

Prostacyclin Mediation of Vasodilation Following Mesenteric Traction

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Eight untreated patients (group I) and four patients who received ibuprofen preoperatively (group II) scheduled for elective abdominal aortic aneurysm repair were studied. Heart rate (HR); systolic, diastolic, and mean arterial pressure (MAP); systolic and diastolic pulmonary artery pressure; pulmonary capillary wedge pressure (PCWP); cardiac output (CO); and central venous pressure (CVP) were recorded pre-induction, before mesenteric traction, and 5, 15, and 30 min post-mesenteric traction. Plasma samples were obtained at these times for analysis of six-keto-prostaglandin F_{1α} (PGF_{1α}) concentration by radioimmunoassay. Group II patients received ibuprofen 12 mg/kg orally 1½ h before surgery. Plasma samples from six group I patients and all group II patients taken 5 min after mesenteric traction were added to isolated helical strips of cat superior mesenteric arteries precontracted with norepinephrine (200 ng/ml) for analysis of reduction in developed force. In group I, abdominal mesenteric traction resulted in a significant decrease in MAP ($P < 0.03$) and SVR ($P < 0.005$) with an increase in CO ($P < 0.05$) at 5 min post-mesenteric traction, which returned to mean pre-mesenteric traction values by 30 min and a significant increase in PGF_{1α} concentrations. There was a significant positive correlation between PGF_{1α} and CO ($P < 0.001$) and a significant negative correlation between PGF_{1α} and SVR ($P < 0.01$) at 5 min post-mesenteric traction. Post-mesenteric traction plasma samples added to the cat mesenteric artery preparation resulted in vasodilation, as demonstrated by a reduction in developed force of 0.563 ± 0.092 grams, as compared to the reduction by pre-mesenteric traction plasma values of 0.12 ± 0.11 grams ($P < 0.01$). Group II patients did not develop significant increases in PGF_{1α}, and 5-min post-mesenteric traction plasma samples did not significantly relax the cat mesenteric artery preparations. There were no changes in MAP, SVR, and CO in group II patients. Flushing of the head and neck in association with mesenteric traction was noted in group I only. (Key words: Blood pressure; systemic vascular resistance. Gastrointestinal tract: mesenteric traction. Heart: cardiac output. Hormones: prostacyclin; prostaglandin F_{1α}. Reflexes. Surgery: abdominal.)

IN A PREVIOUS STUDY, we demonstrated that traction on the abdominal mesentery resulted in decreased systemic vascular resistance, increased cardiac output, and flushing of the head and neck.¹ These results were in direct contrast to those presented by several authors who presumed that the fall in blood pressure seen with mesenteric traction was due to a fall in cardiac output.²⁻⁵ The time sequence between onset of traction and the hemodynamic and cutaneous findings suggest that they are mediated by the release of hormonal substances. The splanchnic organs are capable of producing a variety of substances, including peptides, amines, and lipids, which might play a role in this response.⁶ Once such vasodilator produced in response to deformation of blood vessels is prostacyclin (PGI₂). Prostacyclin has been shown to be a potent vasodilator⁷ that is released from the gastrointestinal mucosa of many species,⁸ including humans.^{††} We, therefore, examined the potential role of PGI₂ in the hemodynamic changes associated with traction on the abdominal mesentery and the effect that ibuprofen, a PGI₂ inhibitor, has on blunting this response.

Materials and Methods

Twelve ASA physical status II-IV adult patients scheduled for elective abdominal aortic aneurysm repair gave informed consent to participate in this study, which was approved by our Institutional Review Board. The patients ranged in age from 63-79 yr, in weight from 53-94 kg, and in height from 140-177.5 cm. Ten patients had a history of arteriosclerotic cardiovascular disease and hypertension. Four patients were receiving beta adrenergic blocking drugs, while eight were receiving other antihypertensive agents. All cardiovascular medications were administered the morning of surgery. Eight patients who did not receive pre-treatment with ibuprofen constitute group I. Four patients, group II, were given ibuprofen 12 mg/kg orally 1½ h preoperatively. All patients were premedicated with 0.08 mg/kg of morphine sulfate and glycopyrolate 0.2 mg

