INTESTINAL PROSTANOIDS IN SHOCK
AND
POSTPRANDIAL INTESTINAL HYPEREMIA

BY

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ABSTRACT

INTESTINAL PROSTANOIDS IN SHOCK AND POSTPRANDIAL INTESTINAL HYPEREMIA

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The gastrointestinal tract produces and releases a number of prostanoids which affect many of its functions, such as secretion, absorption, motility, blood flow, and metabolism. Recent studies suggest that endogenous intestinal prostanoids may play a role in the regulation of blood flow and oxygen uptake during nutrient absorption. Evidence has also accumulated which suggests a pathophysiological role for prostanoids in several diseases of the gastrointestinal tract. The purpose of this study was to elucidate which of the endogenous prostanoids play a role during physiological conditions (i.e. at rest and during nutrient absorption) and pathological conditions (i.e. hemorrhagic shock). With this in mind, the first part of this study tested the effects of intraluminal placement of normal saline (NS), digested food (F) and F plus archidonate (AA) on jejunal blood flow, oxygen uptake and prostanoid production. After it was found that prostanoid production was indeed increased by luminal placement of F or F + AA, the vascular effects of local i.a infusions of prostanoids at concentration similar to those observed in response to luminal placement of F or F + AA was studied. In an attempt to determine the stimulus for food- induced increases in jejunal prostanoid production the effects of NS, bile , intestinal distension and pump-induced hyperemia were individually tested for their effect on prostanoid production.

Also in an attempt to determine which prostanoid may be involved, the effects

mimic changing luminal content from NS to F did not significantly alter the JVR. However, infusions of a mixture of the four or two prostanoids mimicking a situation of changing luminal content from NS to F + AA or from F to F + AA, respectively, increased the JVR in a dose dependent fashion and abolished the F induced decrease in JVR.

Luminal placement of NS, 10% bile, or mechanical distension by air did not alter jejunal blood flow and prostanoid release. This indicates NS and bile, which were used to prepare the food mixture, and luminal distension by air, to simulate the jejunal volume change observed during food placement, did not directly contribute to the food- induced increase in prostanoid prduction. However, a pump-induced hyperemia which mimicked postprandial hyperemia significantly increased the rate of PGI_2, TXA_2, and PGE_2 releases from the jejunum while it did not alter the PGF_2 release. This study indicates part of the stimulus for the food-induced prostanoid release might be secondary to the food-induced increase in blood flow.

The selective thromboxane receptor antagonist SQ- 29548 had no effect on postprandial intestinal hyperemia but significantly potentiated the increases in oxygen uptake and capillary exchange capacity. The latter was assesed by the capillary filtration coefficient.

Local intra-arterial infusion of a TXA_2 agonist (U- 44069) , in a free flow intestinal preparation, decreased both mucosal and muscularis blood flow of the jejunal wall. The decrease in mucosal blood flow was significantly greater than the decrease in the muscularis. In constant flow rate conditions, infusion of U-44069 decreased blood flow the mucosal and increased the muscularis blood flow. Infusion of SQ-29548, in both conditions, restored the U-44069 induced blood flow changes to control levels. This study indicates greater sensitivity of the mucosal vasculature to TXA_2 than of the muscle vasculature, which might favor a redistribution of blood flow within the intestinal layers.

of a thromboxane receptor antagonist and/or agonist were studied. Their effects on resting and postprandial jejunal blood flow, oxygen uptake, capillary exchange capacity and blood flow distribution between mucosal and muscularis layers were determined.

In the last part of this study the role of intestinal prostanoids in the development and progress of irreversible hemorrhagic shock was studied in dogs subjected to hemorrhagic hypotension. Arterial pressure was maintained between 30-40 mmHg for 3 hours followed by reinfusion of the remaining shed blood. Intestinal production of 6-keto-PGF_1 and TXB_2 were measured every hour. In separate dogs subjected to the same hemorrhagic shock protocol, a glucose oleic acid (GOA) solution was perfused continously into the lumen of an isolated intestinal segment while intestinal prostanoid production was measured every hour. At the end of the experiment intestinal biopsy was taken to determine if there are morphological changes associated with severe hemorrhagic shock. The main findings of the study are as follows:

Placement of a digested food into the jejunum significantly increased local blood flow, oxygen uptake and jejunal prostanoid release. Prostanoids were released in the order of $PGE_2 > PGI_2 > TXA_2$ and $> PGF_2$. Arachidonate placed into the lumen with the food solution abolished the vascular and metabolic changes associated with food placement. Accompanying the arachidonate action was a significant increase in jejunal venous concentration and release of TXA_2 and PGF_2 compared to food placement alone. A TXA_2 receptor antagonist (SQ-29548) reversed the arachidonate vascular and metabolic action, indicating TXA_2 is partly responsible for the vascular and metabolic actions of arachidonate added to the food.

Local intra-arterial infusion of the TXA_2 receptor agonist U-44069, and PGF_2 increased, while PGI_2 and PGE_2 decreased jejunal vascular resistance (JVR) in a dose dependent fashion. Infusions of a mixture of the four prostanoids to

In dogs subjected to hemorrhagic hypotension for 3h followed by reinfusion of the remaining shed blood, arterial and intestinal venous TXB_2 concentrations significantly increased during hypotensive and post-transfusion periods. However, the 6-keto-PGF_1 concenterations increased during hypotension but decreased during post-transfusion periods. The intestinal TXB_2 release increased progressively, whereas 6-keto-PGF_1 release decreased. There was no significant change in the control dogs.

Perfusion of a GOA solution intraluminally in dogs subjected to a similar hemorrhagic shock protocol abolished the shock-induced increase in intestinal venous concentration and release of TXA_2, whereas venous concentrations and release of 6-keto-PGF_1 increased progressively during hypotension and post-transfusion periods. Accompanying the changes in prostanoid release were a significant decrease in the magnitude of intestinal vascular resistance and mucosal damage. This study shows an imbalance in intestinal production and release of TXA_2 and PGI_2, in favor of TXA_2, during severe hemorrhgic hypotension and after blood transfusion. The imbalance may contribute to the development of irreversible hemorrhagic shock and reperfusion injury. Part of the mechanism for the benefical effect of GOA perfusion during severe hemorrhagic shock seems to be related to its effect on reversing the shock-induced imbalance in prostanoid production.

This dissertation is dedicated with love to my parents, and family for their love and support.

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INTRODUCTION

Recent studies suggest that endogenous intestinal prostanoids may play a role in the regulation of blood flow and oxygen consumption during nutrient absorption, and in the pathogenesis of a variety of shock conditions. Inhibition of cyclooxygenase by indomethacin or mefenamic acid potentiates (52,117), whereas administration of arachidonic acid attenuates (102), the food-or oleic acid-induced increases in intestinal blood flow and oxygen uptake. These studies, however, raise more ques tions because of complex arachidonic acid metabolism and the antagonistic vascular effects of prostanoids. PGE_2 and PGI_2 are vasodilators (22,43,49,56), whereas PGF_2 and TXA_2 are vasoconstrictor (22,38,56) in the small intestine.

Supportive evidence for the involvement of prostanoids in the progression of shock is accumulating. Cyclooxygenase inhibitors, such as aspirin and indomethacin, are known to reduce thromboxane and prostacyclin production induced by endotoxemia in dogs (40,70), rabbits (27) and rats (20), with an associated increase in survival. Administration of prostacyclin (93), thromboxane synthetase inhibitors (111), and thromboxane receptor antagonists have been shown to improve the condition of animals in severe shock conditions induced by trauma, splanchnic artery occlusion, and hemorrhage, respectively. There is, however, no study that measures these two prostanoids during the course of severe irreversible hemorrhagic shock. Furthermore, most studies measure their concentration in the systemic blood rather than in the venous blood of an organ.

The purpose of this study was to determine intestinal prostanoid production during nutrient absorption and during various stages of severe hemorrhagic shock and after blood transfusion. After it was found that food indeed increased prostanoid production, the vasoactivity of PGI_2, PGE_2, PGF_2 and a TXA_2 agonist were determined individually or in a mixture. In an attempt to determine the constituents of food responsible for intestinal prostanoid release, NS, bile, intestinal distension, and pump-induced hyperemia were individually tested. Also, the effects of a thromboxane receptor agonist and/or antagonist on resting and postprandial intestinal blood flow, oxygen uptake, capillary exchange capacity and intestinal blood flow distribution between mucosal and muscularis layers were determined in an attempt to determine which prostanoids may be involved.

LITERATURE REVIEW

Postprandial Intestinal Hyperemia

It has long been thought that, during the digestion of food, blood is diverted from other tissues of the body to the viscera. The fact that the viscera appear congested has been taken as evidence of an increased blood supply to these organs. It was in 1910, Brodie et al. (15) documented the first evidence of a postprandial hyperemia in the canine small intestine by using a plethysmograph method. At the same time suggestions were made that the drowsiness one feels after a meal may be due to a redistribution of blood away from the brain to the intestine. In 1934, Her rick et al. (74) made the first blood flow measurement to quantify the cardiovascular events during digestion utilizing the thermostromuhr method in conscious dogs. This study indicated that during digestion of food the blood flow in the femoral, carotid, mesenteric arteries and the external jugular vein markedly increased. These findings were substantiated by Reininger et al. (119) who measured blood flow by the ^{42}K fractional distribution technique in both fed and unfed rats. These investigators reported that during digestion, there is a uniform increase in the blood flow to all organs of the fed rats. The cardiac output also significantly increased during digestion. The aforementioned studies questioned the prevailing concept that digestion results in diversions of blood flow from other organs to the digestive tract.

However, more recent systematic studies have yielded different results. In 1968 Fronek et al. (50) measured the systemic and regional hemodynamic changes during food intake and digestion in dogs. During anticipation and food intake (injestion) a significant increase in cardiac output, heart rate, arterial blood pressure and flow in brachiocephalic artery were observed while the flow in superior mesenteric and iliac artery dropped significantly. During digestion (at 1 and 3 hours after injestion), there were no significant changes in cardiac output, heart rate, and mean arterial blood pressure, whereas the flow in the superior mesenteric artery increased significantly and flows in the brachiocephalic and iliac arteries decreased. These findings were further substantiated by studies conducted by Vatner et al. in 1970 (145,146). In these studies, blood flow measurements were made utilizing pulsed ultrasonic flow meters, Doppler ultrasonic telemetry flow meters or Zepeda 400-cycle square-wave electromagnetic flow meters. Anticipation and injestion of food were characterized by transient increase in cardiac output, heart rate, arterial pressure, mesenteric resistance and renal resistance while iliac and coronary resistance decreased transiently. Mesenteric flow began to increase within 5 min after eating and reached a peak within 30-90 min, gradually returning to preprandial control levels 2-6 hrs later. Iliac flow was decreased slightly 30-60 min postprandially. Within 10-30 min, renal and coronary flow and resistance returned to preprandial control levels and remained there during peak mesenteric vasodilation.

In 1970's and the early 1980's, studies were conducted which more carefully characterized the cardiovascular responses to feeding. Two distinctly different phases were noted, the anticipation and injestion of food phase, and the digestion phase. In the former the cardiovas cular changes, (i.e., increased cardiac output, heart rate, arterial pressure, mesenteric resistance and renal resis tance, and decreased coronary resistance) were associated with a generalized sympathomimetic stimulation and generally lasted for a very short time, (5-30 min). This was followed by the digestion phase of cardiovascular response which is manifested by a significant increase in the mesenteric blood flow (30-90 min) and the return of cardiac output, heart rate, arterial pressure, renal resistance and coronary resistance to preprandial level (145,147). Even though these recent findings ruled out the possibility of redistribution of blood flow away from other vascular beds to the intestine there is still the unexplained fact of how the increases in mesenteric blood flow are achieved. Vatner et al. in 1974 (147), and Gallavan et al. in 1980 (55) have suggested that small increases (5-10%) in cardiac output could account for the sustained increase in mesenteric blood flow, these changes may be missed due to technical error inherent in the current methods used to determine cardiac output.

The postprandial increase in superior mesenteric blood flow is not shared equally by all mesenteric organs. It is selective to those participating in digestion. Even within the intestine itself, various regions are perfused to different degrees. For example, the introduction of food into the stomach of the conscious dog increases blood flow only in the celiac artery (29). Likewise, fatty acids placed in the colon of dogs elicit an organ-specific colonic hyperemia (84). Furthermore, with a rise in superior mesenteric blood flow elicited by food in the intestine, little or none is distributed to the stomach and colon. Within sequential segments of the small intestine, all regions are not perfused equally at any one time (29,41). Chou et al. (29) demonstrated that intraduodenal placement of food increases blood flow in the superior mesenteric artery, but does not increase celiac flow or blood flow to an isolated adjacent jejunal segment. These studies indicate that the postprandial hyperemia is localized to that portion of the gastrointestinal tract that is exposed to chyme.

The selectivity of postprandial hyperemia extends to the various layers of the gut wall. Differences in blood flow distribution exist among the mucosa, submucosa, and muscularis. Using radioactively labelled microspheres, Chou et al. (29,30) showed the local distribution within jejunum favored the mucosa. This preferential distribution to mucosa was also reported by Gallavan et al. (55). On the other hand, blood flow to the muscularis layers does not change over the first 90 min after a meal, during which time superior mesenteric blood flow increases over 100%. Post prandial gastric and colonic hyperemia are also attributed to increased mucosal flow

(55). Thus it appears that mesenteric postprandial hyperemia is quite selective in its distribution to regions that are closely tied to digestive and absorptive processes, and that the mucosal region receives the largest share of the increase.

At the local intestinal level, the nature of the food material in the lumen is the determinant of the vascular response. For example, Kvietys et al. (87) demonstrated that luminal osmolarity over the range 180-1000 osmole/kg is not a significant factor in contributions to local hyperemia, but the concentration of the nutrient is. When chyme was analyzed for its local hyperemia-stimulating activity (32), the partially digested fats and carbohydrates were specifically effective. Undigested food elicited no response (32). Additionally, bile apparently plays an important role. In the jejunum, bile has no effect by itself, but enhances the hyperemic effect of digested food. In contrast, bile salts alone elicit hyperemia in the ileum (82).

Chou et al. (32) and Kvietys et al. (82) conducted the first systematic study of the effects of the various constituents of chyme on intestinal blood flow using isolated loops of canine small intestine. These studies show that only glucose was capable of increasing jejunal blood flow when placed in the lumen at physiological concentration (150 mM). The long-chain fatty acids, oleic acid and the monoglyceride monolein, had no effect on intestinal blood flow when placed in the lumen in aqueous solution. However, solubilization of these lipids, by increasing the pH of the solution (pH = 9) (31) or by addition of either gallbladder bile (82) or sodium taurocholate (32), resulted in their ability to increase intestinal blood flow by 20-30%. At physiological concentrations, it appears that few, if any, of the common dietary amino acids have an effect on intestinal blood flow. The by-products of protein digestion are relatively potent vasodilators of the intestinal circulation (Brodie et al. (15); Brandt et al. (14); Siregar et al. (140)). The peptides responsible for vasoactivity are unknown, although it is possible that some fragments cleaved from the parent protein may have amino acid sequences similar to those of the active portions of vasoactive peptides of the gut.

The effect of the various nutrients on intestinal blood flow might be mediated by a variety of regulatory pathways. Some of the factors involved include tissue oxygen tension (60,129,112) , intestinal peptides such as neuro tensin and vasoactive intestinal polypeptide (51,57), paracrine substances such as prostanoids (52,102,103,104,117) and histamine (33), and intrinsic nerves (27,30,146) .

The possible role of hormonal components in postprandial mesenteric hyperemia was suggested due to the vasodilator effect a variety of gastrointestinal peptides showed during exogenous administration into the mesenteric vascular bed (7,19,26,41,101,116). In 1967 Burns and Schenk (19) found intravenous infusion of secretin and gastrin increased superior mesenteric blood flow. Other investigators (7,26,41,101) also found administration of CCK, gastrin, and secretin increased intestinal blood flow. However, a recent study (51) which measured the concentrations of these peptides in the venous blood found it to be less than that required to dilate the intestinal vasculature.

The involvement of extrinsic nerves in the postprandial hyperemia has been ruled out, since vagal stimulation and vagotomy did not alter intestinal blood flow (78,85,144,145), and the postprandial hyperemia was not affected by alpha- or beta adrenergic blockade (41,42,146). The role of intrinsic nerves remains controversial. The hyperemia produced by mechanically stroking the intestinal mucosa and that produced by transmural electrical field stimulation have been shown to be mediated by an intramural neural reflex (10). The reflex involves the release of 5- hydroxytryptamine (5-HT or serotonin) and possibly vasoactive intestinal polypeptide (VIP) (8,9,10). Luminal placement of a 50% glucose solution (3,000 mOsmol/kg) increases intestinal blood flow as well as motility, and both effects were blocked after exposing the mucosal surface to a local anesthetic, dibucaine hydrochloride (110). These studies seem to indicate that stimulation of mechano- or osmoreceptors on the mucosal surface initiates a local neural reflex that increases intestinal blood flow and motility.

Recent studies by Gallavan et al. (51) found a close temporal relationship between jejunal vasoactive intestinal polypeptide (VIP) release and the bile-oleate-induced jejunal hyperemia. Furthermore, this increase in VIP release was not seen when either bile or oleic acid was placed in the lumen alone (treatments which also failed to produce hyperemia). Since VIP is found only in the neural tissue of the small intestine (89) and is a vasodilator in the canine small intestine (39), a portion of the bile- oleate-induced jejunal hyperemia may be mediated by a neural pathway involving VIP-ergic neurons. Fahrenkrurg et al. (39) have also reported a correlation between intestinal VIP release and the hyperemia induced by mechanical stimulation of the mucosa.

Nyhof et al. (110) provided evidence against local neural mechanism for intestinal postprandial hyperemia. Methysergide, hexamethonium, and tetrodotoxin failed to alter either the vascular or metabolic responses to luminal placement of glucose or oleic acid. Exposing the mucosa to dibucaine (a local anesthetic) blocked or attenuated the increases in blood flow and oxygen uptake. The inhibition of the nutrient-induced intestinal hyperemia by dibucaine is due, at least in part, to its effect on oxygen consumption and glucose transport of the mucosal epithelial cells. These findings therefore indicate that local intestinal nerves may not play a significant role in the initiation and maintenance of nutrient-induced jejunal hyperemia.

Several studies have shown an increase in oxygen consumption as well as an increase in blood flow when foodstuffs are introduced into the gastrointestinal tract (30,53,55). The mesenteric metabolic control theory has been based on the assumption that delivery of oxygen to parenchymal cells is the controlled variable rather than the blood flow when foodstuffs are introduced into the gastrointestinal tract (60,64,131,132,138). Of the possible mediators of the metabolic hyperemia only adenosine and changes in tissue PO_2 have been examined in the mesenteric circulation. Adenosine has been proposed as a mediator of metabolic hyperemia in a variety of tissues and is a potent intestinal vasodilator (65). However, exogenously administered adenosine decreases ileal oxygen consumption, the capillary filtration coefficient, and PS product and redistributes blood flow from the mucosa to the muscularis (65,137). The role of endogenous adenosine in the regulation of intestinal blood flow during digestion and absorption requires further study.

Chou et al. (33) determined the role of histamine in postprandial intestinal hyperemia utilizing H_1- and/or H_2- receptor blockers. Metamine, an H_2 receptor antagonist, had no effect on the food-induced increase in flow and oxygen uptake, whereas tripelennamine, an H_1 receptor antagonist, significantly attenuated the food-induced increases in blood flow and blocked the increases in oxygen consumption. A 30% increase in flow was reduced to 15% after administration of this agent. They concluded that endogenous histamines may play a role in postprandial intestinal hyperemia, and the effect is primarily mediated by the H_1-receptors.

Gallavan and Chou (52) and Procter et al. (117) have shown that inhibition of prostanoid synthesis significantly potentiated the jejunal vascular and metabolic re sponse to food. Conversely, Mangino and Chou (102), and Procter et al. (117) have reported that stimulation of prostanoid synthesis significantly inhibits the food-induced increases in jejunal blood flow and oxygen consumption. The inhibitory effect of prostanoids on the jejunal response to food is complicated by the antagonistic biological actions of prostanoids in the gastrointestinal tract. PGI_2 and PGE_2 are vasodilators (22,43,49,56) whereas PGF_2 and TXA_2 are vasoconstrictors (22,38,56) in the small intestine.

Prostanoids

In 1930, Raphel Kurzork and Charles Lieb (81) discovered that human seminal plasma contracted uterine smooth muscle. Shortly thereafter, broader biological impli cations were realized from the research of Maurice Goldblatt and Ulf S. Von Euler (59) who demonstrated that the compounds in semen were active on a number of smooth muscles and lowered blood pressure when injected in animals. Von Euler called these factors prostaglandins (indicating the first anatomical region of origin).

Arachidonic acid and other prostaglandin precursors are not normally found in the free state in the cell but occur bound in phospholipids, neutral lipids and with cholesterol (11,114). Since esterified fatty acids are not substrates for the enzymes which make prostaglandins, the first step in prostaglandin biosynthesis is the release of these fatty acids from their combination in lipids. The most important source of fatty acids for prostaglandin formation is phospholipids.

The backbone of the phospholipid structure is a 3- carbon compound called glycerol . The 1' position is usually occupied by a saturated fatty acid (i.e., does not have any double bonds such as palmitic acid) and 2' position is taken up by an unsaturated fatty acid (such as arachidonic acid). The 3' position is taken up with a base (usually choline, ethanalamine, serine or inosital) attached to the glycerol backbone by phosphate linkage.

Release of arachidonic acid from membrane phospholipids can be achieved enzymatically by one or another of several phospholipase enzymes (47,125). Phospholipase A_2 attacks at the 2' position liberating the unsaturated fatty acid and leaving a 2' lysophosphatide. Phospholipase c removes the phosphorylated base leaving a diglyceride which can then be broken down by a specific diglyceride lipase enzyme to release both fatty acids in free form (76).

The most important enzyme normally responsible for liberating fatty acids in prostanoid biosynthesis is phospholipase A_2. In some cells, e.g., platelets, the concerted action of phospholipase c and diglyceride lipase is necessary to release arachidonic acid. The biosynthesis of all prostanoids (Fig 1)is initiated by the same

FIGURE 1

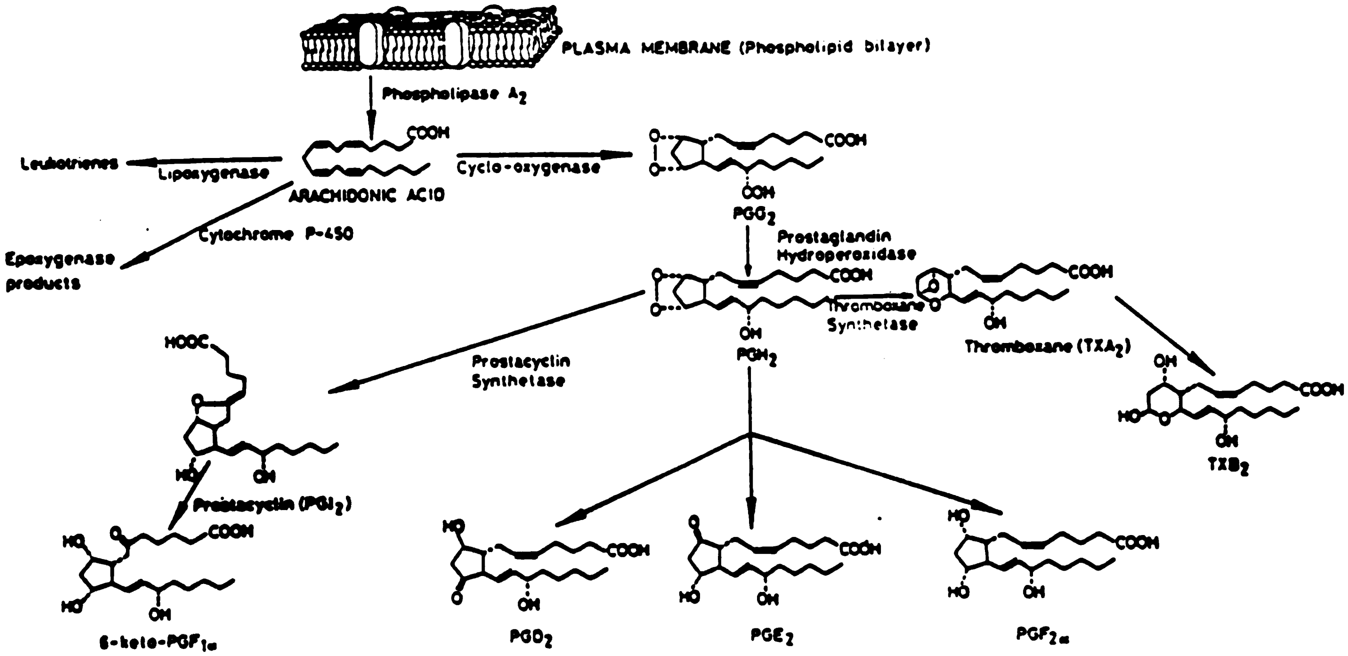


Figure 1. Biosynthetic pathway of the major eicosanoids

pair of enzymes: a cyclooxygenase, which catalyzes the oxygenation of arachidonic acid to the cyclic endoperoxide prostaglandin G_2 and a hydroperoxidase, which converts prostaglandin G_2 to prostaglandin H_2 (Fig. 1) (125). After this point, most cells are highly specific in their metabolism of prostaglandin H_2 to the biologically active products, a selectivity that usually is linked to the function of the cell and its communication with cells that carry receptors for that specific prostaglandin or thromboxane A_2. As a group, these active metabolites of prostaglandin H_2 have been termed prostanoids.

