were administered placebo a score of 0 flushing was observed in two patients, a score of 1 in four patients, and a score of 2 in seven patients. The mean score for facial flushing was 1.46 ± 0.24 (mean ± SEM) in the placebo group and 0.36 ± 0.17 in the treatment group. The difference between mean scores was significant ($P < 0.01$). Isoflurane was used in six patients in the placebo group and in 11 patients in the ibuprofen group. This difference was not significant. Phenylephrine was used in eight patients in the placebo group and two patients in the treatment group. This difference is significant ($P < 0.05$). There was no difference between groups in blood loss or in replacement with packed red blood cells or crystalloid, or in length of operation. There was no difference between groups in the hematocrit and no evidence of elevated BUN or creatinine in the first 2 postoperative days (table 2). One patient in the placebo group developed a myocardial infarction following tracheal extubation accompanied by a prolonged episode of tachycardia 15 h after surgery. One patient in the ibuprofen group died the first postoperative day of a massive myocardial infarction. Following the study period the aneurysm in this patient was ruptured during surgery. The patient experienced severe hypotension for an extended time.

Using the Spearman correlation coefficient, significant correlation ($P < 0.001$) was found in the placebo group between the 6-keto-$PGF_{1\alpha}$ concentration and MAP, CI, SVR, PVR, and HR; the *r* values were −0.46, +0.59, −0.60, −0.47, and +0.49, respectively. When the peak prostacyclin concentration was correlated with the flush score, a significant correlation was found in the placebo group ($P < 0.01$, $r = 0.64$). There was no correlation with TXB_2 concentration and any variable in the placebo group. In the ibuprofen-treated group, there was a significant correlation between 6-keto-$PGF_{1\alpha}$ concentration and HR ($P < 0.01$, $r = 0.30$) and between TXB_2 concentration, and MAP and HR ($P < 0.001$, $r = 0.46$; $P < 0.01$, $r = 0.33$, respectively).

Discussion

The results of this study are consistent with studies that indicate that high concentrations of prostacyclin are released during bowel manipulation in aortic surgery. In-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/72/3/443/636092/0000542-199003000-00009.pdf by guest on 09 April 2024

TABLE 1. Hemodynamic Variables in Placebo Group (P) (n = 13) and Ibuprofen-treated Group (I) (n = 14) during Abdominal Exploration

	Group	Time (min)					
		0	5	10	15	30	45
CVP	P	9.2 ± 1.4	9.1 ± 1.2	9.0 ± 1.2	7.2 ± 1.2	7.2 ± 1.2	7.8 ± 0.9
	I	9.3 ± 0.9	8.2 ± 1.0	9.1 ± 1.3	7.9 ± 0.9	8.4 ± 1.0	9.3 ± 1.2
PCWP	P	13.1 ± 1.4	12.2 ± 1.8	11.7 ± 1.6	10.6 ± 1.4	9.0 ± 1.1	9.8 ± 1.2
	I	12.3 ± 1.2	13.5 ± 1.3	12.2 ± 7.0	11.1 ± 1.0	10.6 ± 1.3	12.2 ± 1.6
PAP	P	20.5 ± 1.5	20.3 ± 1.8	20.4 ± 1.0	20.5 ± 2.1	18.0 ± 1.6	17.7 ± 1.7
	I	19.3 ± 1.6	19.7 ± 2.1	18.5 ± 1.4	17.2 ± 1.2	16.7 ± 1.4	18.2 ± 2.0
PVR	P	153 ± 17	112 ± 16	117 ± 13	141 ± 19	161 ± 21	166 ± 20
	I	149 ± 22	130 ± 23	117 ± 12	120 ± 13	137 ± 1.7	120 ± 15

Values are mean ± SEM. No significant differences ($P < 0.05$) were found between groups.

hibition of prostanoid synthesis by the enzyme inhibitor ibuprofen and its associated hemodynamic changes in the ibuprofen-treated group, but not in the placebo group, supports the hypothesis that prostacyclin is the causative agent.