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im approximately 1 h prior to induction of anesthesia. Intravenous, radial artery, and thermodilution pulmonary artery catheters were inserted, and baseline awake hemodynamic measurements were obtained. Heart rate (HR), systolic, diastolic, and mean arterial pressure (MAP), systolic (PA_s), and diastolic pulmonary artery pressure (PA_D), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were recorded from Cobe transducers utilizing a Hewlett-Packard® monitor. Cardiac output was determined in triplicate at end-expiration utilizing 10 ml of room temperature 5% dextrose in H₂O injected into the right atrial lumen of an Edwards Laboratory triple lumen pulmonary artery catheter (Model 93A-831H) connected to an Edwards Laboratory Model 9520A cardiac output computer. Systemic vascular resistance was calculated according to a standard formula.⁹

Anesthesia was induced with fentanyl 4–6 µg/kg iv, thiopental 4–6 mg/kg iv, and 60% N₂O in O₂. The trachea was intubated and ventilation controlled after injection of vecuronium 0.08 mg/kg. Isoflurane was administered when clinically indicated by a 20% increase in HR or systemic systolic blood pressure. Prior to cross clamping the aorta, mesenteric traction was accomplished by exteriorizing the small bowel and applying retractors to allow exposure of the abdominal aorta. Inspired concentrations of N₂O and isoflurane, if used, were not changed during the study measurements, and no vasoactive drugs were given during the study period. The surgeons maintained the traction, but did not begin aortic dissection until the 5-min post-traction data were obtained. Hemodynamic measurements were made and 20 ml blood samples obtained from the radial artery catheter prior to induction of anesthesia, immediately prior to mesenteric traction, and 5, 15, and 30 min after the traction. All samples were immediately centrifuged. The plasma was harvested and frozen at -20° C for subsequent analysis of 6-keto-PGF_{1α} (PGF_{1α}) concentrations by the radioimmunoassay method of Ingerman-Wojenski *et al.*¹⁰ This method measures the concentration of PGF_{1α}, the stable breakdown product of PGI₂. The limit of detection of this assay was 0.25 pmol/ml. The PGF_{1α} antiserum (produced in our laboratory) employed in this study at a dilution of 1:2,500 exhibited the following cross-reactivities expressed in pmol for inhibition of 50% binding: PGF_{1α}, 1.0; PGF_{2α}, 80; PGE, 100; 6, 15-diketo-PGF_{1α} > 1,000, PGD₂ > 1,000, TxB₂, > 1,000 and arachadonic acid > 100,000. Plasma samples from all patients taken 5 min post-traction were also added to isolated helical strips of cat superior mesenteric arteries according to the method of Glucksman and Lefer.¹¹ This method uses transverse strips of the superior mesenteric artery taken from within 1 cm of its origin at the

aorta. The strips were placed in 10 ml tissue baths containing a freshly prepared solution of: KCl 4.75 mM, KH₂PO₄ 1.19 mM, MgSO₄ · 7 H₂O 1.19 mM, CaCl₂ · 2 H₂O 2.54 mM, NaCl 118 mM, NaHCO₃ 12.5 mM, and glucose 10.0 mM. The bath temperature was maintained at 36.5 ± 0.5° C and perfused with 95% O₂ + 5% CO₂. The arterial strips were allowed to equilibrate for 60–180 min. The arterial strips did not exhibit spontaneous changes in tone in the absence of norepinephrine once equilibration was complete. Developed forces were measured with a Grass FT-03 strain-gauge transducer and recorded on a Grass Model 7 oscillographic recorder. Mesenteric artery strips were precontracted with 200 ng/ml of norepinephrine and the developed force was recorded in response to 2 ml of plasma added to 10 ml of Krebs-Henseleit solution to yield a final volume of 12 ml. The stable analog of PGI₂, iloprost was used as a reference standard.

A two-way ANOVA with repeated measures on time were used to determine the significance of differences among dependent variables. To determine the relationship between 6 keto PGF_{1α} concentrations and SVR or CO at 5, 15, and 30 min after traction, a Pearson correlation coefficient was calculated for the relation of 6 keto PGF_{1α} to CO and SVR. A *P* < 0.05 was considered significant. All data are expressed as means ± standard error of the mean.