The rate limiting step in prostanoid biosynthesis is the liberation of arachidonic acid from phospholipids, making free fatty acid available for metabolism by cyclooxygenase (114). In some cells, free arachidonic acid also may be metabolized by lipoxygenase enzyme to products that include the leukotrienes, and by mixed-function oxygenases to epoxyeicosatrienoic acids. As a group, these highly varied oxygenated metabolites of arachidonic acid are called eicosanoids, reflecting their origin from a 20-carbon (eicosa-) polyunsaturated fatty acid.

Prostanoids and the Gastrointestinal Tract

Ever since the discovery of prostanoids, use has been made of isolated gut smooth muscle as bioassay preparation for prostanoids. Over and above the practical application many other aspects of gastrointestinal function may to some extent depend upon the generation of endogenous prostanoids, or be influenced by the administration of exogenous prostanoids (4,16,34,44,52,54,58,79,80,90,102-104,117,128). The list of gut function so affected includes transport of water and electrolytes in the colon and intes tine (16,35,44,79). Evidence has also accumulated which sug gests a pathophysiological role for prostanoids in several diseases of the gastrointestinal tract (5,36,93,122).

The effects of prostanoid synthesis inhibition on the postprandial jejunal vascular and metabolic response was examined by Gallavan and Chou (52). Their findings indicate that indomethacin and mefenamic acid, which are cyclooxygenase inhibitors, reduced resting jejunal blood flow and markedly enhanced the food-induced jejunal hyperemia and oxygen consumption. Mangino and Chou (102) have reported that stimulation of prostanoid production utilizing exogenously administered arachidonic acid, significantly attenuated the food-induced increases in jejunal blood flow and oxygen uptake. These findings suggest that endogenous prostanoids may act to limit the magnitude of postprandial jejunal vascular and metabolic response. Other studies performed by Proctor (117) showed that oleic acid, but not glucose, induced functional hyperemia was potentiated by the local application of cyclooxygenase inhibitors in rats.

The aforementioned studies performed utilizing cyclooxygenase inhibitors and arachidonic acid raise many questions. One of the questions is which prostanoid(s) is/are responsible for the biological effects observed during nutrient absorption. Mangino and Chou (103) reported that inhibition of thromboxane synthesis utilizing imidazole and U-63557A (Upjohn) during nutrient absorption enhanced jejunal oxygen uptake without altering the magnitude of the hyperemia. Additional study by the same group (104) indicated that inhibition of thromboxane synthesis potentiates the magnitude of postprandial capillary filtration coefficient. These studies suggest thromboxane A_2 might play a role in limiting O_2 uptake and capillary density during nutrient absorption. However, the observed results might also be due to a diversion of the common substrate arachidonic acid to the formation of other eicosanoids (118).

Prostanoids and Nutrient Transport and Metabolism in the Gastrointestinal Tract

Gallavan and Chou (54) reported that inhibition of cyclooxygenase during nutrient (enzymatically digested fat, carbohydrate and protein) absorption significantly enhanced the rate of glucose utilization and absorption in canine jejunum.

Previous studies by the same group have reported (52) that the postprandial hyperemia and oxygen consumption was potentiated by cyclooxygenase inhibitors. These results indicate that endogenous prostanoids may act to limit glucose absorption and hence limit the magnitude of postprandial jejunal hyperemia and oxygen uptake. Several pieces of evidence support this hypothesis. A study by Sit et al. (141) showed that the magnitude of the postprandial changes in blood flow and oxygen consumption were related to the rate of active glucose transport and its utilization by the intestinal tissue. Exogenous administration of PGE_2 and PGF_2 into the canine isolated jejunal loop decreased glucose absorption irrespective of their vascular effects (4). Similar study in humans showed that administration of PGE_1 decreased the glucose absorption rate. Coupar and McColl (34) have shown that glucose absorption was inhibited by exogenous administration of PGE_1, PGE_2 and PGF_2 in the rat jejunum. The mechanism by which these prostanoids affect glucose transport seems not to be related to their action on adenylcyclase since dibutryl 3'5'-cAMP enhanced glucose absorption.

Prostanoid Effect on Jejunal Water and Electrolyte Transport

Prostanoids appear to play an important role in the physiologic regulation of intestinal fluid transport. Field et al. (44) have reported that addition of arachidonic acid stimulates secretion, c AMP accumulation and PGE_2 production in vitro in rabbit ileal mucosa. Brunson et al. (16) reported that administration of prostanoids (PGE_1, PGE_2) or their precursor arachidonic acid increased intestinal fluid secretion in the rat jejunum in vivo both when administered intraluminally or intra-arterially. The mechanism by which prostanoids elicit this secretory action is dual. At low doses, PGE_2 (approximately 10^{-9}M) acts mainly by local secretory nervous reflexes as judged by the block with i.v. hexamethonium or locally applied Lidocaine and not accompanied by any increase in tissue cAMP. At higher concentrations (10^{-8}- 10^{-7}) of PGE_2 there seems to be a non- neurogenic effect on the enterocytes associated with an increase in tissue cAMP. Konturek et al. (79) have reported that administration of PGE_2 and 16.16.DMPGE_2 (2 ug/kg/h) into the mesenteric artery significantly enhanced net water secretion by the canine jejunum and ileum. Conversely, administration of indomethacin (5 mg/kg/hr) enhanced water absorption. Administration of PGF_2, PGI_2 (2 ug/kg/h) and AA (10 ug/kg/hr) did not significantly alter intestinal net water movement. Stimulation of the receptor mediated endogenous prostanoid production by whole rat ileal mucosa enhanced intestinal prostaglandin and cAMP production, and a rise in mucosal short circuit current (an indicator of chloride secretion) (148). Lawson et al. (90) showed that intestinal epithelial tissue cAMP production is enhanced directly by PGE_2 or by stimulating its synthesis by bradykinin. These studies suggest endogenous prostanoids might regulate intestinal water and electrolyte transport under physiological conditions and enhanced prostanoid production during pathological conditions might contribute to the pathophysiology of diarrheal diseases.

Prostanoids are capable of stimulating alkaline secretion from the gastroduodenal mucosa, whereas inhibitors of prostanoid biosynthesis inhibit this secretion, causing mucosal damage (58). Bicarbonate secretion is involved in the protective action of prostanoids on gastrointestinal mucosa and endogenous prostanoids are a significant factor in mucosal defense against various noxious agents. Konturek et al. (80) have reported that natural PGE_2, PGF_2, but not PGI_2 were an effective stimulant of duodenal alkaline secretion. Stable analogues such as 16-16DMPGE_2 and PGI_2 were relatively more potent stimulants than their parent prostanoids. Conversely, inhibition of prostanoid synthesis by indomethacin suppresses duodenal alkaline secretion.

Konturek et.al. (80) reported that infusion of PGE_2 and PGF_2 either i.v. or directly into the artery supplying small intestine have an opposite effect on motility; PGE_2 inhibits while PGF_2 stimulates intestinal motility. Infusion of PGI_2 also inhibits intestinal motility. Conversely, inhibition of endogenous prostanoid synthesis by indomethacin results in an increased intestinal motility. This study suggests that the predominant action of prostanoids generated in the intestinal wall is the inhibition of intestinal contractility and that this effect might be mainly due to release of PGI_2.

Intestinal Response During Hemorrhagic Shock

Shock is a condition in which acute circulatory failure occurs because of derangement of circulatory control or loss of circulating fluid. Shock can result from many physiological disturbances. When acute circulatory metabolic dysfunction occurs during infection with microorganisms, the condition is termed "septic shock." Hypovolemic shock occurs when the volume of blood within the vascular compartment decreases or shifts, resulting in inadequate perfusion of the body as a whole. This form of shock can occur from severe hemorrhage, burns or dehydration. Neurogenic shock results from a malfunction of the central nervous system caused by drug intoxication or by injury leading to circulatory failure.

The hemodynamic responses that preced hemorrhagic shock lead to a reduction in the volume of venous blood returning to the heart. This results in stimulation of the autonomic system which may maintain a fairly normal cardiac output until the blood volume decreases by 15%, at which time compensatory mechanisms usually fail (123,127). In severe hemorrhagic shock, regional blood flow to the mesenteric, renal and femoral arteries is disproportionately decreased. Flow in these vessels is apparently reduced in favor of maintaining circulation to the carotid, coronary and hepatic arteries. Because of the high alpha-receptor activity in the splanchnic area, shock can induce a pronounced vasoconstriction (120,154). Within the intestinal wall, the mucosal blood flow is selectively decreased. Thus, the transitory vasoconstriction induces ischemia in the mucosa of the gut.

Intestinal ischemia induces a characteristic damage to the small intestinal mucosa within a short period of time (151). The lesions that are chracteristic of ischemic injury are localized to the villi. Mucosal damage ranges from the development of subepithelial space at the very tip of the villus to full scale damage depending upon the severity and duration of ischemia. In pronounced phases of ischemic mucosal damage, it is typical to find the deeper layers of the intestinal wall to be histologically normal (23). The pathogenesis of these lesions is controversial. Three major pathophysiological factors have been implicated: tissue hypoxia (100), superoxide radical (61) and pancreatic proteases (13).

Reactions of the small intestine during ischemia and shock have been reported to be very important for survival. Lillehei (96) demonstrated that cross-perfusing the small intestine of a dog during a period of hemorrhagic hypotension with blood from a healthy donor dog prevented the intestinal mucosal damage and reduced mortality from 80% to 10%. Other studies also have shown that prevention of intestinal mucosal damage prevents the development of general cardiovascular derangements accompanying shock. The degree of intestinal mucosal damage has been directly correlated to the degree of cardiovascular derangements (97,99). The ischemic intestine releases into blood material "toxic" to the circulatory system, probably from the ulcerated villi (96). In vitro experiments show that the intestinal venous blood collected immediately after a period of regional intestinal ischemia contains substances that exert a negative inotropic effect on the heart (94,115). This substance ("the intestinal factor of irreversible hemorrhagic shock,") was termed a cardiotoxic or myocardial depressant factor (MDF) (94). The cardiotoxic material released from the ischemic intestine has been characterized it has a molecular weight of 500 to 1000 daltons and is water soluble. It is not a single myocardiac depressant but several such substances that have been suggested by Haglund and Lundgren (69).

The involvement of prostanoids in the pathogenesis and treatment of irreversible shock has been recently reported. The use of cyclooxygenase inhibitors in shock was shown to increase survival of experimental animals (17,20,40,70). However, cyclo-oxygenase inhibitors exert broad-ranging rather than selective effects on prostanoid synthesis. Recently, prostacyclin (PGI_2) has been found to possess a variety of actions which are useful in the treatment of shock. This prostanoid is a very potent inhibitor of platelet aggregation, a vasodilator, and is also a good membrane stabilizer (1,21,66,92,107,108,109). It also prevents MDF formation in shock (46,93,95). Conversely, administration of thromboxane synthetase inhibitors has been found to prevent lysosomal disruption, and toxic factor formation during shock (92,93). Prostacyclin, therfore, may be a potenial benefical factor, wheras TXA_2 is a deleterious factor in shock. No study has been done to determine the origin of these prostanoids in shock. The splanchnic organs are known to play a significant role in the development and progress of irreversible hemorrhagic shock. Therefore, the balance of these prostanoids (TXA_2 and PGI_2) may play an important role in the pathogenesis of irreversible hemorrhagic shock.

Nutritional requirements in shock

In a variety of shock conditions an early hyperglycemia followed by hypoglycemia has been documented. The hypoglycemia observed in shock condition is associated with mortality (67,71,72,75,105,106,139,143). Strawitz and Hiff (143) in 1960 reported that the average survival time in fasted rats was 36 min as opposed to an average of 65 min in a fed group subjected to standard hemorrhagic shock. Moffat et al. (106) reported intravenous administration of glucose to dogs has significantly delayed physiologic decompensation and severity of metabolic changes when compared to equally treated severe hemorrhagic shock dogs receiving no treatment. These and other studies concluded that administration of glucose may have a merit in the therapy of prolonged hypovolemic shock. Hinshaw et al. (75) reported that glucose adminstration has a similar salutary effect in endotoxin shock.

In 1970 Chiu et al. (24) reported that during the development of intestinal mucosal lesions in low-flow states, a significant reduction in mucosal ATP content and oxygen uptake occurs. This correlates with the histological findings that epithelial damage starts at the tips of the villi, extending gradually toward the crypts. Intraluminal glucose administration in the presence of intestinal ischemia protected the intestinal mucosa from ischemic damage.

Gump et al. (67) reported that radiolabelled glucose administered in post-hemorrhagic shock following reperfusion was found to be incorporated into C14 lipids in higher quantity when compared to control values. Fat metabolism appears to be less sensitive to hypovolemic insult and may represent a more effective energy substrate. Lang et al. (88) also reported that the free fatty acid oxidation by the gut was not altered by endotoxin.

In 1982, Halper et al. (71,72) perfused a glucose- oleic acid solution through the lumen of the small intestine during severe hemorrhagic shock. The perfusion prevented the terminal hypoglycemia, histopathological damage of the intestinal mucosa, the release of cardiodepressants from the splanchnic region and prolonged survival rate, compared to untreated and saline-perfused dogs. These investigators concluded that part of the mechanism by which luminal perfusion of glucose-oleic acid solution protects against severe hemorrhagic shock might be related to the prevention of hypoglycemia.

MATERIALS AND METHODS

Surgical Preparation

All experiments were conducted on mongrel dogs of both sexes (15-25 Kg), fasted for 24 h. The animals were anesthetized with pentobarbital sodium (30 mg/kg, i.v.) and supplemented as needed to maintain a surgical plane of anesthesia. All animals were ventilated with a positive pressure respirator (Harvard Apparatus, Millis, MA) that was adjusted to achieve normal blood pH, O_2 tension, and CO_2 tension before each experiment. Systemic arterial pressure was continuously monitored through a cannula in the femoral artery.

In all series, a midline abdominal incision was made, and a segment of the jejunum (30-45g) about 30 cm aboral to the ligament of Treitz was exteriorized (Fig. 2). After a rubber tube was placed into the lumen of the segment for placement and withdrawal of solutions, both ends of the segment were tied and cut away from the adjacent jejunum to exclude collateral flow (32). Luminal pressure was continuously recorded through the rubber tube by a pressure transducer (Statham P23Gb) during the presence of a solution in the lumen. Before cannulation of blood vessels, heparin sodium (500U/kg) was administered intravenously. The segment was covered with a plastic sheet and kept at 37^o C with a heat lamp and a thermoregulator (Yellow Springs Instruments, Model 63RC, Yellow Springs, OH). At the end of all experi ments, the animals were euthanized by an overdose of pentobarbital sodium or potassium chloride.

Preparation of Solutions

The food solution used contained equal parts by weight of fat, carbohydrate, and protein. It was prepared by adding 30g high fat test diet, 15g high protein test diet and 5g high carbohydrate test diet (U.S. Biochemical, Cleveland, OH) to 400 ml

FIGURE 2

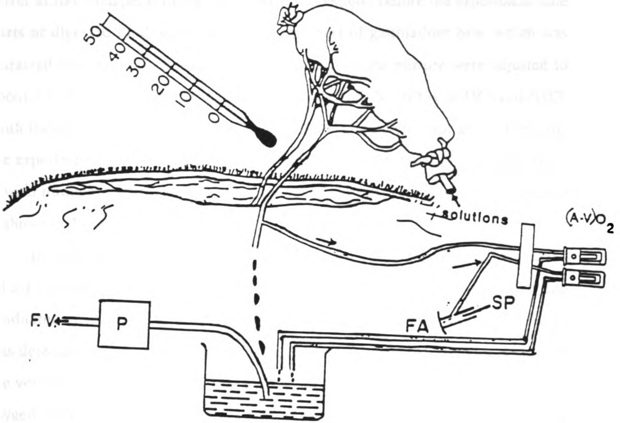


Figure 2. Schematic representation of the preparation used in most experiments

of 0.1 N $NaHCO_3$ containing 750 mg of a pancreatic enzyme preparation (Viokase, VioBin, Monticello IL) (52,102). The mixture was then gently mixed with a magnetic stirrer at room temperature for 5 h to permit digestion. Before the experiment nine parts of digested food were mixed with one part of gallbladder bile, which was extracted from the animal. The pH and osmolality of the mixture were adjusted to about 7.4 and 300 mosmol/Kg, respectively, with either $NaHCO_3$ or HCl and NaCl. Both the digested food plus bile and the normal saline were kept at 37^o C during the experiment. For simplicity, the term "food", instead of "digested food plus bile", is used throughout the text. The composition of glucose oleic acid (GOA) solution is shown in Table 1.

In Series I (n = 16), the single vein draining the jejunal segment was cannulated for measurement of venous outflow by timed collection with a stopwatch and graduated cylinder. Arteriovenous oxygen content difference [$(A\text{-}V)O_2$] (Fig. 2) was determined continuously by perfusing femoral arterial blood and a portion of the venous outflow at 6 ml/min through separate cuvettes of an arteriovenous oxygen content difference analyzer (A-Vox Systems, San Antonio, TX) (133) with a Gilson pump (Minipuls 2, Gilson Medical Electronics, Middleton, WI). The venous outflow and outflows from the cuvettes were directed to a reservoir. The blood in the reservoir was pumped back into the animal via a femoral vein at a rate equal to the total outflows. Oxygen uptake was calculated as the product of blood flow and $(a\text{-} v)O_2$.

When blood flow reached a steady state, the lumen content was changed to food solution. The data obtained during the last 3 min of 15-min normal saline or food placement period were used for analysis, because the blood flow and $(A\text{-}V)O_2$ at that time were in a steady state (32,52,83,102).

The objective of the first series of experiments was to determine jejunal productions of PGE_2, PGI_2, TXA_2, and PGF_2 when the jejunal lumen contained normal saline,

TABLE 1

Composition of Glucose-Oleic Acid Solution

Chemicals	mM	Grams/L
Glucose	150.0	27.0
NaOH	0.18	0.007
Taurocolic Acid[1]	6.01	3.1
NaCl	77.6	4.5
KCl	1.3	0.1
$NaHCO_3$	6.0	0.5
$MgCl_2$ $6H_2O$	0.53	0.107
NaH_2PO_4 H_2O	0.21	0.029
$CaCl_2$[2]	0.45	0.05
Oleic Acid[3]	40.0	11.0 (12.5 ml/L)

[1] Sodium salt, practical grade. ICN Nutritional Biochemicals, Cleveland,OH.

[2] The solution was stirring when $CaCl_2$ was added. Solution was then sonified and pH adjusted to 7.3.

[3] 90% grade, United States Biochemical Corp., Cleveland,OH.

food, normal saline plus arachidonate and food plus arachidonate. The rationale for adding arachidonic acid to the food is to determine the effects of enhanced prostanoid synthesis on blood flow, oxygen uptake and the relative synthesis of vasodilator and vasoconstrictor prostanoids during nutrient absorption. Depending upon the cell types and the metabolic activity under study, substrate loading with arachidonate magnify the cellular responses to a particular stimulus, in this case nutrient absorption. A previous study has shown that arachidonate added to food attenuates the food-induced vascular and metabolic changes (102). However, which prostanoids are responsible for arachidonate action are unknown.

After reaching a steady state by repeated luminal placement of normal saline, luminal contents were changed sequentially and randomly to digested food, normal saline plus arachidonate and food plus arachidonate. Each solution remained in the lumen for 15 min. The arachidonate concentration in normal saline or food solution was 6.5×10^{-4}M (200 ug/ml). This intraluminal dose of arachidonate was selected from a study performed in a similar in vivo jejunal preparation (102). In another intestinal in vivo study, the minimum concentration of arachidonate in the lumen, which significantly increased intestinal prostanoid production and secretion, was 6×10^{-3} M (16). These intraluminal doses of arachidonate were higher than the doses required to induce a similar effect during intra-arterial administration (5×10^{-3} - 2.3×10^{-4} M) (102) or direct application to in vitro cell preparations (2×10^{-5} M) (44,90). The reasons for the dose differences in the two routes of administration are not known. However, this is also true for other vasoactive agents exogenously administered in the intestine.

In six animals, SQ-29548 (a TXA_2 / endoperoxide receptor blocker, a gift from Squibb, Princeton, NJ,) 1.6 ug i.a. bolus was injected into a side branch of the single artery of the segment at the end of the experiment when the lumen still contained food plus arachidonate. The objective was to determine the effect of this

TXA_2 receptor blocker on the food plus arachidonate induced changes in blood flow and oxygen uptake.

For the determination of prostanoid concentration blood samples were collected in plastic test tubes containing the cyclooxygenase inhibitor mefenamic acid (Sigma Chemical, St. Louis, MO) (5 ug/ml of blood). The samples were taken simultaneously from a femoral artery and the venous outflow of the jejunal segment 9 and 15 min after luminal placement of each solution. The venous outflow was measured at the time of blood sampling. Blood samples were centrifuged immediately for 10 min. The plasma was removed and stored at -20 ^{o} C until radioimmunoassay.

The objective of Series II and III (n = 9) of experiments was to determine the effect of intra-arterial infusions of PGI_2, PGE_2, PGF_2 and U-44069 (a TXA_2 analog) (a kind gift from Upjohn Co., Kalamazoo, MI) on jejunal blood flow. The single artery perfusing the gut segment was cannulated, and the segment was perfused at a constant rate with the aortic blood by interposing a Masterflex pump (Cole- Parmer Instruments, Chicago, IL) between the single artery and a femoral artery. The perfusion pressure was monitored via a catheter in the perfusion line attached to a pressure transducer (Statham P23Gb). Pump flow rate was adjusted until perfusion pressure was 10 mmHg below the systemic arterial pressure and then maintained constant throughout the experiment. The venous outflow was directed to a reservoir and pumped back into the animal via a femoral vein at a rate equal to the total outflows. Solutions containing one or a mixture of more than two of the following prostanoids were infused upstream from the Masterflex pump while perfusion pressure was continously recorded. The vasoactivity of individual prostanoids was determined first in a series of experiments. Following this, the vasoactivity of local arterial infusion of a mixture of prostanoids at concentrations similar to those produced by luminal placement of food or food plus arachidonate was determined. The local blood concentration of prostanoids to be achieved were selected from the data obtained from Series 1 and were calculated from the pump blood flow rate, hematocrit, and prostanoid infusion rate. All prostanoids except prostacyclin were kept as a stock solution in ethanol (10 mg/ml). Fresh PGI_2 solution was prepared in 50 mM Tris buffer (pH 9.37 at 0^0 C) immediately before infusion. The infusates of U-44069 and PGF_2 were prepared by diluting the stock solution in 0.9% normal saline and that of PGE_2 was diluted with 0.1M phosphate buffer prior to each experiment.

The objectives of Series IV, V, VI, and VII of experiments were to determine the stimuli for food-induced increases in jejunal prostanoid production. Normal saline (NS), 10% bile (B), intestinal distension and an increase in jejunal blood flow were examined for their individual contribution to the food-induced increases in jejunal prostanoid production.

The experimental preparation used for studying the effects of normal saline, 10% bile, and luminal distension by air was similar to Series I. However, the effects of an increase in jejunal blood flow were studied under constant flow conditions in a similar experimental setup to Series 1l. When blood flow reached a steady state, control arterial and intestinal venous blood samples were taken. Following the collection of blood samples, jejunal blood flow was increased to twice the control blood flow value by increasing the pump speed. Arterial and jejunal venous blood samples were taken 9 and 15 minutes after the blood flow was increased. The blood samples were centrifuged immediately for 10 min. The plasma was removed and stored at -20^0C until radioimmunoassay.

The objective of the eighth series was to determine the jejunal vascular response to a thromboxane A2 analog and receptor blocker. In this series (n=10), the experiment was conducted under constant flow condition. The jejunal preparation was similar to Series II. The perfusion pressure was continuously monitored via a catheter in the perfusion line attached to a pressure transducer. When blood flow reached a steady state, a graded dose of U-44069 (a thromboxane A_2 analog, Upjohn) was administered by intra- arterial bolus injection before and after administration of graded bolus doses of SQ-29548 (A TXA_2 receptor antagonist, Squibb).

The objectives of the ninth series of experiments was to determine the role of endogenous thromboxane A2 on food-induced changes in jejunal blood flow and oxygen uptake. In series IX (n=8), the effects of SQ-29548 on food-induced changes in jejunal blood flow and oxygen consumption were determined. The jejunal preparation was similar to that of Series I. Fifteen ml of normal saline were placed into the lumen for 15 min. This procedure was repeated three to four times until blood flow reached a steady state, at which time the carrier solution for SQ-29548 (ethanol) was administered intra-arterially as a control.

Following this, luminal contents were changed to digested food. After determining the response to food, SQ- 29548 (2.0 ug i.a. bolus) was administered in a side branch of the single artery of the segment. This dose has been determined to inhibit the action of the thromboxane analog (Fig. 17). When blood flow reached steady state the response due to food was determined. Oxygen uptake was calculated as the product of blood flow and the arteriovenous oxygen content difference. Both blood flow and oxygen uptake were expressed as ml/min/100g.

The objective of the tenth and eleventh series of experiments (n=11) was to determine the role of endogenous thromboxane A2 on food-induced changes in jejunal capillary exchange capacity. The single vein draining the segment was cannulated so that venous outflows were measured as described above. Blood flow also was monitored continuously with an extracorporeal electromagnetic flow transducer (BL-2048-E 04, Biotronex Laboratory, Silver Springs, MD) placed in the venous outflow line and connected to an electromagnetic flowmeter (BL610, Biotronex Laboratory). The flowmeter was calibrated periodically by measuring blood flow by timed collection of venous outflow. An arterial side branch was cannulated for administration of drugs. After steady state was reached, measurement of capillary filtration coefficient started.