As described in an earlier study in 13 patients having aortic surgery, Seeling *et al.*[4] reported prostacyclin concentrations after traction of the bowel. The median concentration of 6-keto-$PGF_{1\alpha}$ was 1,169 pg/ml with a range of 60–3,843 pg/ml at 5 min and 1,098 pg/ml with a range of 60–2,860 pg/ml at 15 min after traction of the bowel. In a previous study we demonstrated that the stimulus of this prostacyclin production was most likely the abdominal contents by comparing 33 patients having the transabdominal incision for aortic surgery with 19 patients have the retroperitoneal approach.[3] We found prostacyclin release and reduced SVR only in the group who had manipulation of the abdominal contents during the transabdominal approach; no prostacyclin release or reduced SVR occurred during exposure of the aorta using the retroperitoneal approach. Peak changes in 6-keto-$PGF_{1\alpha}$ (1,689 ± 303 pg/ml) and maximum reduction in SVR occurred 10 min following the onset of the manipulation of the abdominal contents and resolved after 30 min. We documented the parallel association of increased prostacyclin with reduced SVR, reduced MAP, increased HR, and increased CO. The concentrations of prostacyclin in our previous study at 5 and 15 min (647 ± 176 and 1,124 ± 218 pg/ml, respectively) are comparable in concentration and time to those in the study by Seeling *et al.*[4]

TABLE 2. Comparison of Operative and Postoperative Data Between Placebo and Ibuprofen-treated Groups

	Placebo	Ibuprofen
Estimated blood loss (ml)	2,650 ± 604	2,097 ± 444
Replacement fluid		
Packed cells (units)	1.92 ± 0.45	3.11 ± 0.55
Cell saver (ml)	324 ± 234	407 ± 182
Cystalloid (ml)	8,316 ± 687	8,191 ± 490
Surgical time (min)	422 ± 60	372 ± 25
Postoperative day 1		
Hematocrit	32 ± 0.7	31.6 ± 0.7
BUN	8.25 ± 1.7	10 ± 2.0
Creatinine	1.01 ± 0.2	0.82 ± 0.5
Weight (kg)		
Preoperative	74 ± 7.6	70 ± 3.7
Postoperative	83 ± 8.2	79 ± 4.1

Values are mean ± SEM. No significant ($P < 0.05$) differences were found between groups.

Seltzer *et al.* also reported prostacyclin release in aortic surgery.[17] They studied 12 patients, four of whom were pretreated with ibuprofen 12 mg/kg po 1–1.5 h preoperatively. Approximating the values they displayed in graph form, in eight untreated patients they found plasma 6-keto-$PGF_{1\alpha}$ concentrations at 5, 15, and 30 min of 9.0 ± 1.1 (mean ± SEM), 4.9 ± 0.8, and 3.4 ± 0.8 pmol/ml, respectively. Converting these values to picograms per milliliter (the units used in this study), the results of Seltzer *et al.*[17] are the equivalent of 3,168 ± 458, 1,760 ± 280, and 1,126 ± 280 pg/ml, respectively. Thus, the values of Seltzer *et al.*[17] for untreated patients are in the same range as our values in this study at the same time periods (3,179 ± 735, 2,858 ± 593, and 1,114 ± 230 pg/ml, respectively). As in our study, the four ibuprofen-treated patients demonstrated no prostacyclin release.[17] Furthermore, they demonstrated that the plasma of untreated patients was able to produce vasodilation in a cat mesenteric artery preparation, whereas the plasma from the ibuprofen-treated patients was not.[17] This is additional evidence that the response to mesenteric traction is mediated by the humoral vasodilating agent prostacyclin.

Even before prostacyclin release was associated with traction on mesentery, Krausz *et al.* measured prostacyclin release at intervals throughout aortic surgery in 21 patients.[18] They documented inhibition of prostacyclin by aspirin, an irreversible inhibitor of platelet cyclooxygenase.[19] Thirteen patients received 650 mg of aspirin 12 h po prior to the operation; eight received placebo. In the placebo group 6-keto-$PGF_{1\alpha}$ concentrations rose to 950 ± 290 (mean ± SEM) pg/ml 30 min after the start of