Results

In group I patients, abdominal mesenteric traction resulted in a significant decrease in MAP and SVR at 5 min post-traction, which returned to pre-traction values by 15 and 30 min, respectively (table 1). This was associated with a parallel increase in cardiac output that returned to pre-traction levels by 30 min. CVP, PCWP, PAS, PAD, and HR were unchanged from the pre-mesenteric traction values. There was also a significant increase in PGF_{1α} concentrations associated with mesenteric traction (fig. 1). There was a significant positive correlation between the cardiac output and PGF_{1α} levels, *R* = 0.86 (*P* < 0.001), and a significant indirect association between PGF_{1α} and SVR *R* = 0.63 (*P* < 0.01), at 5 min post-mesenteric traction (CO = 4.27 + 0.21 PGF_{1α} and SVR = 1474 - 63PGF_{1α}).

Figure 2 demonstrates vasodilation when the 5-min plasma samples are added to the bathing medium of an isolated cat mesenteric artery preparation which has previously been constricted with norepinephrine. Norepinephrine (200 ng/ml) contracted the cat mesenteric artery strips by 1.56 ± 0.13 grams of developed force (mean ± SEM) in ten isolated vessels. There was adequate plasma available for mesenteric artery preparation testing from six of the eight patients in group I.

TABLE 1. Hemodynamic Alterations in Response to Mesenteric Traction in Eight Patients Who Did Not Receive Ibuprofen Preoperatively (Group I) (Mean \pm SEM)

	Awake	Pre-traction	5 Min	15 Min	30 Min
HR bpm	71.9 \pm 3.4	60.0 \pm 2.7	71.6 \pm 4.9	69.8 \pm 3.0	69.1 \pm 3.5
MAP mmHg	104.9 \pm 4.5	95.8 \pm 7.3	76.9 \pm 4.7†	93.8 \pm 6.2	95 \pm 5.5
CO l/min	6.1 \pm 0.8	4.3 \pm 0.3	6.1 \pm 0.4*	6.0 \pm 0.5*	5.0 \pm 0.5
CVP mmHg	11.0 \pm 2.0	14.4 \pm 1.4	14.3 \pm 1.4	15.4 \pm 1.4	13.9 \pm 1.7
PAS mmHg	33.1 \pm 3.1	38.0 \pm 2.1	35.0 \pm .9	34.2 \pm 1.3	31.9 \pm 3.1
PAD mmHg	19.7 \pm 2.9	20.4 \pm 2.0	18.6 \pm 1.4	19.0 \pm 1.6	17.6 \pm 2.9
PCWP mmHg	17.0 \pm 2.7	23.5 \pm 1.7	20.1 \pm 1.1	20.4 \pm 1.2	18 \pm 2.1
SVR dynes-sec/cm ⁵	1354.3 \pm 151.2	1582.9 \pm 186.6	828.4 \pm 59.1‡	1104.3 \pm 126.2‡	1379.9 \pm 117.8

* $P < 0.05$ vs. pre-traction.† $P < 0.03$ vs. pre-traction.‡ $P < 0.005$ vs. pre-traction.

Control plasma from these patients (pre-traction sample) decreased developed force by only 0.12 ± 0.11 grams (not significant), whereas 5-min post-traction plasma reduced developed force by 0.563 ± 0.092 grams ($P < 0.01$ from control plasma). The stable PGI₂ analog, iloprost (50 ng/ml) decreased developed force in the remaining four strips by 1.17 ± 0.12 grams ($P < 0.001$ from control plasma). Thus, patient plasma contained a humoral substance that is a comparable vasodilator with action similar to PGI₂ and its analogs.