Capillary filtration coefficients (K_{fc}) were determined gravimetrically. Briefly, the jejunal segment was placed on a platform attached vertically to a calibrated force displacement transducer (FT03B, Grass Instruments, Quincy, MA). Normal saline or predigested food was placed in the lumen, and K_{fc} was determined by a sudden elevation of venous pressure from 0 to about 10 mmHg, lasting 10-15 seconds (86). When jejunal venous pressure is elevated, venous outflows from the jejunum fall initially to a low value and subsequently reach a plateau lower than the control level (Fig. 3). The point of attainment of this plateau ("flow equilibration") represents the end of the blood volume shift (63), and measuring the rate of intestinal weight increases from that point divided by the increment in capillary pressure gives K_{fc} (Capillary pressure was estimated using the venous occlusion technique (62,104)). Jejunal K_{fc} was measured before and after intraarterial administration of the thromboxane receptor blocker SQ-29548. For each luminal content, the K_{fc} was determined four times at 4 min intervals, with the last value used to compare the alterations during the experimental conditions.

The objective for the twelveth and thirteenth series of experiments was to determine the effect of a thromboxane A2 analog on jejunal wall blood flow distribution to the mucosa plus submucosa and muscle plus serosa before and after intraarterial administration of SQ-29548. In this series (n = 19) the single artery perfusing the gut segment was cannulated, and perfused at either a constant rate with the aortic blood by interposing a Masterflex pump (Cole-Parmer Instruments, Chicago, IL) between the single artery and a femoral artery, or free flow rate by interposing a three-way stopcock upstream from the pump. A mixing chamber was connected to the arterial line proximal to the pump. During constant flow, the perfusion pressure

FIGURE 3

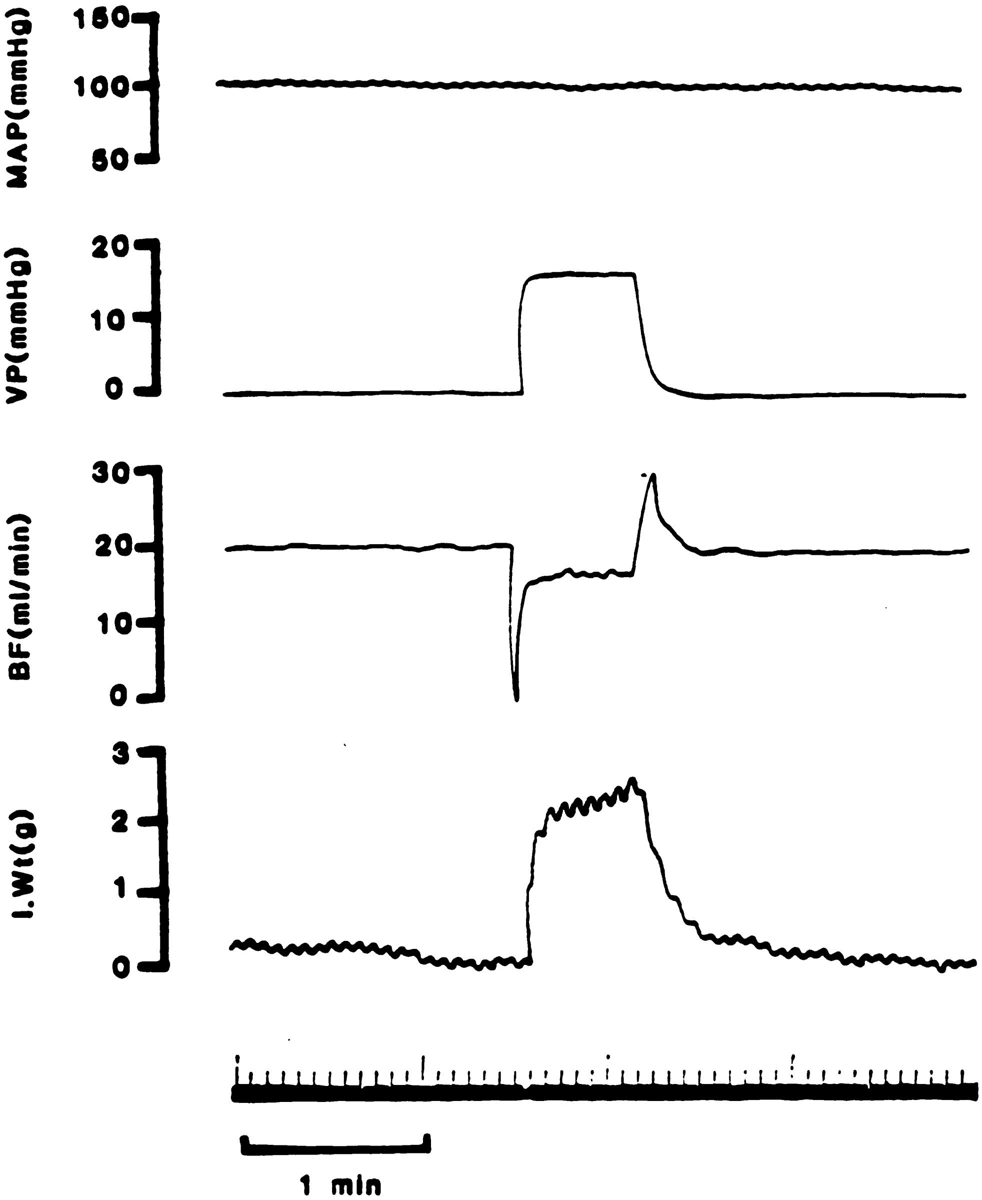


Figure 3 Original polygraph chart recording of the data used to estimate jejunal capillary filration coefficient (Kfc). MAP = mean arterial blood pressure ; VP = intestinal venous pressure ; BF = intestinal blood flow ; I.Wt = intestinal rate of weight change.

was monitored via a catheter in the perfusion line attached to a pressure transducer (Statham P23Gb). Pump flow rate was adjusted until perfusion pressure was 10 mmHg below the systemic arterial pressure and then maintained constant throughout the experiment. The single vein draining the jejunal segment was cannulated for measurement of venous outflow by timed collec tion with a stopwatch and graduated cylinder. Once a steady state had been reached, microsphere injection upstream from the mixing chamber was started.

Radiolabelled microspheres ^{141}Ce (diam = 13.75 ± 0.74 um), ^{46}Sc (diam = 13.56 ± 0.70 um) and ^{85}Sr (diam = 13.75 ± um) were obtained from Medical Products Division/3M, St. Paul, MN 55144. Stock microspheres (25 uCi, 1,125,000 spheres/ml) plus 1 drop Tween 80 were vortexed to achieve uniform distribution prior to injection so that settling and clumping of spheres is prevented. 0.2 ml of the stock microsphere (5 uCi: 225,000 spheres) were injected with a Hamilton syringe into the intestinal arterial line upstream from the mixing chamber. The three types of microspheres were injected randomly during control (first microsphere), during intra-arterial infusion of 0.16 ug/min U-44069, a thromboxane A_2 receptor analog (second microsphere), and after intra-arterial bolus injection of 2.0 ug SQ-29548, a thromboxane A_2 receptor antagonist while U-44069 infusion continued (third microsphere). Jejunal blood flow was measured before and after injection of each microsphere . The above experimental protocol was performed either at free flow (n=12) or constant flow (n=7) conditions. At the end of the experiment the whole isolated jejunal segment was taken and pinned flat in the mucosal surface. The serosa plus muscularis was removed intact by dissecting from the submucosa with a scalpel. Each tissue, serosa plus muscle and submucosa plus mucosa, was cut into about 1 gm pieces and placed in a pre-weighed counting tube. The pre-weighed counting tubes containing tissue samples were weighed again to determine tissue weight. The radioactivity of ^{46}SC, ^{85}Sr, and ^{141}Ce in each tube was measured for

10 min in the Packard 5000 series gamma counter (Packard Instrument Company, 2200 Warrenville Rd., Downers Grove, IL 60515). The energy windows used were ^{46}Sc, 650-2000 KeV; ^{85}Sr, 200-650 KeV; and ^{141}Ce, 15-200 KeV. A spillover of one radioactive sphere count into the channel of another sphere count was corrected. The blood flow to each layer of the intestine was calculated using the following formula:

$$\text{Blood flow to tissue sample} = \frac{\text{TMcpm/gm x JBF ml/min}}{\text{JMcpm/gm}}$$

Where TM = tissue radioactivity

JM = total radioactivity in the jejunal segment

JBF = jejunal blood flow

The objectives of the fourteenth series of expriments were 1) to determine the systemic and local intestinal production of TXA_2 and PGI_2 during various stages of severe hemorrhagic shock and following blood transfusion, and 2) to determine if the benefical effect of glucose oleic acid solution (GOA) perfused through intestinal lumen is related to its effect on shock-induced intestinal PGI_2 and TXA_2 production . In this series (n=19) mongrel dogs (10- 25kg) of either sex were anesthetized with pentobarbital sodium (30 mg/kg, i.v.), and ventilated with a positive pressure Harvard respirator. After laparotomy, a loop of ileum (15-20 cm in length) was exteriorized, and the single vein draining the loop was cannulated after intravenous administration of heparin sodium (500 U/kg). The venous outflow from the intestinal loop was directed to a reservoir, and the collected blood was returned by a pump to the animal through a femoral vein at a rate equal to that of the venous outflow. Both ends of the loop were tied and cut away from the remainder of ileum. The loop was covered with a plastic sheet and kept at 37°C with a heat lamp and a thermo- regulator. Systemic arterial pressure was continuously monitored through a right femoral arterial cannula connected to a Statham pressure transducer (p23 Gb).

Fourteen dogs were bled from the cannulated left femoral artery into a calibrated reservoir over a 30 minute period until the mean arterial blood pressure decreased between 30-40 mmHg. Blood pressure was then maintained at this level for 3 hours by adjusting the height of the blood reservoir. During the hypotensive period, the blood reservoir was frequently shaken to prevent sedimentation of blood cells. At the end of the three-hour hypotensive period, all blood in the reservoir was reinfused back into the animal. The experiment was terminated when blood pressure decreased below 60 mmHg.

In eight of the fourteen dogs, 30-45 min after bleeding, a GOA solution was perfused into the lumen of the segment at a rate of 1 ml/min (GOA treated) . The six remaining dogs were not perfused with GOA (GOA untreated).

Blood samples were collected in plastic test tubes containing the prostaglandin synthesis inhibitor mefenamic acid (5 ug/ml of blood). Simultaneously samples were obtained from a femoral artery and the venous outflow of the isolated ileal segment, before hemorrhage and every hour during and after the hypotensive period. Intestinal blood flow was measured by timed-collection of venous outflow at the time of blood sampling. Blood samples were centrifuged immediately for 10 minutes. The plasma was removed and stored at -20°C until assay. The plasma was analysed for TXB_2 and 6-keto PGF_1 (the stable breakdown products of thromboxane A_2 and prostacyclin, respectively), using radioimmunoassay techniques.

Five control dogs were given treatment identical to dogs in the hemorrhagic shock series except that the dogs were not bled. Blood samples were collected at time periods corresponding to those of hemorrhagic dogs. After termination of all experiments, the intestinal loop was excised, its lumen content emptied, and weighed. The loops weighed 27 ± 2 and 29 ± 2 gm in the control and hemorrhagic shock dogs, respectively. Afterwards an intestinal tissue sample was taken from the GOA perfused ileal segment and a non-perfused adjacent segment for morphological examination of the mucosa for damage. The following grading sequence was used to quantify the morphological changes as described by Chiu et.al (23):

1. Grade 0 - Normal mucosal villi.
2. Grade 1 - Development of subepithelial Gruenhayen's space, usually at the apex of the villi; often with capillary congestion.
3. Grade 2 - Extension of the subepithelial space with moderate lifting of epithelial layer from the lamina propria.
4. Grade 3 - Massive epithelial lifting down the sides of villi. A few tips may be denuded.
5. Grade 4 - Denuded villi with lamina propria and dilated capillaries exposed. Increased cellularity of lamina propria may be noted.
6. Grade 5 - Digestion and disintegration of lamina propria; hemorrhage and ulceration.

Radioimmunoassay

Radioimmunoassay was performed using standard techniques. TXB_2, PGE_2, PGF_2, and 6-keto-PGF_1 antisera (Seragen, Inc., Boston, MA) were appropriately diluted in phosphate buffered saline (0.1 N phosphate buffer, 0.9% NaCl, 0.5% gelatin: PBSG). Aliquots (100 microliters) of the appropriate antisera were mixed with 100 ul aliquots of either standard (Seragen) or plasma samples. The standard solutions were made by serial dilution of the prostanoid standard with the prostanoid-free canine plasma, which was prepared previously by stripping the plasma collected from mefenamate-treated dogs with charcoal.The standard solutions and plasma samples were then mixed with the appropriate radioactive tracer prostanoid (Tritiated, New England Nuclear, N. Billerica, MA), 6,000 cpm in 100 ul of PBSG, so that the total reaction volume was 300 ul. After incubation (0.5-1h at ambient temperature, then 16-24 h at 4 C), the protein bound material was isolated by adding 1.0 ml of dextran-coated charcoal suspension (5 mg/ml of charcoal, 0.5 mg/ml dextran in PBSG). Within 12 min the tubes were vortexed and began centrifugation for 12 min at 1,500 rpm and 0 C. The supernatant of each tube was decanted into a vial containing 15 ml of scintillation cocktail (Safety-Solve, Research Products International, Mt. Prospect, IL), and the radioactivity determined in a beta scintillation counter (Model A300C, Packard, Downers Grove, IL). Duplicate values were averaged and compared with a standard curve performed with each assay. The antisera cross reactivity was as follows: 6-keto-PGF_1 with TXB_2, PGD_2, PGA_2, PGA_1, PGB_1, PGB_2 < 0.01%, PGF_1 (7.8%), 6-keto-PGE_1 (6.8%), PGE_1 (0.7%), and PGE_2 (0.6%); TXB_2 with 6-keto-PGF_1, PGF_1, PGF_2, PGE_1, PGE_2, PGD_2, PGA_2, PGA_1, PGB_1, and PGB_2 < 0.1%; PGE_2 with TXB_2, 6-keto-PGF_1, PGF_1, 6-keto-PGE_1, PGD_2, PGB_1, PGB_2 < 1.0%, PGF_2 (1.3%), PGE_1 (50%), PGA_2 (6.0%), and PGA_1 (3.0%); PGF_2 with 6-keto-PGE_1, PGD_2, PGA_2, PGA_1, PGB_1, PGB_2 < 0.1%, TXB_2 (0.5%), 6-keto-PGF_1 (1.1%), PGF_1 (100%), PGE_1 (1.1%), and PGE_2 (0.3%). Inter- and intra-assay variations were less than 12%, respectively (n=20).

STATISTICAL ANALYSIS

The data were analysed using analysis of variance and Student's t-test for comparison of two paired sample means. Dunnett's multiple comparison procedure was used to compare the significance of the difference between and within groups. Statistical significance was set at $p<0.05$. All values in the text are means ± SEM.

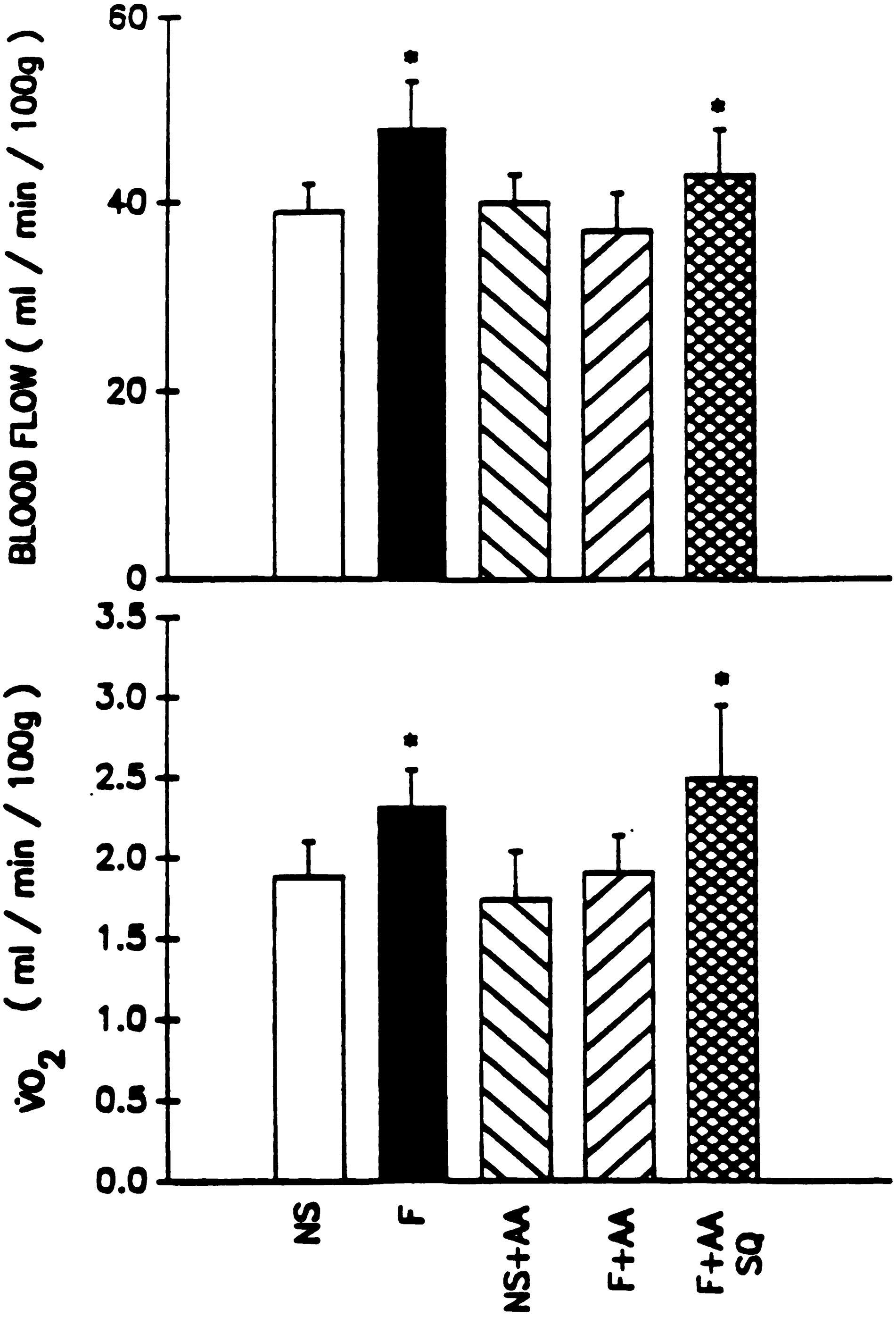
RESULTS

Series I experiments were designed to determine which prostanoid might play a role in food- and arachidonate- induced jejunal response was determined. The arterial and jejunal venous concentrations of 6-keto-PGF_1 (PGI_2 stable metabolite), TXB_2 (TXA_2 stable metabolite), PGE_2, and PGF_2 were determined when the jejunal lumen contained normal saline (NS), food (F), normal saline plus arachidonate (NS+AA), or food plus arachidonate (F+AA). Fig. 4 shows jejunal blood flow and oxygen uptake during placement of these four solutions. Food produced a significantly higher blood flow and oxygen uptake than normal saline in the lumen. Although addition of arachidonate to normal saline did not significantly influence blood flow and oxygen uptake, addition of arachidonate to food abolished the food-induced increases in blood flow (48 ± 5 vs 37 ± 4 ml. min^{-1}. $100g^{-1}$) and oxygen uptake (2.32 ± 0.23 vs 1.91 ± 0.23 $ml.min^{-1}.100g^{-1}$). SQ-29548, a TXA_2/endoperoxide receptor antagonist, was injected i.a. when the lumen still contained food plus arachidonate in six of the nine dogs in this series. The injection significantly increased blood flow from 36 ± 4 to 43 ± 5 $ml.min^{-1}.100g^{-1}$, and oxygen uptake from 1.78 ± 0.31 to 2.49 ± 0.46 $ml.min^{-1}.100g^{-1}$ ($p<0.05$). Thus the inhibitory action of arachidonate on food-induced changes appears to result primarily from the action of its metabolites, TXA_2 and/or endoperoxides.

Fig. 5 shows the arterial and jejunal venous plasma concentrations of four prostanoids when the lumen contained normal saline, food, normal saline plus arachidonate, or food plus arachidonate. The values in Fig. 5 are the averages of the samples values obtained at the 9th and 15th min after jejunal placement of the four solutions in 9 dog experiments. Arterial concentrations of all four prostanoids did not change significantly by changing luminal contents throughout the experimental period, but venous concentrations changed with difference in luminal contents.

Figure 4 Jejunal blood flow and oxygen uptake (VO_2) during luminal placement of normal saline (NS), food (F), normal saline plus arachidonate (NS+AA), and food plus arachidonate (F+AA). n=9. SQ denotes the values after i.a. injection of SQ-29548, a TXA_2/endoperoxide receptor antagonist, when the lumen still contained F+AA. n=6. * $p<0.05$ relative to NS values.

FIGURE 4


BLOOD FLOW (ml / min / 100g)
60
40
20
0
*
*
$\dot{V}O_2$ (ml / min / 100g)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
*
NS
F
NS+AA
F+AA
F+AA SQ

The venous concentration of each prostanoid, with one exception, was always higher than the corresponding arterial concentration in all four conditions, indicating that all four prostanoids were produced and released from the jejunum whether the luminal contents were normal saline, food, or arachidonate in combination with saline or food. The one exception is that jejunal venous and arterial PGF$_2$ concentrations during normal saline placement were not statistically different. As compared to normal saline in the lumen, food tended to increase venous 6-keto-PGF$_1$ and significantly increased venous TXB$_2$, PGE$_2$, and PGF$_2$ concentrations. Addition of arachidonate to normal saline significantly increased only venous PGF$_2$, but addition of arachidonate to food significantly increased venous PGE$_2$, TXB$_2$ and PGF$_2$ concentrations. The venous concentrations of two vasoconstrictor prostanoids, TXB$_2$ (stable metabolite of TXA$_2$) and PGF$_2$ were significantly higher during luminal placement of food plus arachidonate than food alone. Thus, the inhibition of food-induced hyperemia by luminal arachidonate (Fig. 4) might be, at least in part, due to an increase in jejunal production of these two vasoconstrictor prostanoids.

Fig. 6 compares the rate of individual prostanoid releases under the four experimental conditions, calculated as the product of blood flow and veno-arterial concentration difference. In the presence of normal saline in the lumen, PGI$_2$ (6-keto-PGF$_1$ precursor), PGE$_2$ and TXA$_2$ (TXB$_2$ precursor) were released significantly from the jejunum ($p < 0.05$), but PGF$_2$ release was minimal. The relative magnitude of releases (in ng min^{-1} 100g^{-1}) was PGI$_2$ (24 ± 5) > PGE$_2$ (16 ± 12) > TXA$_2$ (11 ± 2) > PGF$_2$ (0.93 ± 2.0). When the relative magnitude of the release was expressed as percent fraction of the sum of all four prostanoid releases, vasodilator prostanoids, PGI$_2$ (44.4%) and PGE$_2$ (31.9%), comprised 76% of the total release during luminal presence of normal saline. Changing the luminal content from salin to food significantly increased the release of all four prostanoids.

Figure 5 Arterial and jejunal venous plasma concentrations of 6-keto-PGF$_1$, TXB$_2$, PGE$_2$, and PGF$_2$ when the jejunal lumen contained normal saline (NS), food (F), normal saline plus arachidonate (NS+AA) and food plus arachidonate (F+AA). n=9. * and ** $p<0.05$ relative to venous concentration obtained during placement of NS and F, respectively.