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/72/3/443/636092/0000542-199003000-00009.pdf by guest on 09 April 2024

surgery. This was associated with a decrease in MAP and an increase in CI. Unfortunately, there was no comment relating the elevation of 6-keto-$PGF_{1\alpha}$ to surgical activity. These authors made no reference to the intestines. They concluded that this represented prostacyclin release from the lung and that it was related to the surgical incision made 30 min earlier. The time after incision leads us to believe that this increase in 6-keto-$PGF_{1\alpha}$ may have occurred during exploration of the abdomen. Our study was designed to investigate the role of prostacyclin during the mesenteric traction response, not to evaluate or advocate routine pretreatment with ibuprofen. However, because of the ability of ibuprofen to interfere with platelet function and autoregulation of the kidney,[20] we observed the patients postoperatively and found no evidence of altered renal function (elevated BUN or creatinine), or renal failure in any patient and no evidence of significant differences in estimated blood loss or fluid replacement between the groups.

Recently, prostacyclin release was associated with peritoneal closure in patients undergoing cesarean section.[21] In four patients Matsumoto *et al.* demonstrated elevated $PGF_{1\alpha}$ concentrations in plasma associated with reduced blood pressure, increased HR, and flushing.[21] The peak concentrations ranged from 2.59 pmol/ml (912 pg/ml) to 6.29 pmol/ml (2,246 pg/ml). Maximal changes were observed at 5 min after the start of the closure. Return to baseline was seen within 20 min. These results suggest that other procedures in the abdomen may be associated with prostacyclin release. Prostacyclin release should now be a consideration in the differential diagnosis of hypotension occurring during abdominal surgery.

Our data provide evidence in humans that low plasma ibuprofen concentrations are effective in inhibiting prostacyclin synthesis. In this study the mean plasma ibuprofen concentration was 20.6 ± 2.31 (mean ± SEM) μg/ml. Individual plasma concentrations in the treatment group suggest effectiveness in prostacyclin inhibition starting as low as 9 μg/ml (fig. 3). All but one placebo patient had an ibuprofen concentration less than the lower limit of detection (0.5 μg/ml). The one patient with a concentration of 0.62 μg/ml may represent the presence of residual ibuprofen or may represent a cross-reactivity with some unknown medication. This low concentration of ibuprofen did not prevent release of high concentrations of 6-keto-$PGF_{1\alpha}$ (<50, 2,047, 2,896, and 1,897 pg/ml at time 0, 5, 10, and 15 min, respectively) in this patient. The effectiveness of low doses in our treatment group may have implications for clinical investigation of ibuprofen in other areas, such as the treatment of septic shock or adult respiratory distress syndrome.

An interesting and previously unreported phenomenon was the delayed increase in concentrations of TXB_2 (fig. 2). Seltzer *et al.*[17] and Matsumoto *et al.*[21] did not report

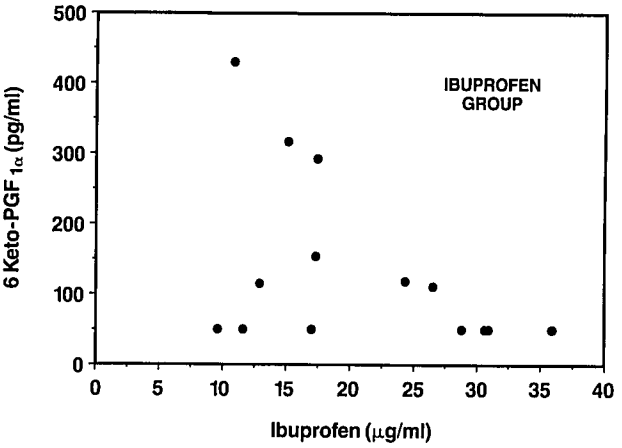

FIG. 3. Plasma concentrations of ibuprofen at preexploration (time 0) plotted against peak concentrations of plasma 6-keto-$PGF_{1\alpha}$ achieved in each of the ibuprofen-treated patients (n = 14).