All group I patients studied developed erythema and flushing of the skin of the face which coincided with the decrease in mean arterial pressure (MAP). No patient required a vasoactive agent to treat the traction-induced decrease in blood pressure. The infusion rates of crystalloid were increased in all cases following the fall in blood pressure. In those patients who received ibuprofen preoperatively (group II), there was no significant changes post-traction in MAP and SVR or cardiac

output (table 2). No flushing was noted in any patients in group II. There was no significant changes in PGI₂ levels in group II (fig. 1). When cat mesenteric artery strips were exposed to plasma samples obtained after mesenteric traction from patients who received ibuprofen, the 5-min plasma samples decreased the developed force by 0.074 ± 0.017 gm, which was not significantly different from their control plasma, which decreased the force by 0.053 ± 0.011 gm. Thus, it appears that there was no vasodilating substance in the plasma of those patients pretreated with ibuprofen. When comparing the hemodynamic changes associated with mesenteric traction between group I and group II, there was no significant difference between groups in the awake or pre-traction values of any of the measurements. The MAP for group I was significantly lower than group II at 5 and 15 min ($P < 0.02$ at 5 min and $P < 0.01$ at 15 min), as was the SVR ($P < 0.02$ at 5 min and $P < 0.05$ at 15 min). There was no difference in CO at any measurement time between groups. The only other significant difference between any of the other values (HR, CVP, PAS, PAD, and PCWP) was that the PAS values of group II was higher than group I at 15 min ($P < 0.04$).

Discussion

Several investigators have described a relationship between abdominal mesenteric traction and a decrease in blood pressure.²⁻⁵ We previously demonstrated that this hemodynamic change is associated with a decrease in systemic vascular resistance and an increase in cardiac output.¹ However, we did not examine the basis for the decreased systemic vascular resistance. Current results in group I patients are consistent with our previous hemodynamic findings. The fact that no vasodilating substance could be demonstrated in plasma from group II patients supports the contention that this response is mediated by a humoral mechanism, rather than by the

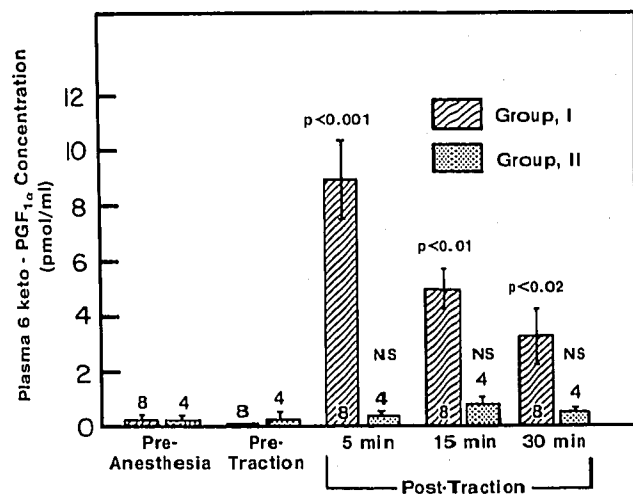


FIG. 1. Plasma 6-keto-PGF_{1α} concentrations (mean \pm SEM) of group I (untreated) and group II (ibuprofen) patients. P values indicate the relationship between pre-anesthetic and post-traction values.

autonomic nervous system; however, a reflex pathway is not totally ruled out. Strunin,³ Kaufman,⁴ Batchelder and Cooperman,⁵ Smith,¹² and Burstein¹³ all attributed the hypotension to a reflex arc consisting of afferent sympathetic stimulation from the mesenteric traction, and resulting in efferent mediated dilation of the splanchnic vasculature. This hypothesis was challenged by Jacobson,⁶ who demonstrated a constriction rather than dilation of the splanchnic vasculature upon sympathetic nerve stimulation.

A humoral mechanism seems more likely to be the cause of the flushing in response to mesenteric traction. In almost every patient in our previous study and in each patient not pretreated with ibuprofen in this study (group I), mesenteric traction was associated with flushing of the head and neck. The flushing dissipated within 30 min, a time that corresponds to the return of all hemodynamic variables to pre-traction values. Furthermore, the changes seen are consistent with generation of PGI₂. Lefler *et al.*¹⁴ demonstrated that PGI₂ exerts a variety of effects on the cardiovascular system, including a decrease in blood pressure associated with a decrease in SVR. This was further supported by Armstrong *et al.*¹⁵ *in vitro*, and demonstrated in humans by Chelly *et al.*¹⁶ PGI₂ is generated and released from the human gastrointestinal mucosa and gastric mucosa from several species.⁸ The patients who received ibuprofen had no vasodilating substances in their plasma at 5 min post-traction, and there was no significant increase in PGF_{1α} after mesenteric traction. Since ibuprofen is known to block prostaglandin synthesis,¹⁷ we feel that low PGF_{1α} levels resulted from its administration and that PGI₂ is probably the vasodilating substance responsible for the hemodynamic effects associated with mesenteric traction. This does not rule out the possibility that ibuprofen may also have blocked the synthesis or release of other vasoactive substances.