FIGURE 5

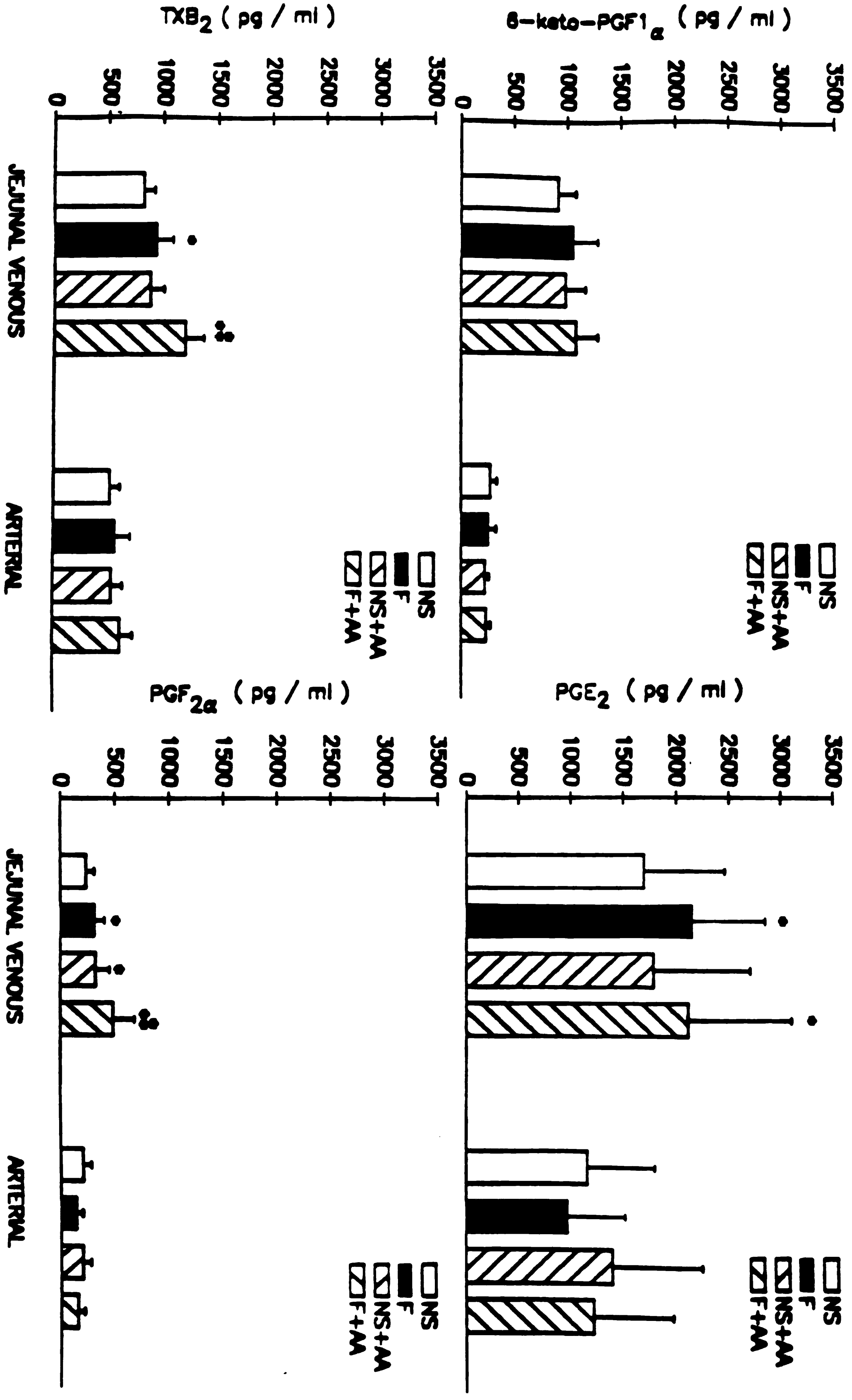
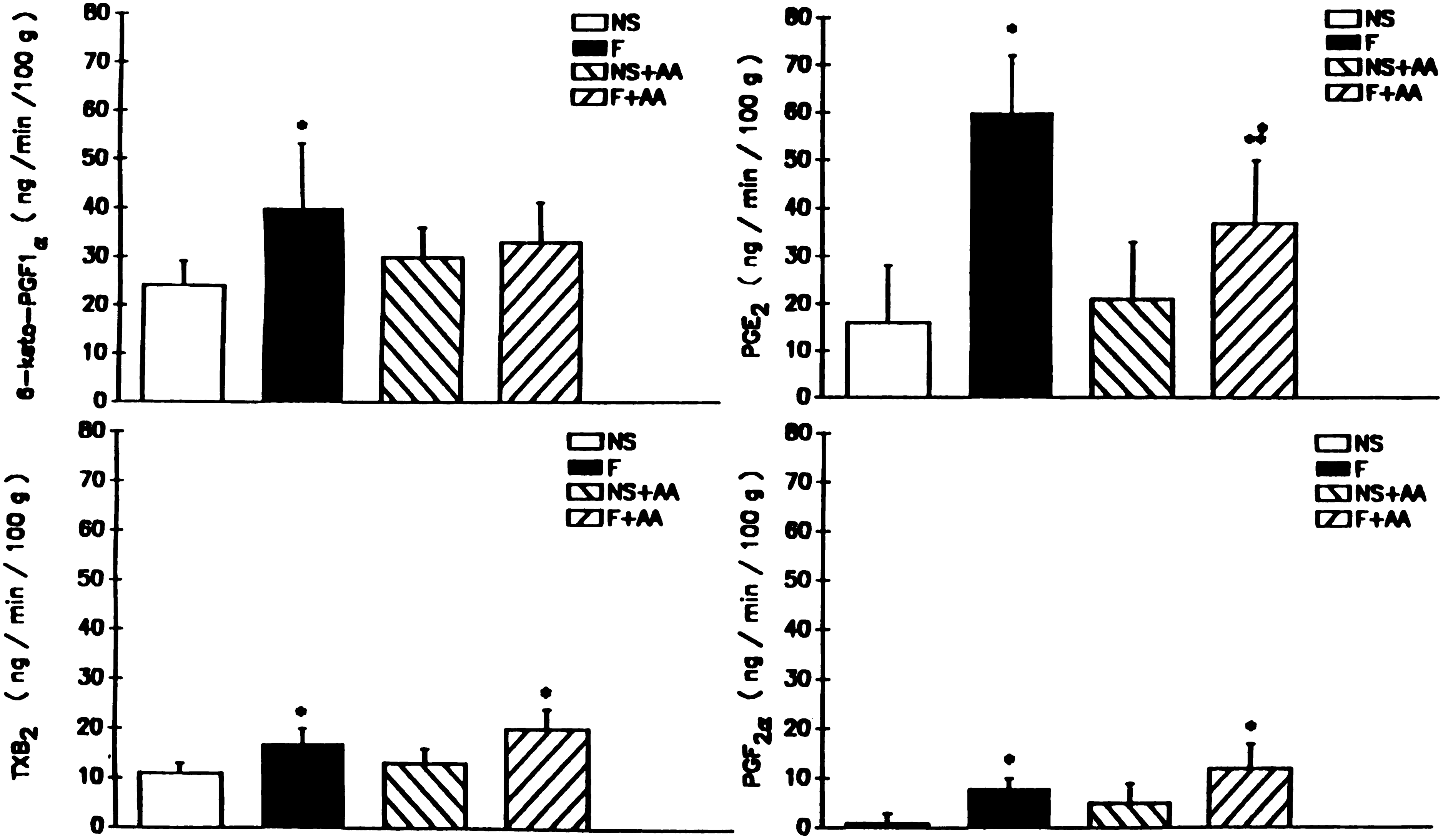

6-keto-PGF1α (pg / ml)
PGE2 (pg / ml)
TXB2 (pg / ml)
PGF2α (pg / ml)
0
500
1000
1500
2000
2500
3000
3500
JEJUNAL VENOUS
ARTERIAL
NS
F
NS+AA
F+AA
*

Figure 6 Jejunal releases of 6-keto-PGF_1 , TXB_2, PGE_2, and PGF_2 (ng min^{-1} $100g^{-1}$) during luminal placement of normal saline (NS), food (F), normal saline plus arachidonate (NS+AA), and food plus arachidonate (F+AA). n=9. * and ** denote values significantly different from those obtained during placement of NS and F, respectively, $p < 0.05$.

FIGURE 6

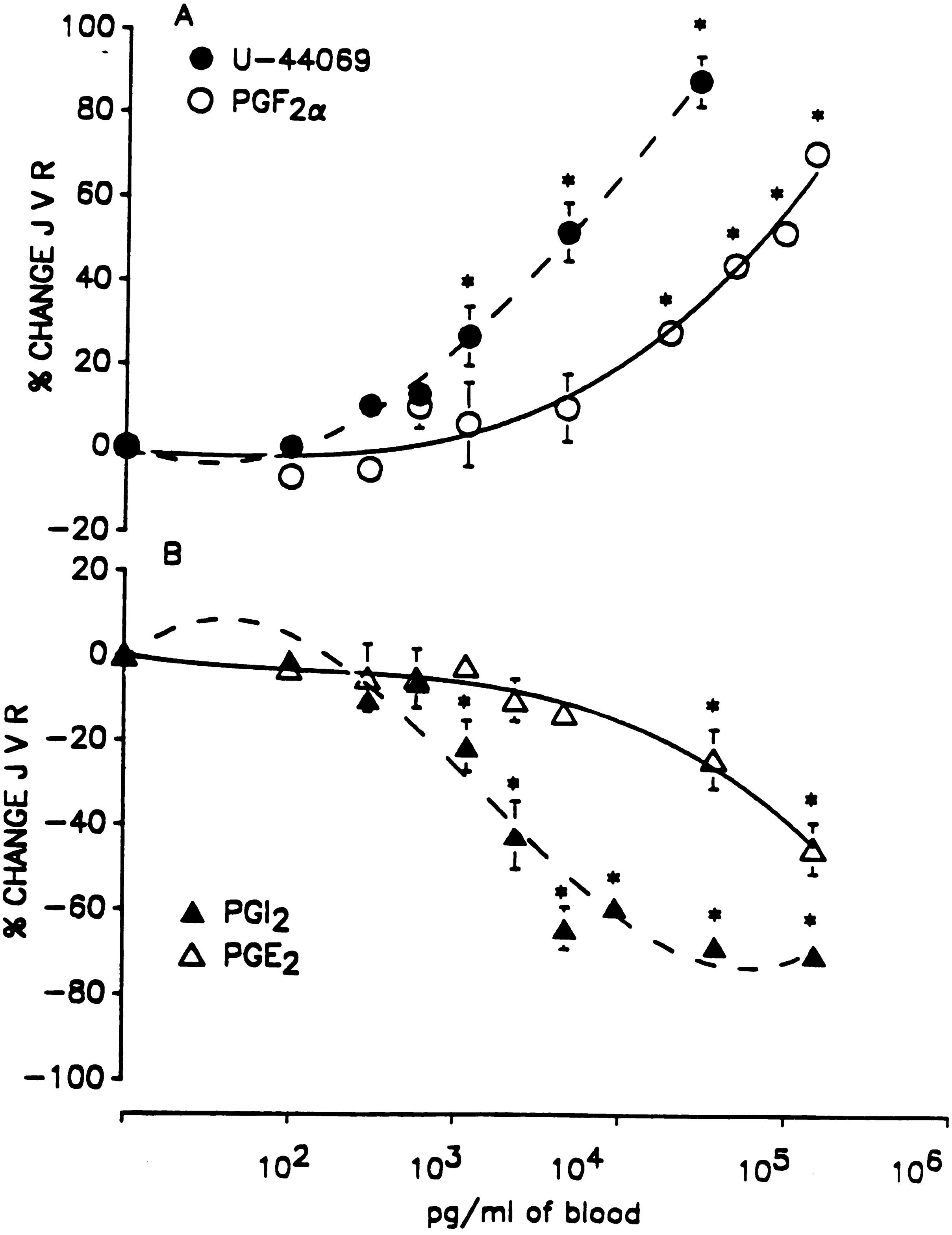

6-keto-PGF1α (ng /min /100 g)
TXB2 (ng / min / 100 g)
PGE2 (ng / min / 100 g)
PGF2α (ng / min / 100 g)
0
10
20
30
40
50
60
70
80
NS
F
NS+AA
F+AA
*

PGI_2 and TXA_2 releases almost doubled, while PGE_2 and PGF_2 releases increased 4-fold and 8-fold, respectively. The relative magnitude of release (in $ng.min^{-1}.100g^{-1}$) became PGE_2 (60 ± 12) > PGI_2 (40 ± 13) > TXA_2 (17 ± 3) > PGF_2 (8 ± 2). However, vasodilator prostanoids, PGE_2 and PGI_2, still comprised 77% of the total release. Addition of arachidonate to normal saline did not significantly alter the releasing rates or relative magnitude of releases of the four prostanoids compared to normal saline alone in the lumen. Addition of arachidonate to food, however, decreased the release of two vasodilators, PGI_2 and PGE_2, and increased the release of the two vasoconstrictors TXA_2 and PGF_2, as compared to food alone in the lumen. Now TXA_2 and PGF_2 comprised 21.4% and 9.7% of the total release, respectively, as compared to 16.3% and 6.4%, with food alone in the lumen. The relative magnitude of releases ($ng.min^{-1}. 100g^{-1}$) were PGE_2 (37 ± 13) > PGI_2 (33 ± 8) > TXA_2 (20 ± 4) > PGF_2 (12 ± 5).

The above experiments indicated that venous concentrations and jejunal productions of the four prostanoids increased when luminal content was changed either from normal saline (NS) to food (F) or from NS plus arachidonate (AA) to F plus AA. The next series of experiments was therefore conducted to determine whether the increase in these prostanoid concentration could directly act on the vasculature to alter vascular resistance. At first the vasoactivity of the individual prostanoid was determined. Infusions of the carriers at the same rates as those of prostanoids did not significantly alter jejunal vascular resistance. As shown in Fig. 7A, U-44069, a TXA_2 analog, and PGF_2 increased jejunal vascular resistance (JVR) in a dose-dependent fashion. The minimum blood concentration required to increase JVR significantly ($p<0.05$) was 1000 pg/ml, and 3×10^4 pg/ml blood for U-44069 and PGF_2, respectively. Both PGI_2 and PGE_2 (Fig 7B) caused a dose-dependent decrease in jejunal vascular resistance. The minimum blood concentration required to cause a significant decrease in JVR was 1000 pg/ml for PGI_2 and

Figure 7 Effects of local intra-arterial infusions of U-44069, a TXA_2 analog, and PGF_2 (A), PGI_2 and PGE_2 (B) on jejunal vascular resistance (JVR). Resting vascular resistance were 3.57 ± 0.73, 3.63 ± 0.36, 2.77 ± 0.53, 2.18 ± 0.28 mmHg/ml/min/100g for PGI2, PGE2, PGF2 , and U-44069, rerspectively. n=5-9. * $p<0.05$ relative to control value.

FIGURE 7


A
U-44069
PGF$_{2\alpha}$
% CHANGE J V R
100
80
60
40
20
0
−20
B
20
0
−20
−40
−60
−80
−100
PGI$_2$
PGE$_2$
10^2
10^3
10^4
10^5
10^6
pg/ml of blood

6×10^4 pg/ml for PGE_2.

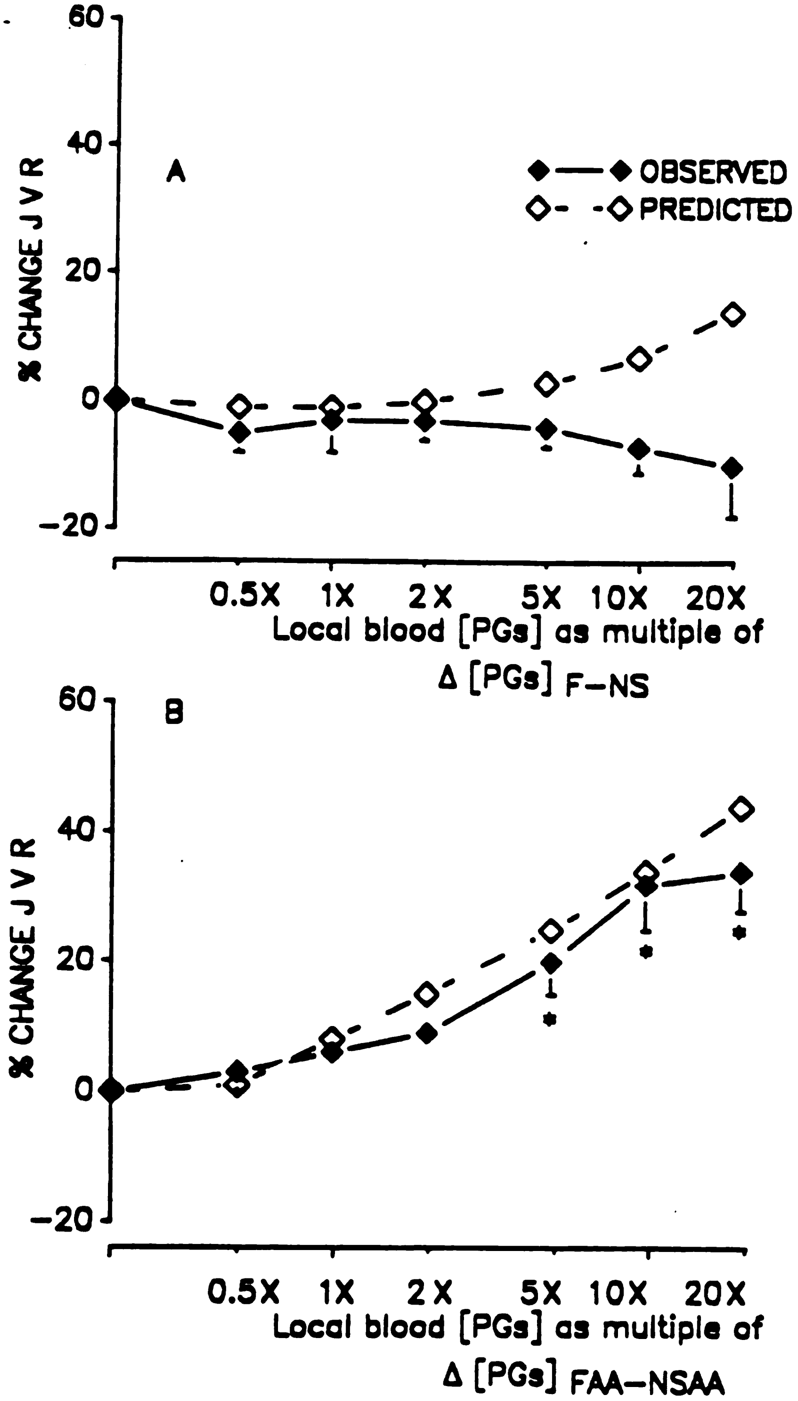
Systemic arterial and jejunal venous blood samples (n = 7) were taken during intra-arterial infusion of PGI_2 to determine the actual blood concentrations. The systemic arterial concentrations of 6-keto-PGF_1 were not altered by local infusion of PGI_2, indicating that there was no recirculation of these prostanoids during infusions. However, the jejunal venous 6-keto-PGF_1 concentrations measured by radioimmunoassay were 31±7% lower than the calculated infused blood concentrations. This might reflect dilution or tissue uptake of the prostanoid within the intestinal wall. Thus the calculated blood concentrations shown in Figs. 7, 8 and 9 might be over-estimating the actual blood concentrations by 31.7%, and the venous concentrations shown in Fig. 5 during luminal placement of various solutions might underestimate the actual tissue concentrations by the same magnitudes.

Figure 8 shows the effect of intra-arterial infusions of mixtures of PGI_2, PGE_2, PGF_2 and U-44069 (a TXA_2 analog) on jejunal vascular resistance. Based on the data from Fig. 5 (venous concentration during placement of NS, F, NS + AA and F + AA) blood flow rate, and hematocrit at the time of the infusion, the infusion rates were pre- calculated to give local arterial concentrations equivalent to 0.5, 1, 2, 5, 10 and 20 times the value of the change in venous concentration when lumen content was changed from normal saline to food, [PGs]F-NS.

As shown in Fig. 8a, i.a. infusions of the four prostanoids, to mimic changing luminal content from normal saline to food (filled diamonds), did not significantly alter the jejunal vascular resistance at all infusion rates. The open diamonds representing the predicted changes in jejunal vascular resistance, were calculated from the summation of the individual prostanoid actions shown in Fig. 7. The equations for the regression lines for the observed and predicted data were $Y = -3.3\log X - 3.7$, $r = 0.77$, and $Y = 8.9\log X - 0.8$, $r = 0.92$ (where $Y = \%$ JVR, and $X = 0.5, 1.0... 20$), respectively, and their slopes were not significantly different. These studies

Figure 8 Effects of local i.a. infusions of mixtures of , PGF_2 , PGI_2, U-44069 and PGE_2 at concentrations 0.5X (times), 1X, 2X, 5X, 10X, and 20X the value of the increases in venous prostanoid concentrations shown in Fig. 5 when luminal content was changed from normal saline to food ([PGs] F-NS) (PGI_2 = 82pg/ml, TXA_2 = 72 pg/ml, PGE_2 = 259pg/ml and PGF_2 = 47pg/ml in the mixture) (A), and food plus arachidonate ([PGs] FAA-NS) (PGI_2 = 82pg/ml, TXA_2 = 72 pg/ml, PGE_2 = 259pg/ml and PGF_2 = 47pg/ml in the mixture) (B). Filled diamonds indicate the actual observed data, whereas open diamonds indicate the predicted data as calculated by the summation of the individual prostanoid vascular effects shown in Fig. 7. Resting vascular resistance was 3.41 ± 0.38 and 3.63 ± 0.36 mmHg/ml/min/100g. n=9.

FIGURE 8

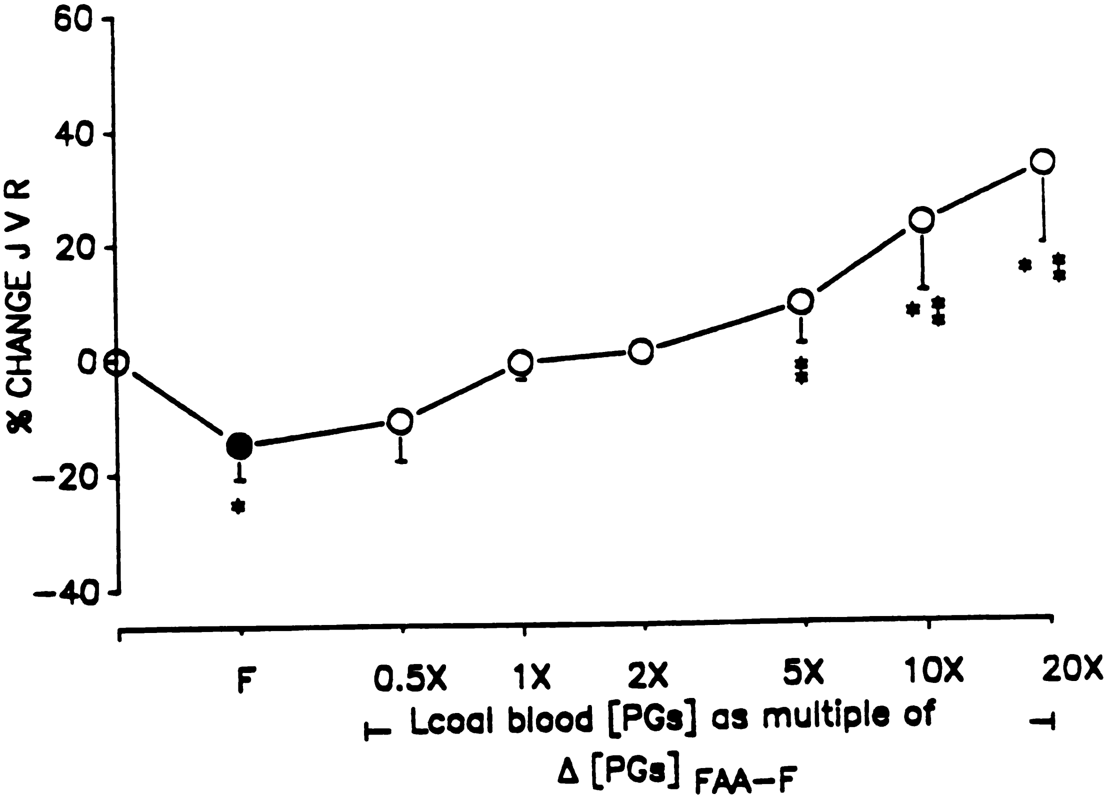

A
B
60
40
20
0
−20
% CHANGE J V R
◆—◆ OBSERVED
◇- -◇ PREDICTED
0.5X
1X
2X
5X
10X
20X
Local blood [PGs] as multiple of
Δ [PGs] F−NS
Δ [PGs] FAA−NSAA
*

indicate that the vascular effects of these prostanoids were additive over the range of the doses studied. When the mixture was infused at the concentrations that simulated changing luminal content from normal saline to food plus arachidonate (Fig. 7B filled diamonds), the mixture produced a dose-dependent increase in jejunal vascular resistance. The minimal concentration required to produce a significant rise in resistance was five times that of [PGs]FAA-NSAA. The open diamonds in Fig 7B show the predicted response. The equations for the observed and the predicted data were $Y = 21.5 \log X + 6.7$, $r = 0.98$ and $Y = 26.5X + 7.9$, $r = 0.99$, respectively, and their slopes were not signifcantly different. The close agreement in predicted and observed responses was also found in data shown in Fig. 9 ($Y = 23.7 \log X - 2.2$, $r = 0.98$, and $Y = 32.7 \log X - 5.5$, $r = 0.94$ for observed and predicted values). These findings further indicate that the vascular effects of these prostanoids were additive over the range of the doses studied.

The infusion experiments described above were performed when the lumen contained normal saline. In the next series of experiments, food was placed into the lumen, then a mixture containing PGF_2 and U-44069 was infused intra- arterially, to mimic the change observed when luminal contents were changed from food to food plus AA. As shown in Fig. 5, changing lumen content from food to food plus arachidonate significantly increased only TXB_2 and PGF_2 concentrations. Figure 9 shows that placement of food (F) per se significantly ($p < 0.05$) decreased jejunal vascular resistance. Infusion of the the two prostanoids mixture increased the jejunal vascular resistance in a dose dependent manner. At concentrations similar to and two times that of [PGs]FAA-F, the infusate completely abolished the food- induced decreases in jejunal vascular resistance. The increased resistance at concentrations above five times that of [PGs]FAA-F were signficantly greater than the value obtained during food placement alone, and the increases in vascular resistance at concentrations above ten times were significantly greater than the resting value.

Figure 9 Effects of luminal placement of food (F) (filled circle) and subsequent local i.a. infusions of a mixture of U-44069 and PGF_2 on jejunal vascular resistance. [PGs]FAA-F at 1X was TXA_2 : 120pg/ml and PGF_2 : 80pg/ml. Resting vascular resistance was 3.13 ± 0.37 mmHg/ml/min/100g. n=9. * and * p,0.05 relative to F and control value.