measurement of TXB_2. Krausz *et al.*,[18] Huval *et al.*,[22] Seeling *et al.*,[4] and Gottlieb *et al.*[5] measured plasma TXB_2, but none of these authors did so at a time corresponding to our observations at 30 and 45 min. Krausz *et al.*[18] and Huval *et al.*[22] who examined prostanoid release during aortic surgery used the same times for data collection: before anesthesia, 30 min after incision, 30 min after aortic cross-clamping, and 5 min after removal of the clamp. Krausz *et al.*[18] reported a preoperative TXB_2 value of 68 ± 13 pg/ml (mean ± SEM), no change after incision but a significant increase during aortic clamping, 111 ± 20 pg/ml (mean ± SEM). Similarly, Huval *et al.*[22] found a preoperative value of 60 pg/ml (estimated from their graph) unchanged until 30 min after aortic cross-clamping 230 ± 30 pg/ml (mean ± SEM). Aspirin[18] and ibuprofen[22] pretreatment suppressed this thromboxane production. As performed by the authors in the two previous studies, Gottlieb *et al.*[5] examined only one time during mesenteric traction, the time of maximum 0-ring retraction. This corresponds to our 5-min time. Gottlieb *et al.*[5] reported the median TXB_2 concentrations, 85 pg/ml, before traction, rising to 146 pg/ml at maximal 0-ring retraction; the range of these results was not reported. In an additional six patients given aspirin, the TXB_2 concentrations were below the detection limit (41 pg/ml) in four patients. In two patients concentrations were reported as 372, 418, and 145 pg/ml and 100, 144, and 120 pg/ml for times before, during traction, and after flow to the extremities was reestablished. The values of these two patients in whom TXB_2 production should be suppressed demonstrated variability not unlike our results (fig. 3). Seeling *et al.*[4] reported prostanoid concentrations before, 5 min after, and 15 min after mesenteric traction only. In 13 patients they reported median TXB_2 concentrations of <60 pg/ml at all three times. However, they also reported

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/72/3/443/636092/0000542-199003000-00009.pdf by guest on 09 April 2024

these ranges: 60–239, 60–439, and 60–415 pg/ml (before, 5 min after and 15 min after, respectively). Our TXB_2 concentrations (mean ± SEM) in the placebo group at the time of mesenteric traction (0, 5, 10, 15, 30, and 45 min) were as follows: 364 ± 80, 416 ± 62, 354 ± 46, 539 ± 71, 1,970 ± 891, and 923 ± 259 pg/ml, respectively.

We found considerable variability in TXB_2 production among our placebo patients. Perhaps thromboxane synthesis reflects the severity of vascular disease. In any event the variability of our data is so great at the 30-min time that the difference in values between ibuprofen and placebo groups is not significant (fig. 3). No other author described data at the 30-min time period when we see the greatest change. Other reports[18,22] indicated that the most significant increase in thromboxane synthesis during aortic surgery occurs during aortic cross-clamping. We did not take samples at that time; our focus was upon mesenteric traction. Our results demonstrate a late rise in TXB_2. This late rise, like prostacyclin, was prevented by ibuprofen. We speculate that this increase represents the regulatory response to elevated prostacyclin synthesis and vasodilation, which in turn stimulates an autoregulatory compensation and synthesis of the vasoconstrictor TXB_2.

In conclusion, this study confirms the hypothesis that prostacyclin mediates the traction response during aortic surgery. In addition, it suggests that prostacyclin release in these patients stimulates a compensatory increase in TXB_2, suggesting that these prostanoids act together in local hormonal-like regulations of vasculature. And finally, ibuprofen in low plasma concentration can prevent prostacyclin release.