The tendency to a slight decrease in MAP or SVR seen in group II suggests that other factors beside PGI might be involved with the response. Neuronal reflexes are not completely ruled out, and the lack of surgical

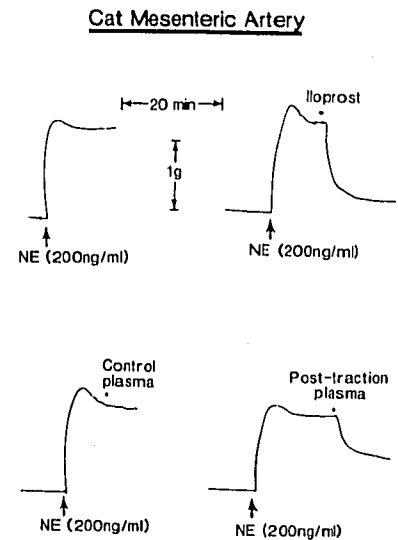


FIG. 2. Representative isometric recordings of isolated cat superior mesenteric artery expressed in grams of developed force. The strip was pre-contracted with norepinephrine (NE) at 200 ng/ml, and at the dot either iloprost 50 ng/ml or 2 ml of a patient plasma sample was added. Control plasma refers to the pre-traction plasma sample.

stimulus during the study period may play a part in this study's results. Huval *et al.*¹⁸ demonstrated an increased PGF_{1α} concentration after surgical incision, but before aortic clamping, in a group of patients undergoing abdominal aortic aneurysmectomy. The plasma sample in their study that showed the highest levels of PGF_{1α} was obtained 30 min after surgical incision. This would likely have been 15–20 min after mesenteric traction. In 11 additional patients, ibuprofen 12 mg/kg was given 1.5 h prior to surgery. Minimal increases in PGF_{1α} were seen in the ibuprofen group.

With only four patients in group II, the possibility exists that a type 2 error (false negative) may exist. Since a type 2 error is possible, the results of this study strongly suggest, but do not absolutely prove, that prostacyclin plays a significant role in the hemodynamic response of mesenteric traction.

In conclusion, these results are consistent with our earlier hemodynamic findings following mesenteric traction. These hemodynamic changes are associated with an increase in PGI₂ levels. The response of PGI₂ and the hemodynamic changes previously seen with

TABLE 2. Hemodynamic Alterations in Response to Mesenteric Traction in Four Patients Who Received Ibuprofen Preoperatively (Group II) (Mean ± SEM)

	Awake	Pre traction	5 Min	15 Min	30 Min
HR bpm	80.0 ± 11.3	67.8 ± 8.6	65.5 ± 8.1	69.5 ± 4.9	67.7 ± 3.4
MAP mmHg	114.2 ± 3.8	112.8 ± 9.0	101.5 ± 8.2	128.8 ± 7.0	111.0 ± 4.6
CO l/min	7.6 ± 1.5	4.9 ± 0.7	5.6 ± 0.7	5.5 ± 0.6	4.8 ± 0.4
CVP mmHg	13.5 ± 1.7	13.8 ± 2.2	12.8 ± 2.3	13.8 ± 1.8	11.8 ± 1.9
PAS mm Hg	41.2 ± 3.4	35.2 ± 5.6	38 ± 3.9	40.2 ± 2.2	31.2 ± 2.4
PAD mmHg	19.8 ± 2.1	21.8 ± 2.4	19.5 ± 2.9	23 ± 0.7	18.5 ± 1.2
PCWP mmHg	22.2 ± 1.9	23 ± 2.2	20 ± 2.7	22.8 ± 1.5	19.2 ± 1.8
SVR $\frac{\text{dynes-sec}}{\text{cm}^5}$	1160.2 ± 192.4	1747 ± 354.2	1345.8 ± 208.5	1775 ± 336.6	1694 ± 231.6

mesenteric traction appear to be blocked by pre-treatment with the prostacyclin-inhibiting agent ibuprofen.

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