FIGURE 9


60
40
20
0
−20
−40
% CHANGE J V R
F
0.5X
1X
2X
5X
10X
20X
*
*
*
* *
* *
Lcoal blood [PGs] as multiple of
Δ [PGs] FAA−F

In the next Series of experiments an attempt was made to determine the stimulus for the food-induced increases in jejunal prostanoid production. In order to study this, the jejunal prostanoid release was determined during luminal placement of normal saline, 10% bile, air distension, and during a mechanical hyperemia.

Intestinal blood flow (ml/min/100gm) during luminal placement of normal saline (54 ± 6), 10% bile (52 ± 7), or an equivalent volume of air (56 ± 8) was not significantly different compared to an empty lumen (55 ± 6).

As shown in Fig. 10, the arterial as well as jejunal venous concentration of 6-keto-PGF_1 and TXB_2 was not significantly altered by luminal placement of normal saline. This finding might indicate that normal saline added to food might not contribute to the food-induced increases in jejunal prostanoid releases.

Fig. 11 shows the effects of luminal distension with air on arterial and jejunal venous prostanoid concentrations. The arterial and jejunal venous concentrations of 6-keto-PGF_1 (n = 6) and TxB_2 (n = 4) were not significantly altered by luminal placement of air. No effect of distension on intestinal prostanoid production might indicate that physical placement of food in the lumen per se is not a contributing factor for the food-induced increase in jejunal prostanoid release.

Fig. 12 shows the effects of a 10% bile solution on jejunal prostanoid production. The arterial and jejunal venous concentrations 6-keto-PGF_1 and TXB_2 during luminal placement of 10% bile were not significantly different compared to the values obtained during NS placement. This finding indicates that the 10% bile used in preparing the food solution might not be a direct stimulus for food-induced increases in prostanoid production. However the bile in the food mixture might have an indirect effect on food-induced jejunal prostanoid production. Previously it has been shown that bile added to food enhanced the food-induced vascular and metabolic changes, possibly through facilitation of nutrient absorption, whereas bile alone did not (82).

Figure 10 Arterial and jejunal venous plasma concentrations of 6-keto PGF_1 and TXB_2 when the jejunal lumen is empty (unfilled bars) or filled with normal saline (filled bars).

FIGURE 10

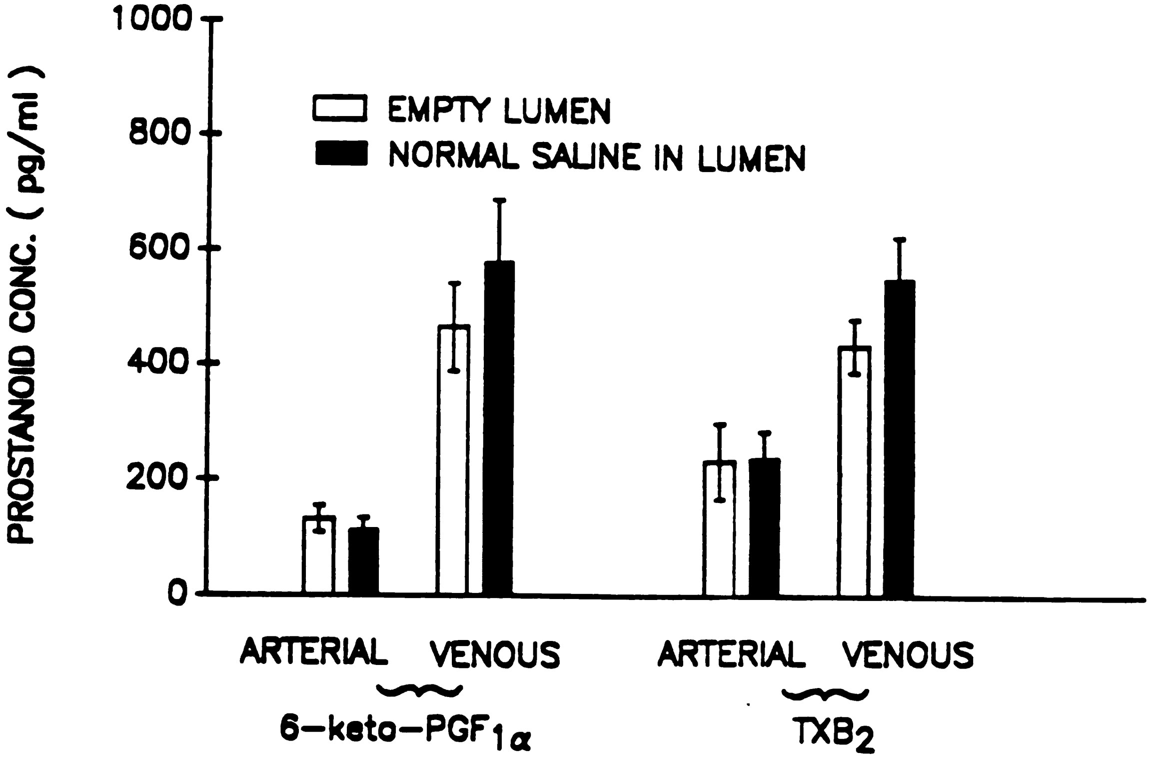

1000
800
600
400
200
0
PROSTANOID CONC. (pg/ml)
☐ EMPTY LUMEN
■ NORMAL SALINE IN LUMEN
ARTERIAL
VENOUS
6-keto-PGF1α
ARTERIAL
VENOUS
TXB2

Figure 11 Arterial and jejunal venous plasma concentrations of 6-keto PGF_1 and TXB_2 when the jejunal lumen is empty (unfilled bars) or filled with air (filled bars).

FIGURE 11

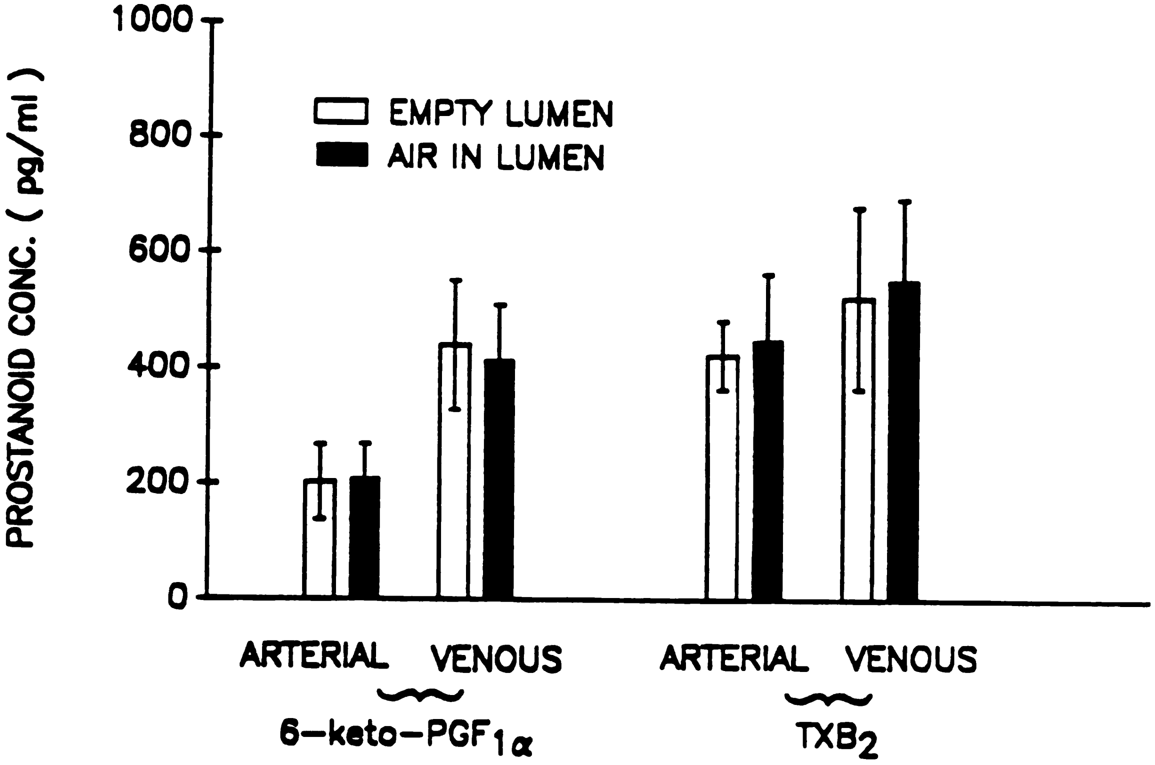
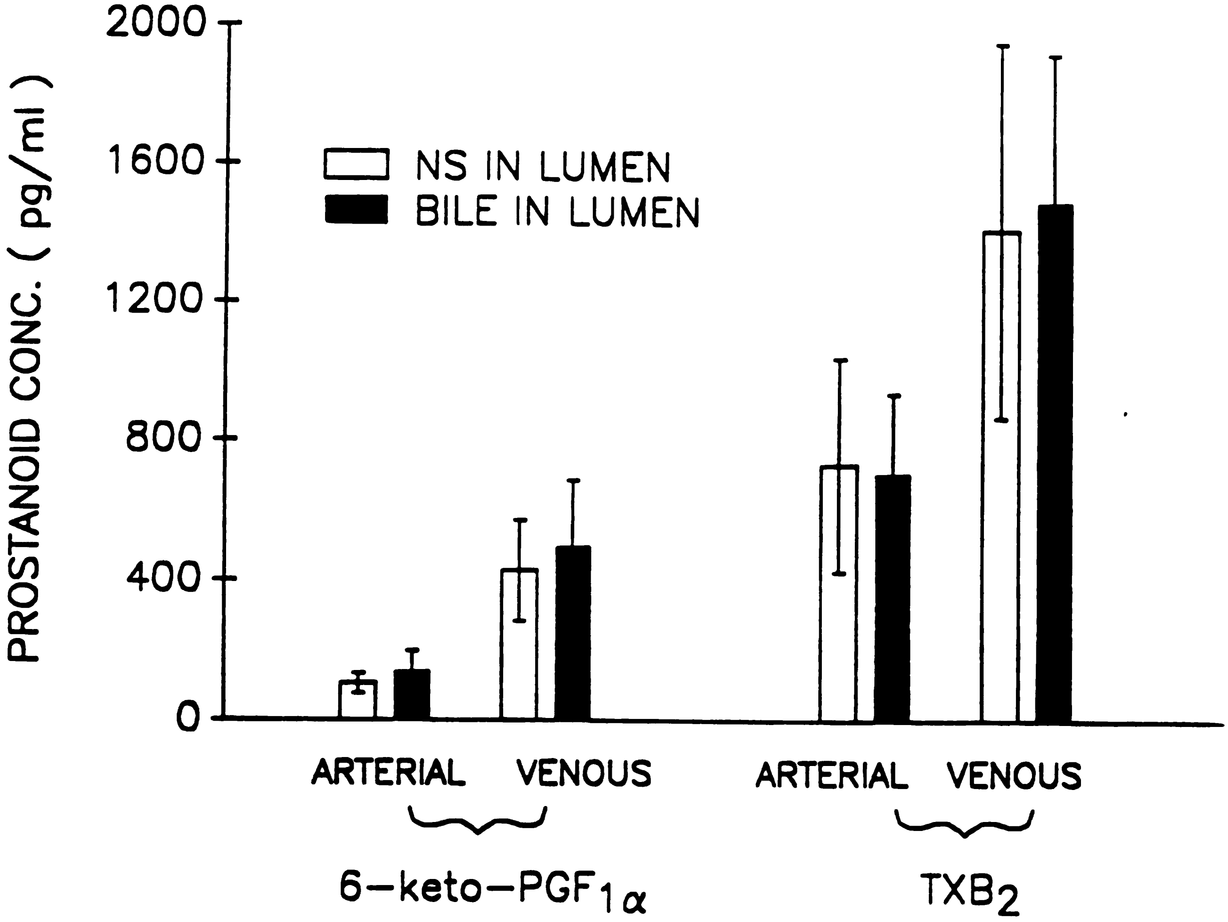

1000
800
600
400
200
0
PROSTANOID CONC. (pg/ml)
☐ EMPTY LUMEN
■ AIR IN LUMEN
ARTERIAL
VENOUS
6-keto-PGF$_{1\alpha}$
ARTERIAL
VENOUS
TXB$_2$

Figure 12 Arterial and jejunal venous plasma concentrations of 6-keto PGF$_1$ when the jejunal lumen contained normal saline (unfilled bars) or 10% bile (filled bars).

FIGURE 12


2000
1600
1200
800
400
0
PROSTANOID CONC. (pg/ml)
NS IN LUMEN
BILE IN LUMEN
ARTERIAL
VENOUS
ARTERIAL
VENOUS
6–keto–PGF1α
TXB2

During nutrient absorption one of the fundamental changes reported to occur is an increase in intestinal blood flow. The effects of a mechanically-induced increase in intestinal blood flow on jejunal prostanoid production was studied in series VII. The objective was to determine whether the food-induced increases in jejunal blood flow is the stimulus for enhanced prostanoid production.

Figure 13 shows jejunal blood flow and perfusion pressure before (control) and after pump-induced hyperemia (mechanical hyperemia). The control jejunal blood flow was 37 ± 5 ml/min/100gm. Blood flow was then increased to 83 ± 7 ml/min/100gm utilizing a pump. Accompanying the increase in jejunal blood flow was a significant increase in perfusion pressure from 95 ± 5 to 176 ± 10 mmHg. The jejunal vascular resistance decreased from 2.56 mmHG/ml/min/100gm (control) to 2.12 mmHg/ml/min/100gm (mechanical hyperemia). This demonstrates a flow dependent vasodilation in the intestine.

The arterial and jejunal venous concentration of PGE_2 6-keto-PGF_1 , TXB_2, and PGF_2 before and after the mechanically-induced hyperemia are shown in Fig. 14. The arterial concentrations of the four prostanoids were not significantly different during control and mechanical hyperemia. Though not statistically significant, the 6- keto-PGF_1 and TXB_2 concentrations tended to decrease while the PGE_2 concentrations tended to increase. The intestinal venous PGF_2 concentration was significantly ($P<0.05$) decreased. The two-fold increase in jejunal blood flow is expected to decrease the jejunal venous concentrations of all the four prostanoids with the same magnitude. However the findings indicate that the increase in jejunal blood flow affected the venous concentrations of each prostanoid differently. This might indicate that the jejunal synthesis of PGE_2, PGI_2 and TXA_2 is increased while PGF_2 is not altered.

The jejunal rate of prostanoid production as calculated from the products of blood flow and veno-arterial concentration differences is shown in Fig. 15 . The rate

Figure 13 Jejunal blood flow and perfusion pressure before (control) and after pump-induced jejunal hyperemia (mechanical hyperemia). Asterisks indicate signifcant change from corresponding control value $p < 0.05$.

FIGURE 13

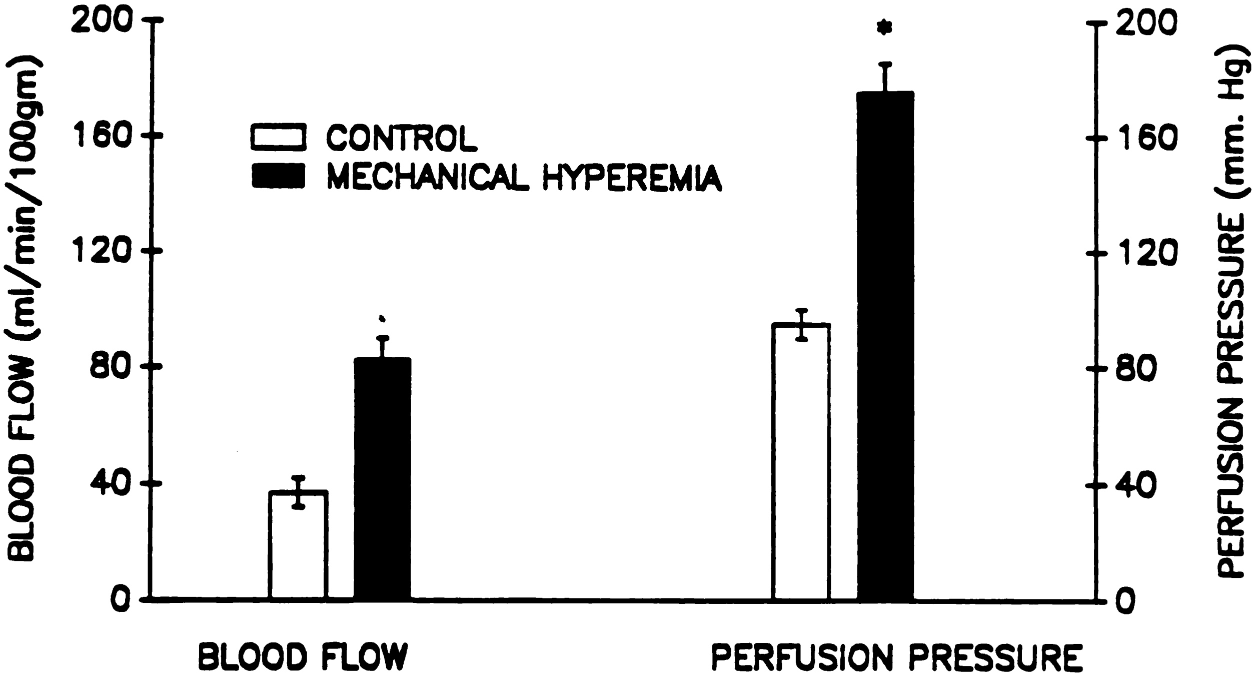

200
160
120
80
40
0
BLOOD FLOW (ml/min/100gm)
CONTROL
MECHANICAL HYPEREMIA
*
*
200
160
120
80
40
0
PERFUSION PRESSURE (mm. Hg)
BLOOD FLOW
PERFUSION PRESSURE

Figure 14 Arterial and jejunal venous plasma concentrations of PGE_2, 6-keto PGF_1, PGF_2 and TXB_2 before (control) and after pump-induced jejunal hyperemia (mechanical hyperemia). Asterisks indicate signifcant change from corresponding control value $p < 0.05$.

FIGURE14

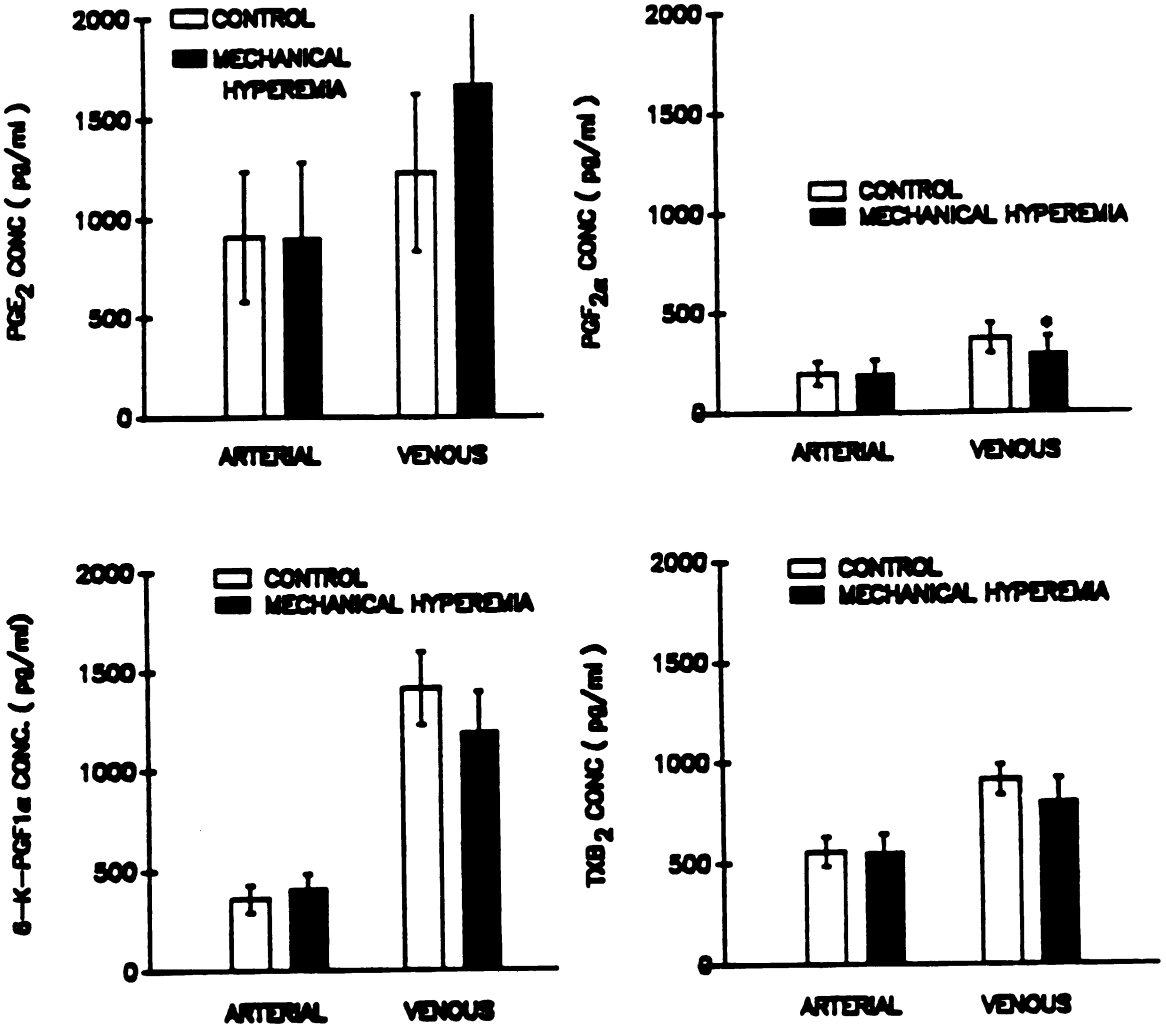
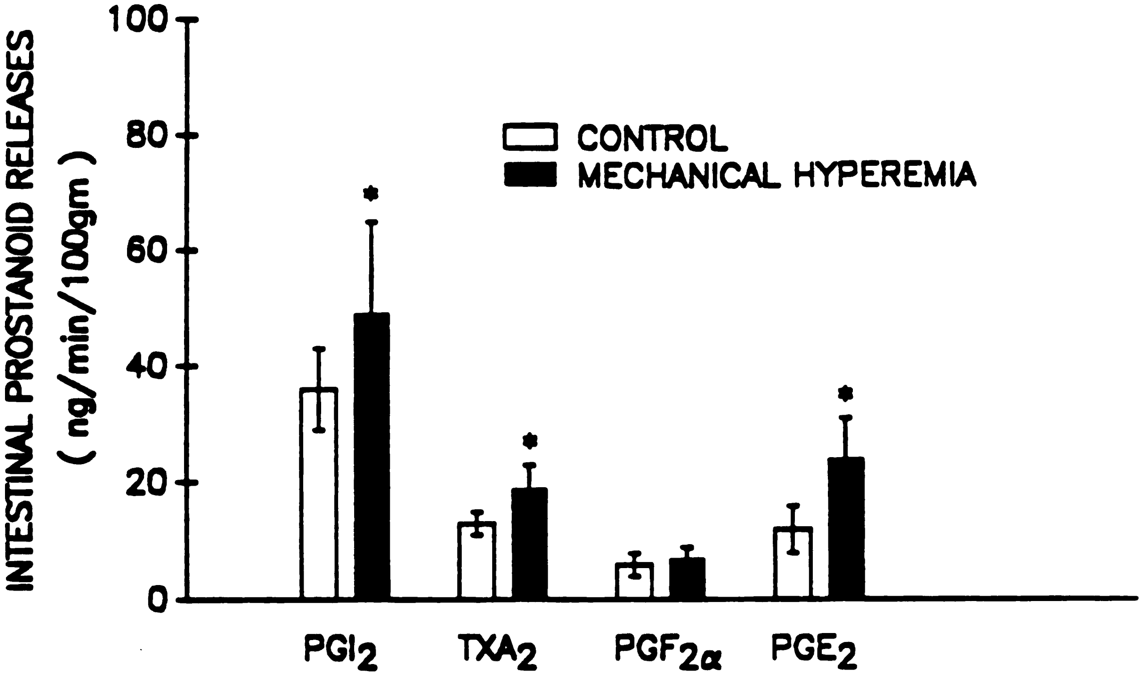

2000
1500
1000
500
0
CONTROL
MECHANICAL HYPEREMIA
PGE2 CONC (pg/ml)
ARTERIAL
VENOUS
2000
1500
1000
500
0
CONTROL
MECHANICAL HYPEREMIA
PGF2α CONC (pg/ml)
*
ARTERIAL
VENOUS
2000
1500
1000
500
0
CONTROL
MECHANICAL HYPEREMIA
6-K-PGF1α CONC. (pg/ml)
ARTERIAL
VENOUS
2000
1500
1000
500
0
CONTROL
MECHANICAL HYPEREMIA
TXB2 CONC (pg/ml)
ARTERIAL
VENOUS

Figure 15 jejunal releases of PGI_2, TXA_2, PGF_2 and PGE_2 ($ng.min^{-1}.100gm^{-1}$) before (control) and after pump- induced jejunal hyperemia (mechanical hyperemia). Asterisks indicate signifcant change from corresponding control value $p < 0.05$.