References

1. Seltzer JL, Ritter DE, Starsnic MA, Marr AT: The hemodynamic response to traction on the abdominal mesentery. ANESTHESIOLOGY 63:96–99, 1985
2. Seeling W, Ahnefeld FW, Hamann H, Heinrich H, Hutschenreiter S, Rosenberg G, Spilker D, Vollmar J: Aortofemoraler Bifurkationsbypass—Der Einfluß des Anaesthesieverfahrens (NLA, thorakale knotinuierliche Katheterperiduralanaesthesie) auf Kreislauf, Atmung und Stoeffwechsel. Anaesthesist 34:417–428, 1985
3. Hudson JC, Wurm WH, O'Donnell TF Jr, Schoenfeld NA, Mackey WC, Callow AD, Su YF, Watkins WD: Hemodynamics and prostacyclin release in the early phases of aortic surgery: Comparison of transabdominal and retroperitoneal approaches. J Vasc Surg 7:190–198, 1988
4. Seeling W, Heinrich H, Oettinger W: Das Eventerationssyndrom: Prostacyclinfreistezung und akuter paO_2—Abfall durch Dünndarmeventeration. [The eventration syndrome: Prostacyclin liberation and hypoxaemia due to eventration of the gut.] Anaesthesist 35:738–743, 1986
5. Gottlieb A, Butkus A, Skrinska V, Augereau JP, O'Hara P, Boutros A: The role of prostacyclin in the mesenteric traction syndrome during anesthesia for abdominal aortic reconstructive surgery. Ann Surg 209:363–367, 1989
6. Moncada S, Gryglewski R, Bunting S, Vane JR: An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature 263: 663–665, 1976
7. Balaa MA, Powell DW: Prostaglandin synthesis by enterocyte microsomes of rabbit small intestine. Prostaglandins 31:609–624, 1986
8. Sanders KM, Northrup TE: Prostaglandin synthesis by microsomes of circular and longitudinal gastrointestinal muscles. Am J Physiol 244(Gastrointest Liver Physiol 7):442, 1983
9. Craven PA, DeRubertis FR: Patterns of prostaglandin synthesis and degradation in isolated superficial and proliferative colonic epithelial cells compared to residual colon. Prostaglandins 26: 583, 1983
10. Boughton-Smith NK, Hawkey CJ, Whittle BJR: Biosynthesis of lipoxygenase and cyclo-oxygenase products from [^{14}C]-arachidonic acid by human colonic mucosa. Gut 24:1176, 1983
11. Fitzgerald GA, Smith B, Pedersen AK, Brash AR: Increased prostacyclin biosynthesis in patients with severe atherosclerosis and platelet activation. N Engl J Med 310:1065–1068, 1984
12. Kaplan JA: Hemodynamic monitoring, Cardiac Anesthesia, 2nd edition, Vol. 1. Edited by Kaplan JA. Philadelphia, Grune & Stratton, 1987, p 203
13. Hales CA, Sonne L, Peterson M, Kong D, Miller M, Watkins WD: Role of thromboxane and prostacyclin in pulmonary vasomotor changes after endotoxin in dogs. J Clin Invest 68:497–505, 1981
14. Rodbard D: Statistical quality control and routine data processing for radioimmunoassays and immunoradiometric assays. Clin Chem 20:1255–1270, 1974
15. Lockwood GF, Wagner JG: High-performance liquid chromatographic determination of ibuprofen and its major metabolites in biological fluids. J Chromatogr 232:335–343, 1982
16. Elston RC, Johnson WD: Essentials of Biostatistics. Philadelphia, FA Davis, 1987, p 250
17. Seltzer JL, Goldberg ME, Larijani GE, Ritter DE, Starsnic MA, Stahl GL, Lefer AM: Prostacyclin mediation of vasodilation following mesenteric traction. ANESTHESIOLOGY 68:514–518, 1988
18. Krausz MM, Utsunomiya T, McIrvine AJ, Allen PD, Levine L, Mannick JA, Shepro D, Hechtman HB: Modulation of cardiovascular function and platelet survival by endogenous prostacyclin released during surgery. Surgery 93:554–559, 1983
19. Roth GJ, Majerus PW: The mechanism of the effect of aspirin on human platelets. I. Acetylation of a particulate fraction protein. J Clin Invest 56:624–632, 1975
20. Clive DM, Stoff JS: Renal syndromes associated with nonsteroidal antiinflammatory drugs. N Engl J Med 310:563–572, 1984
21. Matsumoto, M, Hideo O, Takao O: An increase in prostacyclin accompanies reduction of blood pressure following peritoneal closure in patients undergoing cesarean section (letter). ANESTHESIOLOGY 71:170, 1989
22. Huval WV, Lelcuk S, Allen PD, Mannic JA, Shepro D, Hechtman HB: Determinants of cardiovascular stability during abdominal aortic aneurysmectomy. Ann Surg 199:216–222, 1984

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/72/3/443/636092/0000542-199003000-00009.pdf by guest on 09 April 2024