FIGURE 15


INTESTINAL PROSTANOID RELEASES
(ng/min/100gm)
100
80
60
40
20
0
CONTROL
MECHANICAL HYPEREMIA
*
*
*
PGI2
TXA2
PGF2α
PGE2

of jejunal releases of PGI_2, TXA_2 and PGE_2 were significantly increased while the PGF_2 release was not altered. These findings indicate that part of the food-induced increases in jejunal prostanoid production might be due to the food- induced increases in jejunal blood flow.

The next series of experiments were performed to determine the role of TXA_2 on food-induced vascular and metabolic changes. To study this, U-44069 and SQ-29548 (a TXA_2 receptor agonist and antagonist),respectively were used. At first the jejunal vascular response to the exogenously administered thromboxane A2 analog and receptor blocker was determined. Fig 16 is a representative tracing showing the effect of U-44069 on jejunal perfusion pressure before and after adminstration of SQ-29548. U-44069 caused a significant increase in jejunal perfusion pressure. Adminstration of SQ- 29548 (0.8 ug) significantly attenuated the U-44069-induced increases in jejunal vascular resistance.

Fig. 17 shows the effect of graded doses (0.05-2.0 ug) of a thromboxane analog (U-44069) on % changes in jejunal vascular resistance before and after intra-arterial administration of 0.1, 0.6, and 2.0 ug of a thromboxane receptor blocker (SQ-29548). U-44069 produced an increase in jejunal vascular resistance, that was rapid in onset, in a dose-related fashion. U-44069 in the minimum dose (0.05 ug) used caused a significant ($P < 0.05$) increase in jejunal vascular resistance. The maximum increase in vascular resistance was observed at a dose of 1.5 ug; thereafter any increase in the dose of U-44069 administered did not further enhance the jejunal vascular resistance. The U-44069 vehicle, ethanol, did not alter the jejunal vascular resistance. Administration of 0.1 and 0.6 ug of SQ-29548 prior to U-44069 significantly ($P < 0.05$) attenuated and at a dose of 2.0ug completely abolished the effect of U-44069. This blocking action lasts 40-60 min. SQ-29548 per se had no effect on resting intestinal vascular resistance.

In Series IX, the effects of thromboxane receptor blocker on food-induced

Figure 16 Original polygraph chart recording showing the effect of U-44069 on jejunal perfusion pressure before and after adminstration of SQ-29548 (a TXA_2 / endoproxide receptor blocker).

FIGURE 16

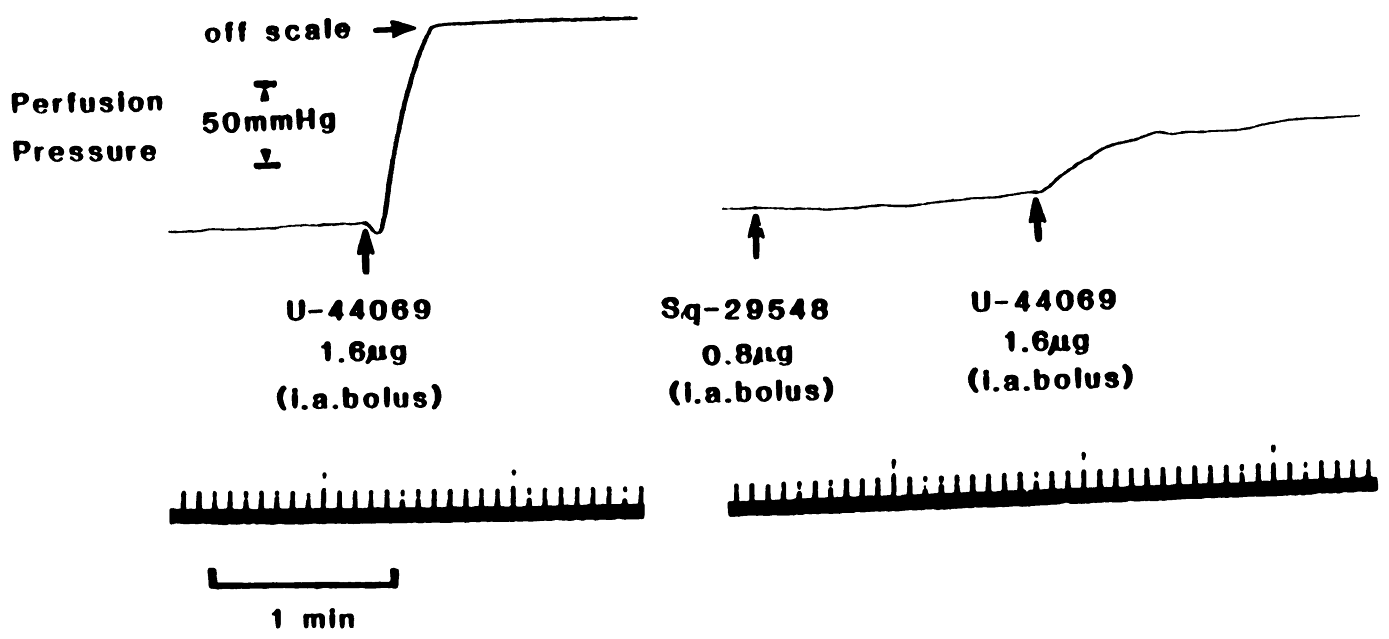
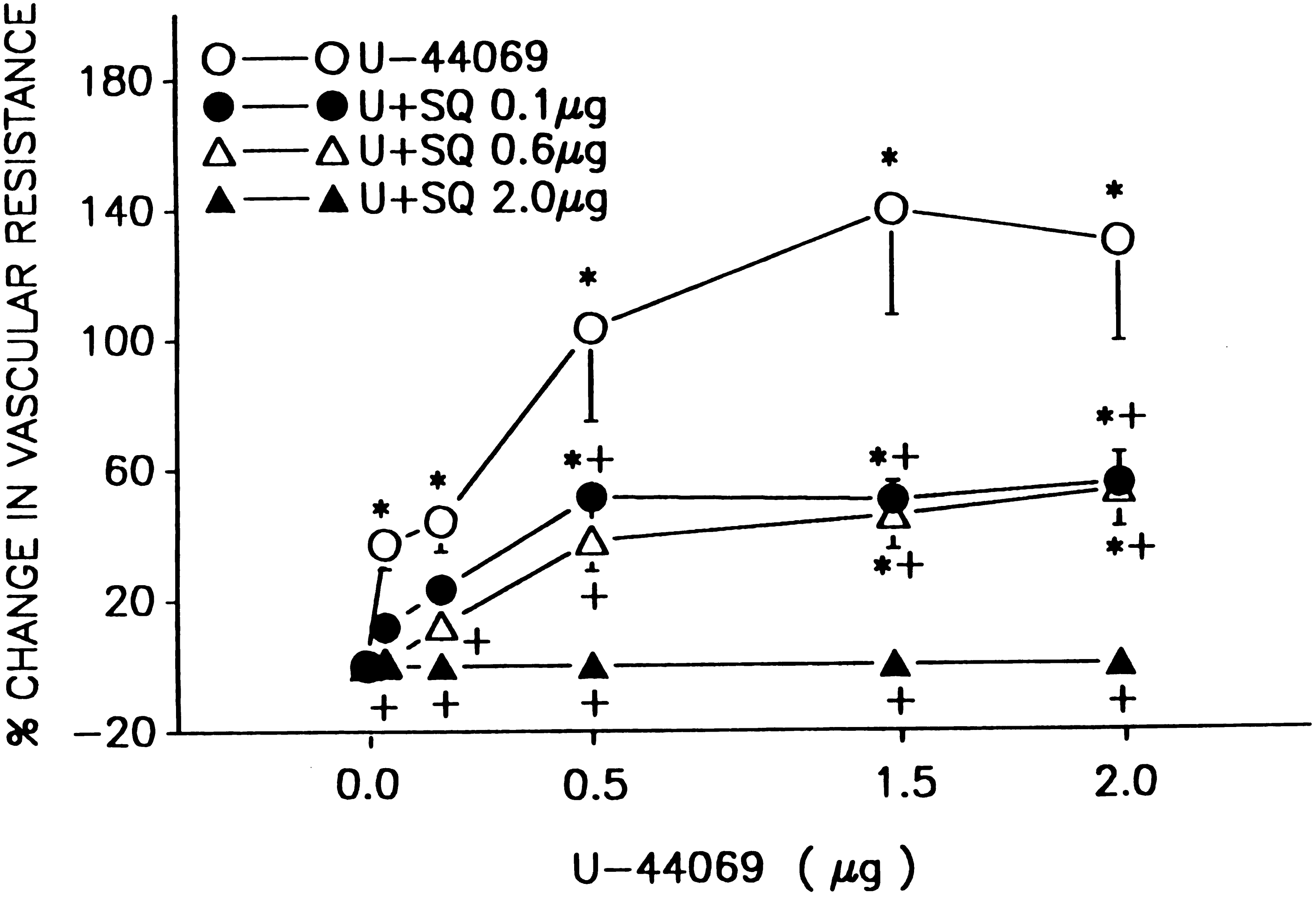

off scale
Perfusion Pressure
50mmHg
U-44069
1.6µg
(i.a.bolus)
Sq-29548
0.8µg
(i.a.bolus)
U-44069
1.6µg
(i.a.bolus)
1 min

Figure 17 The effect of intra-arterial bolus administration of graded dose: of a TXA_2 analog (U-44069) on percent changes in jejunal vascular resistance before (unfilled circles) and after intra-arterial administration of 0.1 ug (filled circle) , 0.6 ug (unfilled triangles) and 2.0 ug (filled triangles) a TXA_2 receptor blocker (SQ-29548). Asterisks and crosses indicate significant differences ($p < 0.05$) from control values and corresponding U-44069 values (unfilled circles).

FIGURE 17


% CHANGE IN VASCULAR RESISTANCE
180
140
100
60
20
-20
○—○ U-44069
●—● U+SQ 0.1µg
△—△ U+SQ 0.6µg
▲—▲ U+SQ 2.0µg
*
+
0.0
0.5
1.5
2.0
U-44069 (µg)

changes in jejunal blood flow and oxygen uptake were determined. Fig. 18 shows jejunal blood flow during luminal placement of normal saline and food plus bile before and after intra-arterial administration of 2.0 ug SQ-29548 . Before administration of SQ-29548, placement of food plus bile in the jejunal lumen significantly increased ($p < 0.05$) jejunal blood flow by 34 ± 6%. After administration of SQ-29548 jejunal blood flow measured during placement of normal saline was not significantly different compared to the corresponding value obtained before SQ-29548 (46 ± 4 before and 45 ± 6 after). After administration of SQ-29548, food plus bile significantly increased ($p < 0.05$) jejunal blood flow by 26.7%. This increase was not significantly different from the corresponding value obtained before SQ-29548.

Jejunal segment oxygen consumption during nutrient absorption before and after administration of SQ-29548 is shown in Fig. 19. The magnitude of oxygen consumption during normal saline before and after SQ-29548 was not significantly different. Before SQ-29548, food increased jejunal oxygen consumption by 28 ± 7%. After SQ-29548 food increased jejunal oxygen consumption by 51 ± 11%. The increase after SQ-29548 was significantly ($P < 0.05$) greater than before.

In Series X, the effect of a thromboxane A2/endoperoxide receptor blocker (SQ-29548) on food-induced changes in capillary filtration coefficient was determined. Figure 20 shows the effects of luminal placement of digested food on jejunal capillary filtration coefficient (K_{fc}) before and after administration of SQ-29548, (2.0 ug i.a. bolus). Placement of food in the lumen significantly increased ($p < 0.05$) jejunal K_{fc} from 0.386 ± 0.041 to 0.508 ± 0.047 ml/min/mm.Hg/100gm. Administration of SQ-29548 *per se* did not alter resting jejunal K_{fc}, but significantly potentiated the food-induced increases in jejunal K_{fc} from 0.416 ± 0.043 to 0.633 ± 0.107 ml/min/mm.Hg/100gm. During nutrient absorption, the absolute and the percent changes in jejunal K_{fc} due to SQ-29548 (0.262 ± 0.089 ml/min/mm.Hg/100gm, 63.3 ± 22.5%), respectively, were significantly greater

Figure 18 Jejunal blood flow before and after administration of SQ-29548 during normal saline (unfilled bars) and food plus bile (filled bars) in the lumen. Asterisks indicate significant increases ($p < 0.05$) above normal saline values.

FIGURE 18

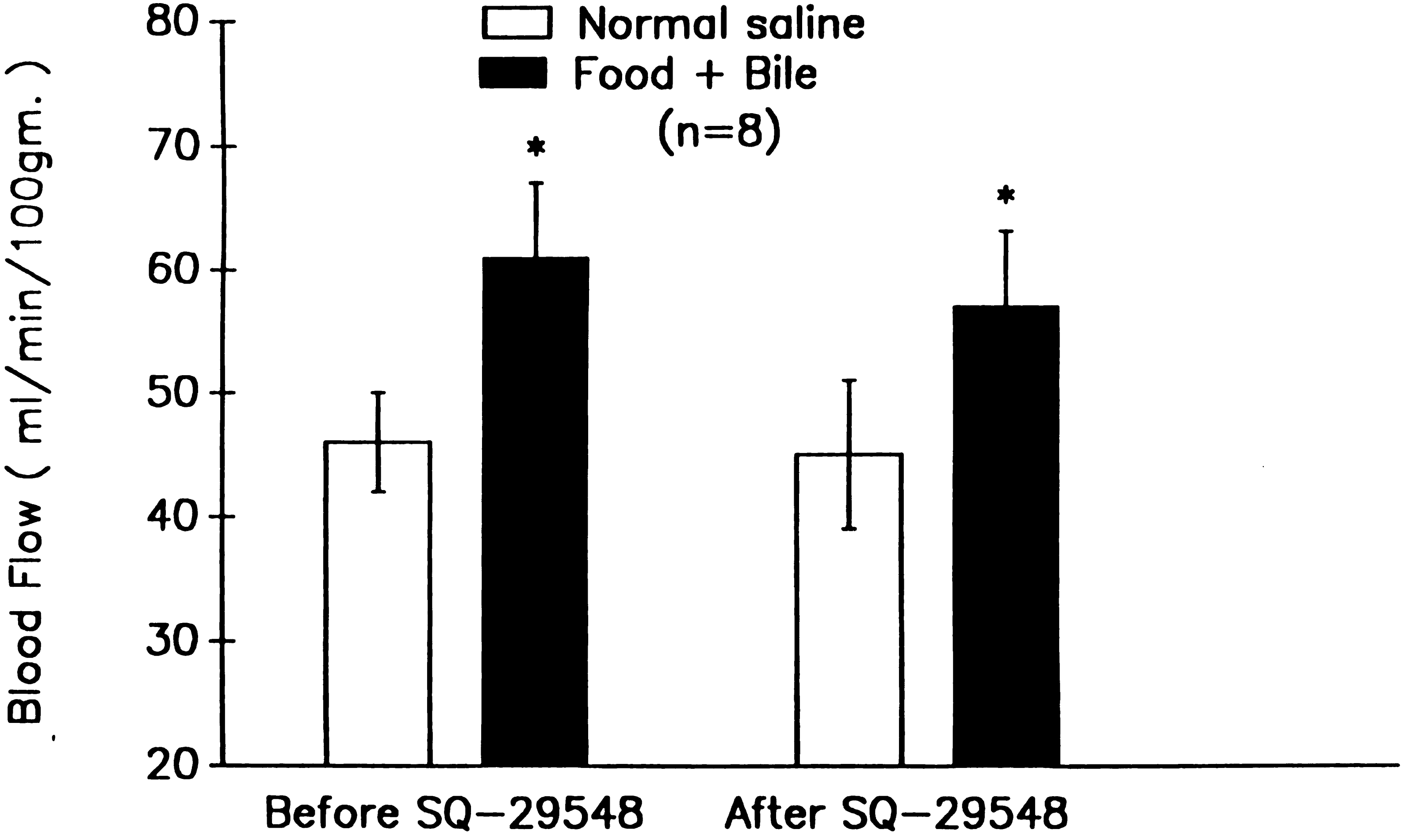

Normal saline
Food + Bile
(n=8)
Blood Flow (ml/min/100gm.)
80
70
60
50
40
30
20
*
*
Before SQ-29548
After SQ-29548

Figure 19 Jejunal oxygen consumption before and after administration of SQ-29548 in the presence of normal saline (unfilled bars) and food plus bile (filled bars). Single and double asterisks indicate significant increases ($p < 0.05$) compared to normal saline and food plus bile values before adminstration of SQ-29548, respectively.

FIGURE 19

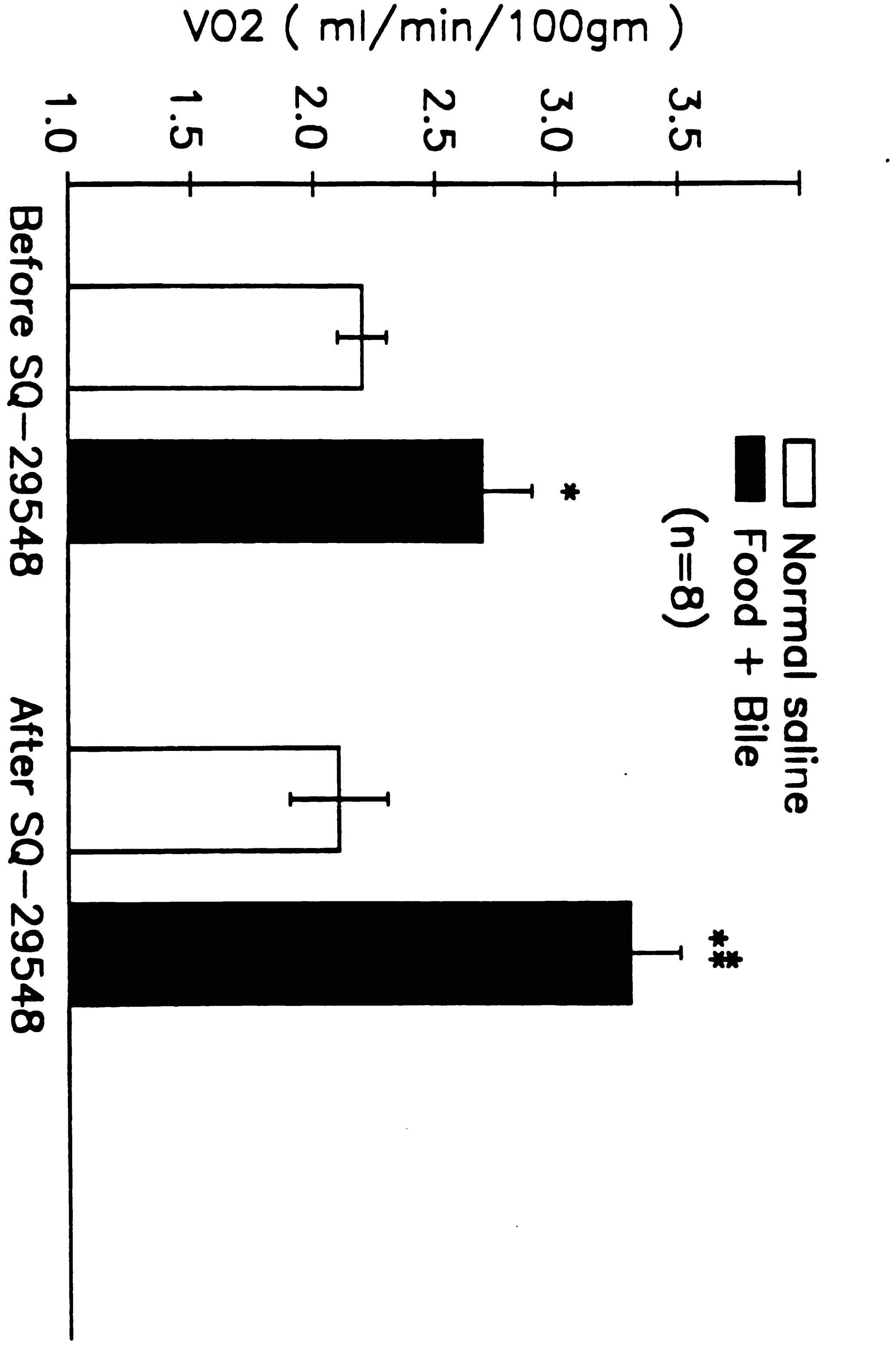

VO2 (ml/min/100gm)
1.0
1.5
2.0
2.5
3.0
3.5
Normal saline
Food + Bile
(n=8)
*
**
Before SQ–29548
After SQ–29548

Figure 20 Jejunal capillary filtration coefficient before and after administration of SQ-29548 in the presence of normal saline (unfilled bars) and food plus bile (filled bars). Single and double asterisks indicate significant increase ($p < 0.05$) above normal saline and food plus bile values before adminstration of SQ-29548, respectively.

FIGURE 20

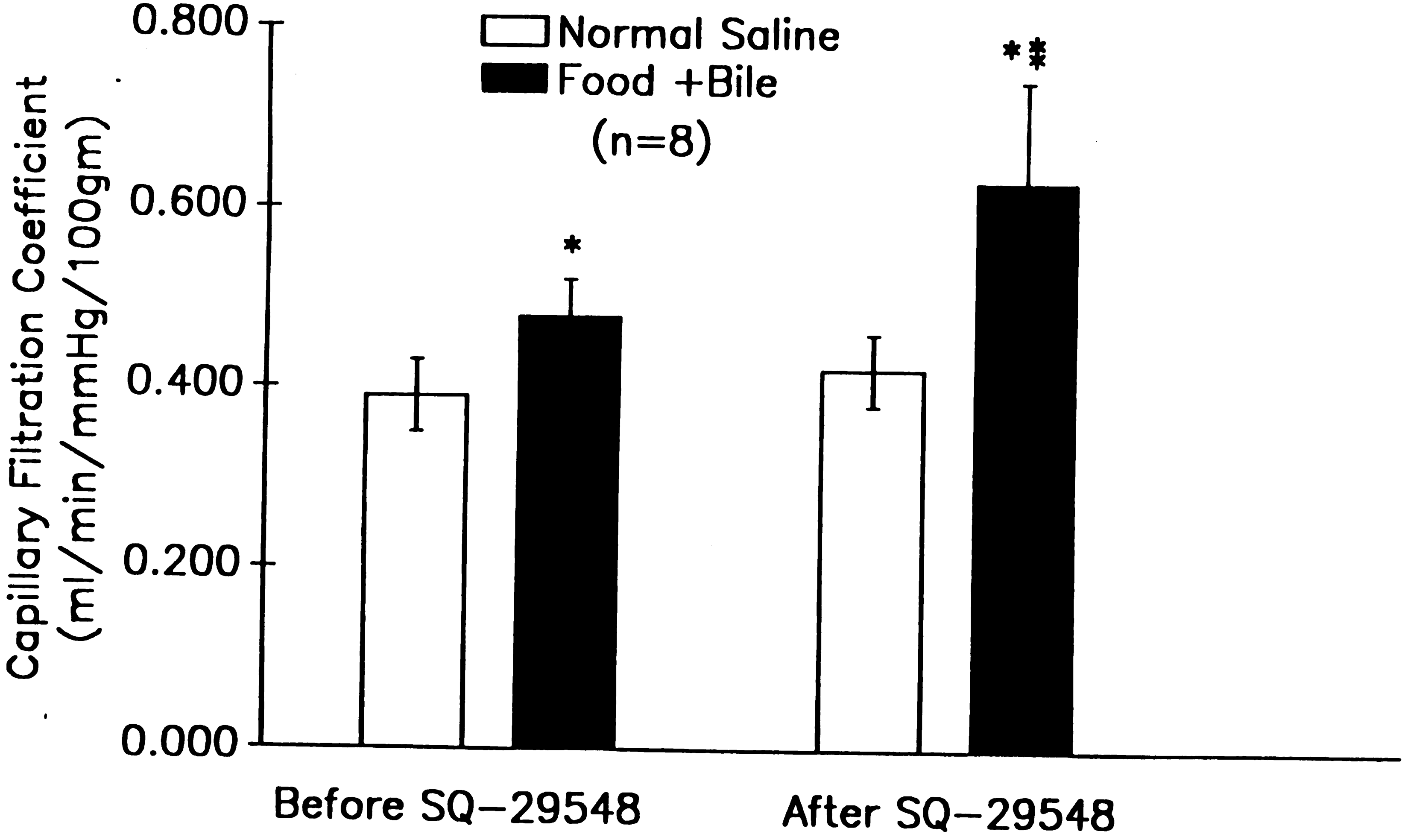
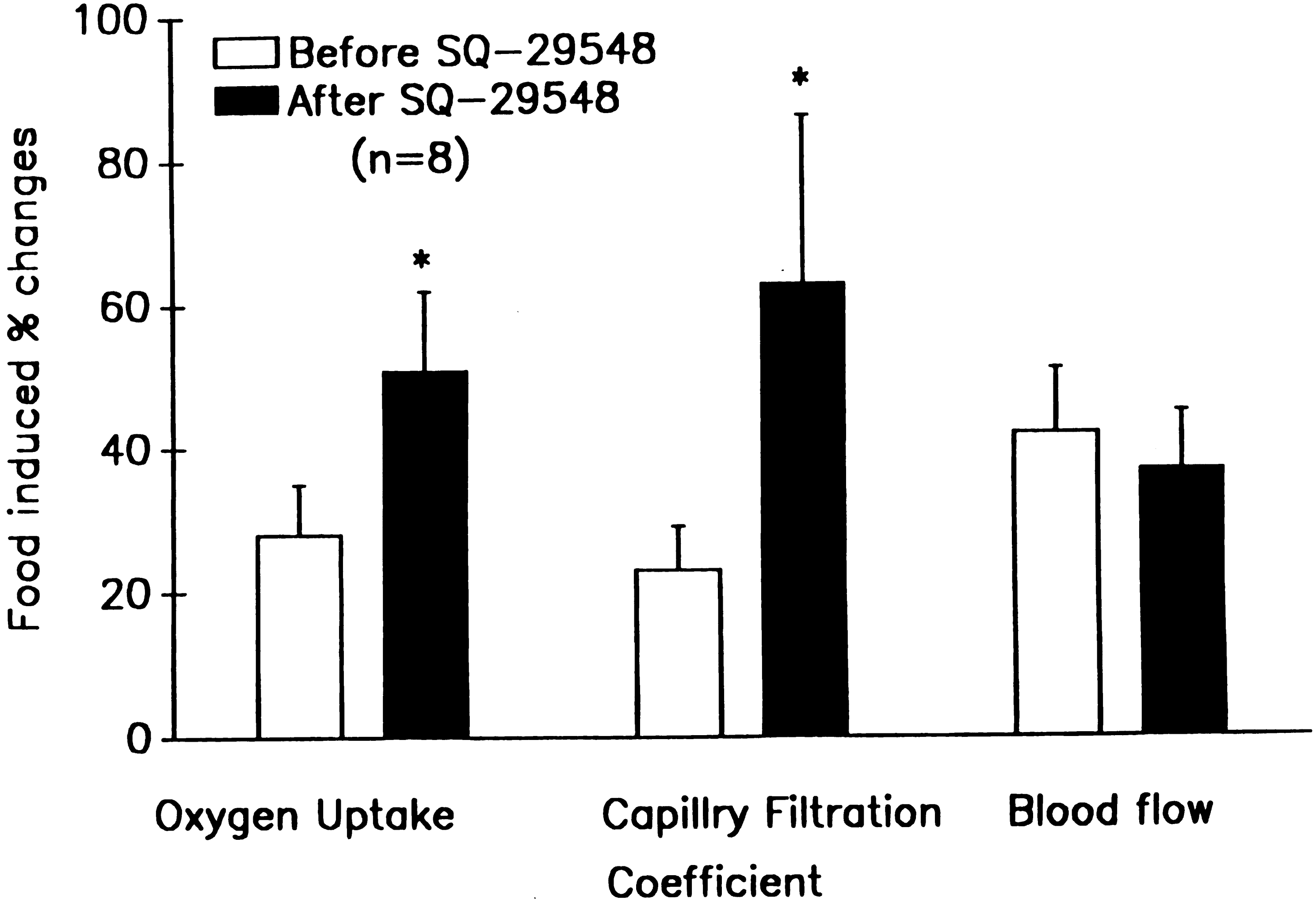

Normal Saline
Food +Bile
(n=8)
Capillary Filtration Coefficient
(ml/min/mmHg/100gm)
0.800
0.600
0.400
0.200
0.000
*
***
Before SQ−29548
After SQ−29548

Figure 21 Food-induced percent changes in jejunal oxygen uptake, capillary filtration coefficient and blood flow before (unfilled bars) and after (filled bars) administration of SQ-29548. Asterisks indicate significant differences ($p < 0.05$) from corresponding values before SQ- 29548.

FIGURE 21


Before SQ−29548
After SQ−29548
(n=8)
Food induced % changes
100
80
60
40
20
0
*
*
Oxygen Uptake
Capillry Filtration Coefficient
Blood flow

($p < 0.05$) than the corresponding values before SQ-29548 (+0.086 ± 0.021 ml/min/mm.Hg/100gm, +22.8 ± 6.4%; $P < 0.05$).

In series XI ($n = 3$) U-44069 (thromboxane A_2 analog), norepinephrine (NE), isoproteranol (I) and adenosine (A) were infused i.a. when luminal food had already raised jejunal K_{fc}. U-44069, NE and A decreased K_{fc} from 0.44-0.49 to 0.25- 0.31 ml/min/mm.Hg/100gm, while I enhanced jejunal K_{fc} from 0.48 to 0.77 ml/min/mm.Hg/100gm. Thus a food induced increase in jejunal K_{fc} could be altered by chemicals.

Figure 21 shows the effects of SQ-29548 on food- induced percent changes in jejunal oxygen uptake, capillary filtration coefficient and blood flow in a summarized form. After treatment with SQ-29548 food-induced increases in jejunal oxygen uptake and capillary filtration coefficient were significantly potentiated ($p < 0.05$); however, there was no change in blood flow.

An attempt was made to elucidate the mechanism by which the TXA_2 receptor blocker potentiated the food-induced increases in jejunal oxygen consumption and capillary exchange capacity without a change in jejunal blood flow. One likely mechanism is a redistribution of blood between mucosal and muscle layers of the jejunal wall by endogenous TXA_2. In order to study this possibility the jejunal wall blood flow, distribution to each layer was measured utilizing a microsphere technique during infusion of U-44069 and SQ- 29548. The studies were conducted under free-flow (series XII) or constant-flow (series XIII) conditions. Systemic arterial blood pressure (123 ± 4 mmHg) was unaffected by local infusions of U-44069, SQ-29548 and microspheres. Figure 22 shows mucosal plus submucosal (mucosa) and muscularis plus serosal (muscle) blood flows at rest (control), and during intra-arterial infusion of U-44069 (0.16 ug/min) with and without prior administration of SQ- 29548 (2.0 ug i.a. bolus) under a free flow condition. At rest, mucosal and submucosal blood flow was 0.72 ± 0.10 ml/min/gm and muscularis plus serosal

Figure 22 Mucosal plus submucosal (mucosa) and muscularis plus serosal (muscle) blood flows during i.a. infusion of U-44069 before and after SQ-29548 administration. Asterisks and crosses indicate significant differences compared to control and U-44069 values respectively ($p < 0.05$). Jejunal segment was perfused at free flow rate.

s serosal
SQ-29548
npared to
erfused at

FIGURE 22

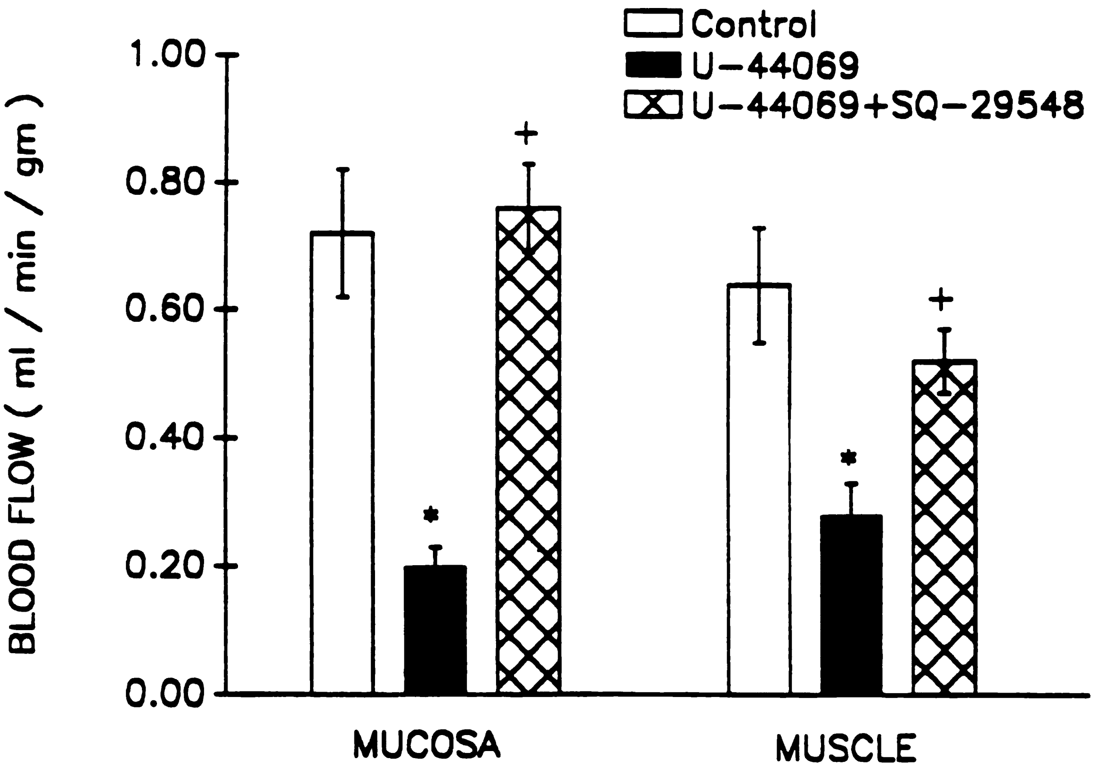
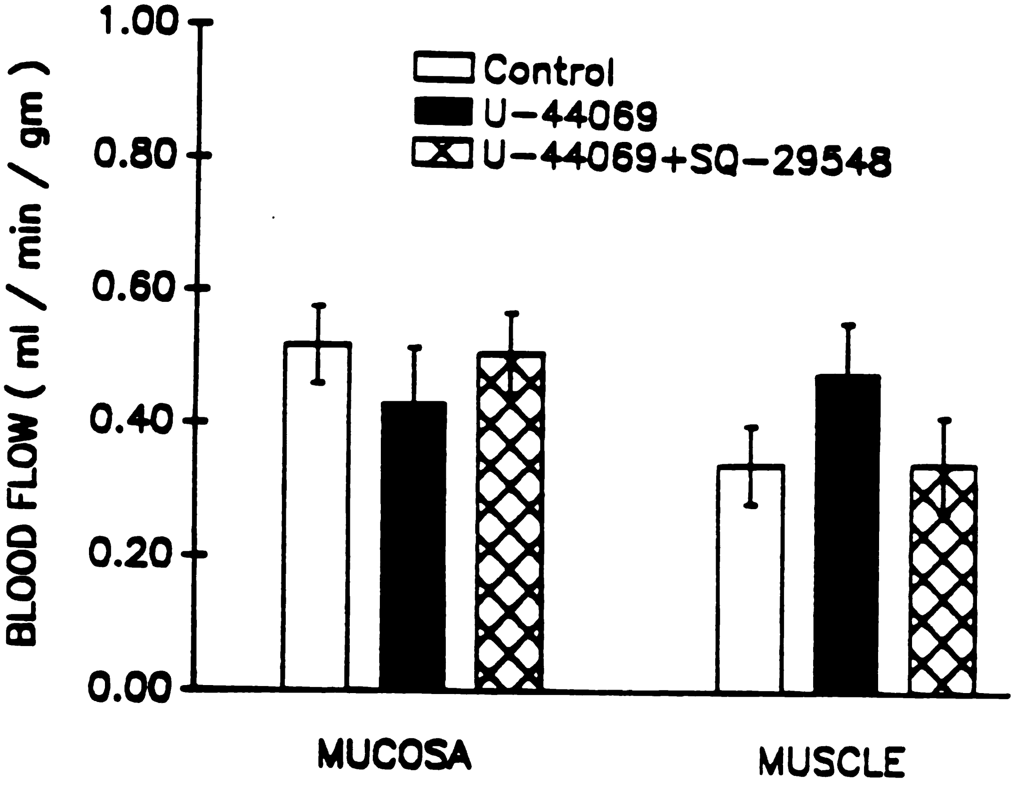


Figure 23 Mucosal plus submucosal (mucosa) and muscularis plus serosal (muscle) blood flows during i.a. infusion of U-44069 before and after SQ-29548 administration. Jejunal segment was perfused at constant flow rate. See text for statistical analysis.

FIGURE 23


1.00
0.80
0.60
0.40
0.20
0.00
BLOOD FLOW (ml / min / gm)
Control
U-44069
U-44069+SQ-29548
MUCOSA
MUSCLE

blood flow was 0.64 ± 0.09 ml/min/gm. Infusion of U-44069 significantly ($p<0.05$) decreased both mucosal and muscularis blood flow to 0.20 ± 0.03 and 0.28 ± 0.05 ml/min/gm respectively. The percent decrease in blood flow to the mucosa (-67 ± 5%) was significantly higher than the muscle (-53 ± 6%) ($p<0.05$). Administration of SQ-29548 (a thromboxane A_2 receptor blocker) blocked the U-44069-induced decreases in blood flow. SQ-29548 significantly increased ($p<0.05$) mucosal blood flow to 0.79 ± 0.07 ml/min/gm and muscle blood flow to 0.52 ± 0.05 ml/min/gm. The percent increase in blood flow to the mucosa (+329 ± 60%) was significantly greater than to the muscle (+165 ± 75%) ($p<0.05$). Even though the mucosal plus submucosal and muscularis plus serosal vascular bed of the jejunal layers are affected by the thromboxane A_2 analog, the response of the mucosal plus submucosal layer is significantly ($P<0.05$) greater than the muscularis plus serosal layer.

Figure 23 shows, under constant flow conditions, mucosal plus submucosal (mucosa) and muscularis plus serosal (muscle) blood flow at rest (control) and during U-44069 infusion before and after administration of SQ-29548. Administration of U-44069 during constant flow conditions decreased mucosal and increased muscularis blood flow. The percent decrease in mucosal blood flow (-19 ± 9%) was significantly ($P<0.05$) different from the percent increase in muscularis blood flow (+52 ± 22%) ($p<0.05$). Administration of SQ-29548, while U-44069 was being infused, increased mucosal and decreased muscularis blood flow. The percent changes in mucosal plus submucosal blood flow (+34 ± 17) was significantly different from the corresponding values of the muscularis plus serosa (-24 ± 14) after SQ-29548 ($p<0.05$). These actions of U-44069 and SQ-29548 under free and constant flow conditions might indicate that endogenous thromboxane A_2 induces a greater vasoconstriction in the mucosal plus submucosal vascular bed than the muscularis plus serosal vascular bed.

The next Series of experiments were designed 1) to determine relative rates of production of TXA_2 and PGI_2 during various stages of severe hemorrhagic shock and after blood transfusion, 2) to determine whether the small intestine is a significant site for increased prostanoid production and 3) to determine whether the possible mechanism of the benefical effects of diet, particularly a Glucose Oleic Acid (GOA) solution, in severe hemorrhagic shock is related to its effect on prostanoid production. Previous studies have shown that placement of GOA into the intestinal lumen prevent intestinal mucosal damage and increase survival of animals in severe hemorrhagic shock (71,72). Intestinal TXA_2 and PGI_2 production during various stages of severe hemorrhagic shock and following blood transfusion were determined to study this.

Three groups of dogs (n = 18), control (sham- operated), GOA treated hemorrhagic shock dogs (GOA + shock), and GOA untreated hemorrhagic shock dogs (shock) were used in Series XIV. The mean arterial blood pressures (MABP) of untreated hemorrhagic shock (n = 6), sham-operated control dogs (n = 5), and GOA-perfused shock dogs (n = 8) are illustrated in Figure 24. The resting blood pressures in all groups were comparable (126-132 mmHg). The MABP in the sham-operated control dogs did not change significantly during the 5 hour experimental period. In both hemorrhagic shock groups, the blood pressure was maintained between 30-40 mmHg for 3 hours by controlled bleeding. In untreated and GOA-treated shock groups , after all the remaining shed blood was reinfused at the end of three hours, the MABP rose and was 87.5 ± 15 and 73 ± 10 at hour (hr) 4 and 74 ± 15 and 65 ± 8 mmHg at hr 5, respectively. These values were significantly lower than the pre-hemorrhagic and the corresponding sham-operated control values ($P < 0.05$). The bleeding volumes in both hemorrhagic shock dogs are shown in Table II. The maximum bleeding volume was 43 ± 4 and 34 ± 6 ml/kg at 1.5 hours in the untreated and treated shock dogs respectively. In order to maintain the same hypotensive state at hr 2 and 3, 3% and 17% of the shed blood was reinfused

Figure 24 Mean arterial blood pressure of severe untreated hemorrhagic shock dogs (triangles) (n=6), of sham- operated control dogs (filled circles) (n=5) and GOA perfused dogs (unfilled circles) (n=8) over the time of experimental procedure. In the hemorrhagic shock groups blood pressure was stablized between 30-40 mmHg for 3 hrs (0-3) by controlled bleeding. At the third hour all the shed blood was transfused. About 30-45 minutes after bleeding, a glucose oleic acid (GOA) solution was perfused into the lumen of the segment at a rate of 1 ml/min in the GOA-treated group. Single and double asterisks denote significant differences relative to prehemorrhagic, and corresponding control values respectively $p < 0.05$. Each point represents mean ± SEM.

FIGURE 24

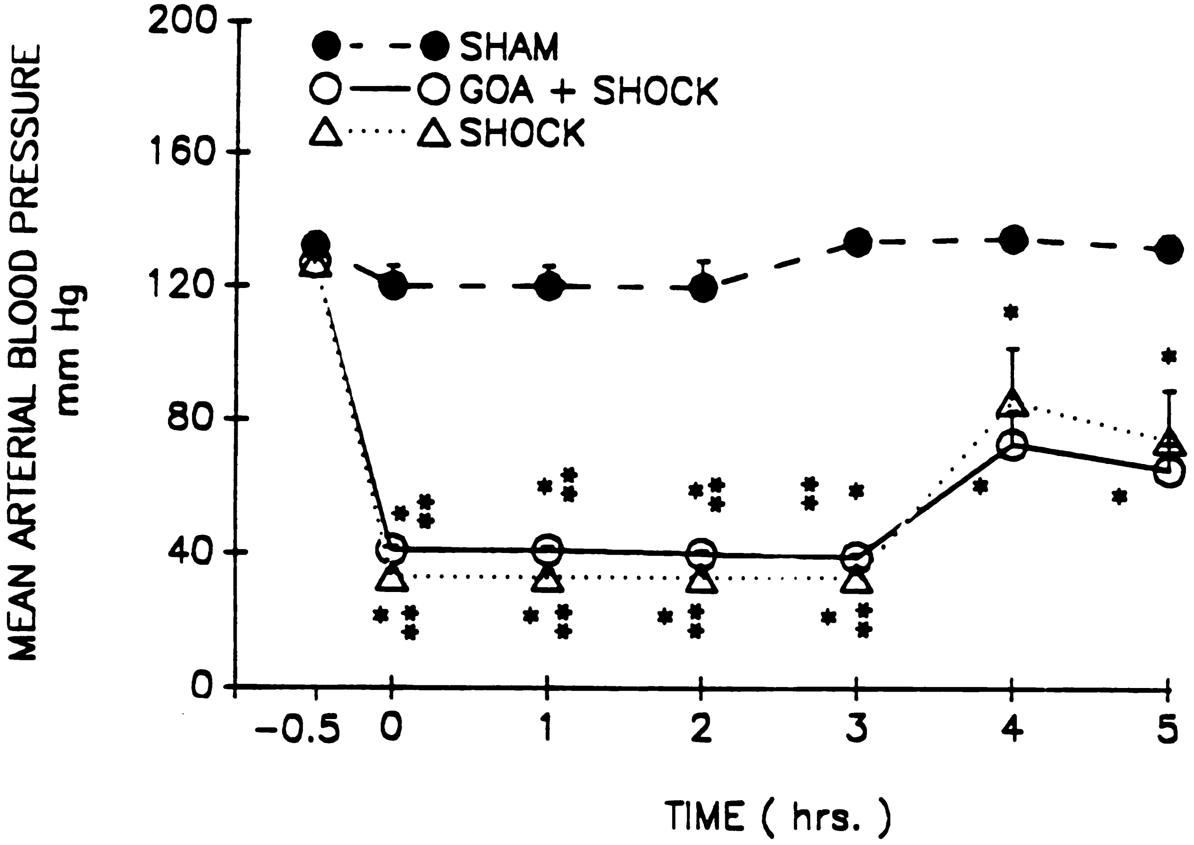

200
160
120
80
40
0
MEAN ARTERIAL BLOOD PRESSURE
mm Hg
● - - ● SHAM
○——○ GOA + SHOCK
△······△ SHOCK
-0.5
0
1
2
3
4
5
TIME (hrs.)

TABLE II

Bleeding Volumes in GOA treated and Untreated Hemorrhagic Shock Dogs

Time (h) (after MABP was maintained between 30 and 40 mm HG)

Volume	0	0.5	1	1.5	2	2.5	3
ml							
GOA	419 ±70	631 ±125	706 ±122	728 ±138	667 ±142	729 ±128	610 ±129
SHOCK	395 ±51	530 ±58	646 ±58	661 ±78	641 ±90	620 ±90	551 ±85
ml/Kg							
GOA	19 ±2	28 ±5	33 ±5	34 ±6	32 ±6	35 ±5	29 ±6
SHOCK	26 ±4	34 ±4	42 ±3	43 ±4	41 ±5	40 ±5	35 ±4

All values are means ± SEM

TABLE III

Heart Rate Values for GOA treated and untreated Hemorrhagic Shock and Sham-Operated Dogs (mean ± SEM)

Time (h)	Heart rate (beats/min) GOA	Shock	Sham
-0.5	165 ± 14	160 ± 6	157 ± 6
1	171 ± 17	160 ± 12	163 ± 9
2	216 ± 15	152 ± 13	152 ± 13
3	195 ± 19	146 ± 14	158 ± 14
4	194 ± 15	139 ± 8	158 ± 10
5	207 ± 10	147 ± 8	164 ± 13

TABLE IV

Hematocrit Values for GOA treated and untreated Hemorrhagic Shock and Sham-Operated Dogs (mean ± SEM)

Time (h)	Hematocrit (vol. %) GOA	Shock	Sham
-0.5	43 ± 1	36 ± 3	35 ± 2
1	41 ± 2	39 ± 3	38 ± 3
2	41 ± 2	37 ± 3	36 ± 2
3	41 ± 2	40 ± 3	37 ± 2
4	44 ± 3	46 ± 3*	37 ± 2
5	45 ± 3	47 ± 3*	37 ± 2

* Values significantly different from time -0.5 value ($P<0.05$)

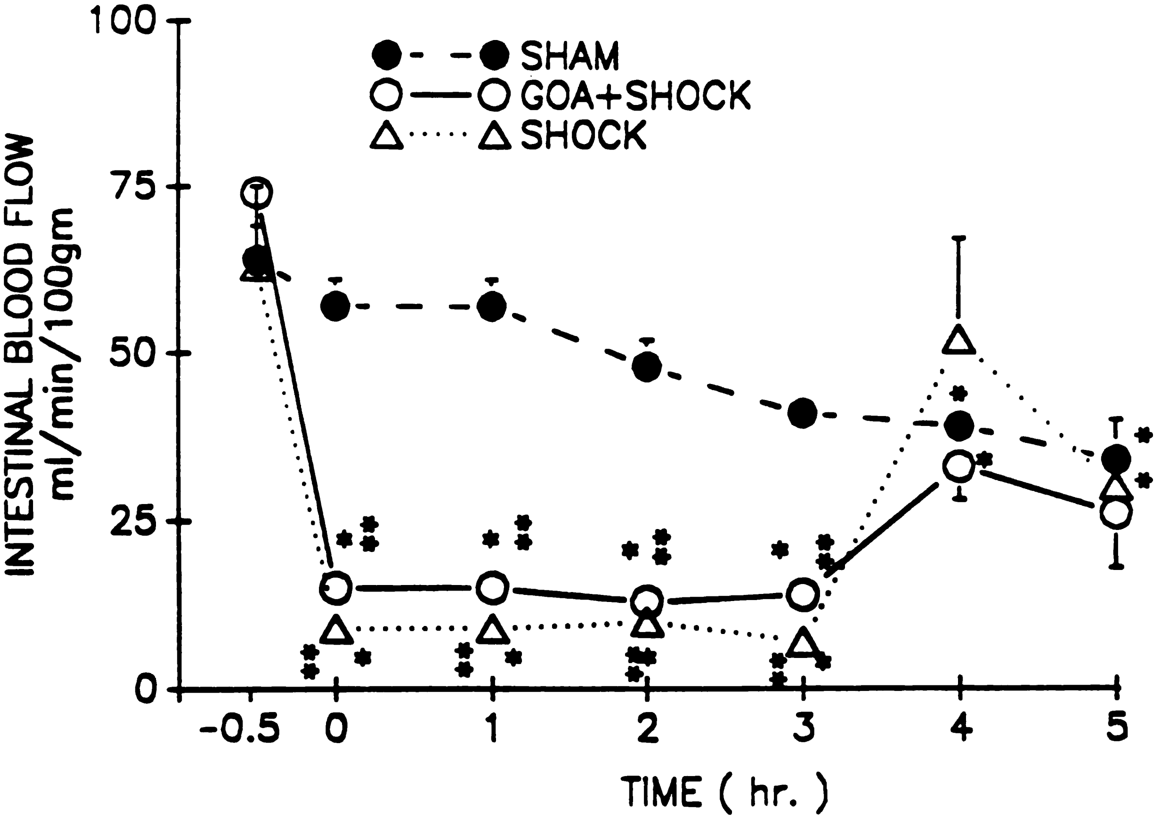
(decompensation stage of shock). The heart rate and hematocrit values for both groups are shown in Table III and IV. The only significant change from control (-0.5 hr) in the three groups was an increase in hematocrit at hr 4 and 5 in untreated hemorrhagic dogs.

Fig. 25 shows intestinal blood flow during the experimental period in control and GOA-treated and untreated hemorrhagic shock dogs. The blood flows in all groups at the initiation of the experiment were comparable (62.5 ± 11.8 vs 63.6 ± 5.5 vs 74 ± 12 ml/min/100 gm tissue). In the untreated hemorrhagic shock group, blood flow fell significantly to 9.1 ± 1.2 ml/min/100 gm tissue during the three-hour hemorrhagic period. When the remaining shed blood was reinfused, blood flow increased significantly one hour after the reinfusion to a level (51.8 ± 14.6) which was not significantly different from the prehemorrhagic value (hr 4, Fig. 25). Flow then decreased significantly to 29.5 ± 5.4 ml/min/100 gm tissue one hour later. In the GOA-treated shock group, blood flow fell significantly to 14.6 ± 2.2 ml/min/100gm during the hemorrhagic period. One hour after reinfusion of the remaining shed blood , flow increased to 33 ± 5 ml/min/100gm, which was significantly lower than the value at -0.5 hr. Flow then decreased to 26 ml/min/100gm one hour later. Intestinal blood flow of the control group did not change significantly until hr 4 and 5. These two values were significantly lower than the -0.5 hr value, but were not significantly different from the corresponding hr 4 and 5 values of the hemorrhagic dogs.

Fig. 26 shows the intestinal vascular resistance (IVR) in the GOA treated and untreated hemorrhagic shock dogs and sham-operated control dogs during the experimental periods. The inital IVR values were comparable in all groups. In the GOA-treated and sham-operated dogs the IVR did not significantly change until hr. 5, at which time the IVR significantly increased in the sham-operated control dogs compared to pre-hemorrhagic values. In the untreated-shock dogs, the IVR

Figure 25 Intestinal blood flow of untreated hemorrhagic shock dogs (triangles), sham-operated control dogs (filled circles) and GOA-treated shock dogs (unfilled circles) during the 5 hrs experimental period. single and double asterisks denote significant differences relative to prehemorrhagic, and corresponding control values, respectively $p < 0.05$. Each point represents mean ± SEM.

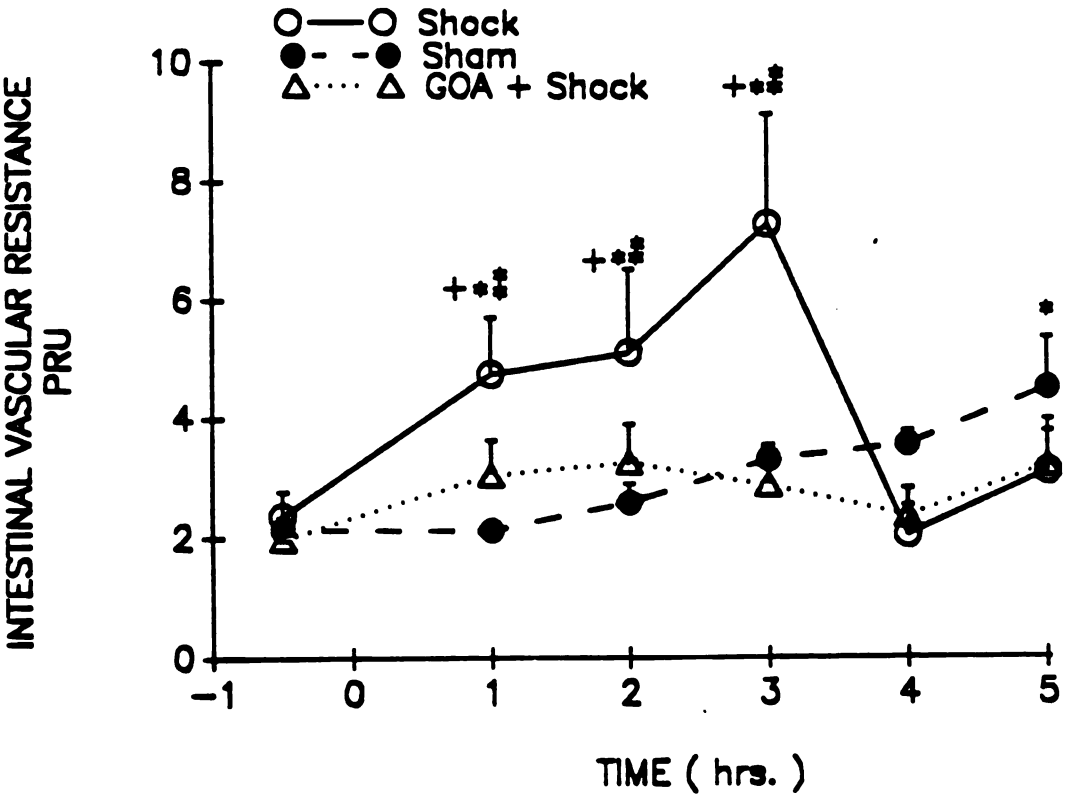
FIGURE 25



100
75
50
25
0
INTESTINAL BLOOD FLOW
ml/min/100gm
SHAM
GOA+SHOCK
SHOCK
-0.5
0
1
2
3
4
5
TIME (hr.)

Figure 26 Intestinal vascular resistance of untreated hemorrhagic shock dogs (triangles), sham-operated control dogs (filled circles) and GOA-treated shock dogs (unfilled circles) during the 5 hrs experimental period. single and double asterisks and crosses denote significant differences relative to prehemorrhagic, corresponding control and GOA-treated shock values respectively $p < 0.05$.

FIGURE 26



O—O Shock
●- -● Sham
Δ···· Δ GOA + Shock
INTESTINAL VASCULAR RESISTANCE
PRU
10
8
6
4
2
0
-1
0
1
2
3
4
5
TIME (hrs.)
+*‡
+*‡
+*‡
*

FIGURE 27

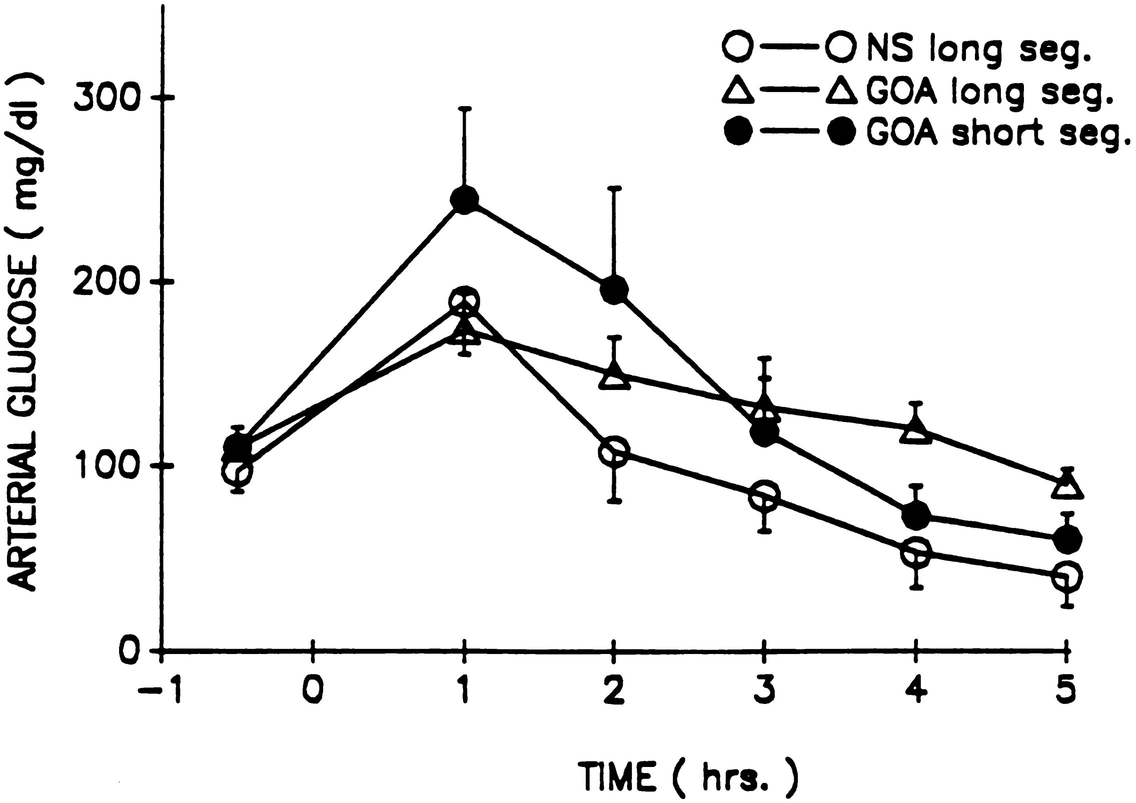


Figure 27 Arterial blood glucose concentration in hemorrhagic shock dogs treated with normal saline (unfilled circles) or GOA (triangles) perfused through the entire small intestinal lumen (from previous study (71)) or GOA perfused through a short segment (filled circles) (present study).

progressively increased during the hypotensive period. The values obtained at hrs 1, 2 and 3 were significantly higher than the pre-hemorrhagic values and the corresponding sham-operated and GOA-treated values. Upon transfusion of the remaining shed blood the IVR returned back to pre-hemorrhagic values (hrs. 4 and 5).

The time course of changes in arterial blood glucose concentration of the GOA-treated shock dogs perfused through an isolated intestinal segment (GOA short seg.) is shown in Fig. 27. Plotted on the same figure is the data obtained from a previous hemorrhagic shock study (71,72) in which normal saline (NS long seg.), or GOA (GOA long seg.) was perfused through the entire small intestinal lumen. In all groups, the prehemmorhagic blood glucose levels were comparable. During the hypotensive period a significant increase in blood glucose levels was observed in all groups (hr.1). After the inital hyperglycemia peak, the blood glucose levels progressively decreased in all groups. The normal saline-treated groups developed severe hypoglycemia at hrs. 4 and 5. GOA perfusion through an entire or short small intestinal segment prevented the severe hypoglycemia.

The concentrations of the stable metabolite of prostacyclin, 6-keto-PGF_1 , in the arterial and intestinal venous plasma are illustrated in Fig. 28 and Fig. 29. In the sham-operated control, the concentration did not change significantly throughout the experimental period, while in the untreated hemorrhagic shock group, the concentrations tended to increase at hr 3 and 4 in the arterial plasma (Fig 28) and at hr 2 and 3 in the venous plasma (Fig 29) compared to the pre-hemorrhagic values (-0.5 hour). However, the transient increase in the venous concentration was followed by a return to prehemorrhagic values during the post transfusion period (hr 4 and 5). In the GOA-treated shock group, the arterial concentration increased significantly at hrs 3, 4, and 5 compared to the prehemorrhagic concentration. The values at hrs 4 and 5 were significantly higher compared to untreated shock and sham-operated control dogs. Intestinal venous 6-keto PGF1 concentration significantly

Figure 28 The arterial 6-keto PGF_1 (stable metabolite of PGI_2) concentration (ng/ml) in the untreated hemorrhagic shock dogs (triangles), sham-operated control dogs (filled circles) and GOA-treated shock dogs (unfilled circles) during the 5 hrs experimental period. single and double asterisks and crosses denote significant differences relative to prehemorrhagic, corresponding control and untreated shock values respectively $p < 0.05$. Each point represents mean ± SEM.

Figure 29 Intestinal venous 6-keto PGF_1 concentration (ng/ml) in the untreated hemorrhagic shock dogs, sham-operated control dogs and GOA-treated shock dogs during the 5 hrs experimental period. Single and double asterisks and crosses denote significant differences relative to prehemorrhagic, corresponding control and untreated shock values respectively $p < 0.05$. Each point represents mean ± SEM.

FIGURE 28

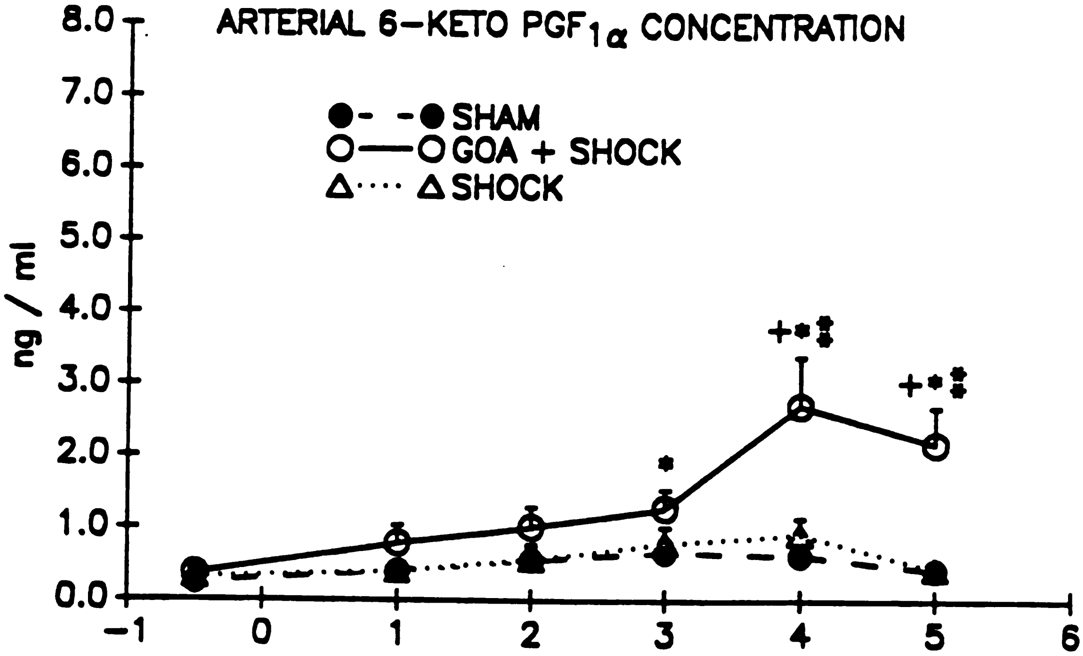
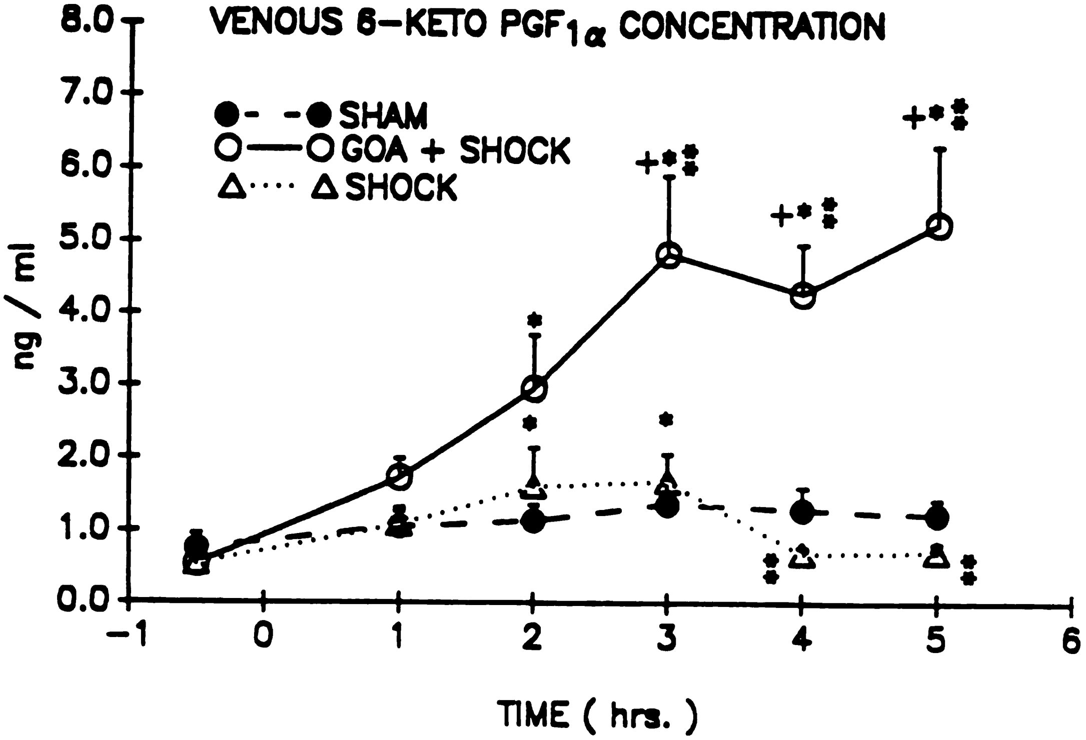


FIGURE 29



increased at hrs 2, 3, 4, and 5, compared to prehemorrhagic values. The concentrations at hrs 3, 4, and 5 were also significantly higher than sham-operated control and untreated shock values. In all groups the 6-keto-PGF$_1$ venous concentrations were higher than the corresponding arterial concentrations.

Fig. 30 and Fig. 31, respectively, shows arterial and intestinal venous plasma concentrations of thromboxane B$_2$, a stable metabolite of thromboxane A$_2$, in the treated shock, untreated shock, and sham-operated control groups. Arterial and venous TXB$_2$ concentration in the sham-operated control dogs did not show a significant change during the entire experimental period. In the untreated hemorrhagic shock dogs, however, both arterial and venous plasma TXB$_2$ concentrations significantly increased at 1, 2, 3, 4, and 5 hours ($P < 0.05$). The peak values measured were 5.15 and 3.26 ng/ml in the intestinal venous and arterial plasma, respectively, at hr 5, (i.e., 2 hours after blood transfusion). The TXB$_2$ concentrations in venous samples obtained between hr 2 and 5 were significantly higher than those of the corresponding arterial samples obtained at the same time. This indicates that TXA$_2$ was being produced and released from the intestine during that period. In the GOA-treated animals the arterial TXB2 concentrations increased at 1,2,3,4,and 5hrs compared to the prehemorrhagic and sham- operated dogs. The magnitude of increases in the arterial TXB2 concentrations were similar to the corresponding untreated shock dogs. Intestinal venous TXB2 concentrations in the GOA-treated groups were significantly increased at hrs. 2,3,4 and 5 compared to prehemorrhagic value. The values at hrs. 4 and 5 were significantly greater than the corresponding sham-operated values. However, the magnitude of increases at 2,3 and 5 hrs were significantly lower than the untreated shock dogs.

In two untreated hemorrhagic shock dogs, the experiment extended for another 3 hours. Arterial TXB$_2$ concentration increased from 2.6 and 4.6 at hr 5 to 5.1 and 9.1 ng/ml at hr 8, respectively, while the intestinal venous concentration

Figure 30 The arterial TXB_2 (stable metabolite of TXA_2) concentration (ng/ml) in the untreated hemorrhagic shock dogs (triangles), sham-operated control dogs (filled circles) and GOA-treated shock dogs (unfilled circles) during the 5 hrs experimental period. single and double asterisks denote significant differences relative to prehemorrhagic and corresponding control values respectively $p < 0.05$. Each point represents mean ± SEM.

Figure 31 Intestinal venous TXB_2 concentration (ng/ml) in the untreated hemorrhagic shock dogs , sham- operated control dogs and GOA-treated shock dogs during the 5 hrs experimental period. Single and double asterisks and crosses denote significant differences relative to prehemorrhagic, corresponding control and GOA-treated shock values respectively $p < 0.05$. Each point represents mean ± SEM.

FIGURE 30

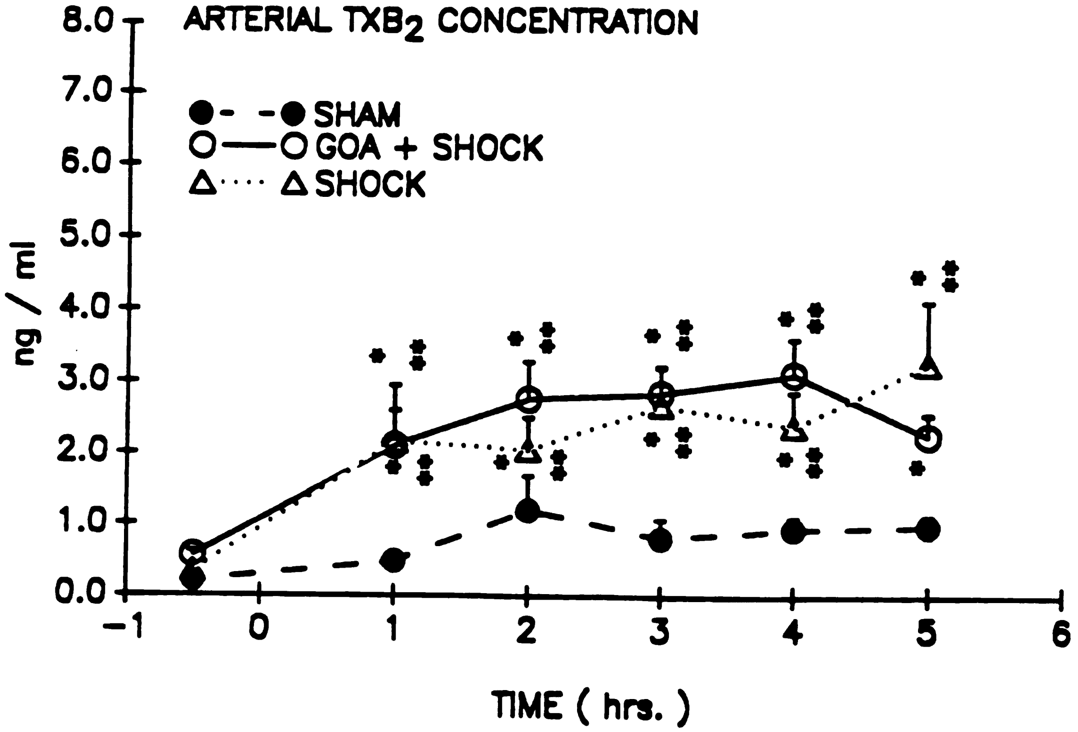
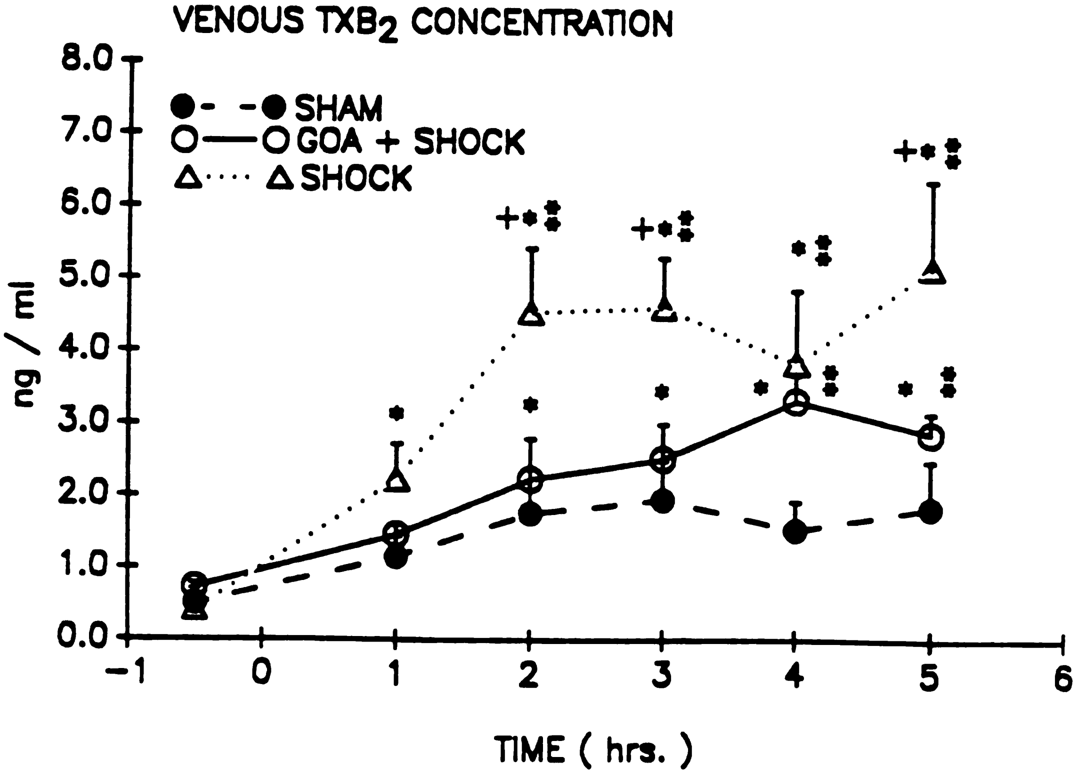


FIGURE 31



increased from 6.4 and 7.5 at hr 5 to 9.5 and 13.2 at hr 8, respectively. Arterial 6-keto-PGF_1 changed from 0.14 and 0.22 at hr 5 to 0.30 and 0.27 at hr 8, while venous concentration changed from 0.84 and 0.30 at hr 5 to 1.20 and 0.84 ng/ml at hr 8. This indicates that the TXB_2 concentration continued to increase while the 6-keto-PGF_1 concentration remained relatively steady for another 3 hours.

In three experiments, blood samples were obtained from the arterial reservoir at hour 3 before reinfusion started. The TXB_2 concentration in the reservoir was 0.99 ± 0.2 ng/ml, whereas the corresponding arterial plasma TXB_2 concentration was 3.25 ± 0.87 ng/ml. Concentrations of 6- keto-PGF_1 in the arterial reservoir and arterial plasma were 0.22 ± 0.06 and 0.67 ± 0.3 ng/ml, respectively. This indicates that the increased arterial TXB_2 and 6-keto-PGF_1 concentration after blood reinfusion was not due to transfusion of the reservoir blood.

Thromboxane A_2 and prostacyclin have antagonistic effects, and their resultant effects depend on the balance of the changes in their concentrations. The ratio of TXB_2 to 6- keto-PGF_1 in arterial and intestinal venous plasmas are illustrated in Fig. 32 and Fig. 33, respectively. In the sham-operated controls, there was no significant change in the ratio throughout the experimental period in either blood samples. In the untreated hemorrhagic shock group, the arterial blood ratio increased progressively during the hypotensive period, and the values at hr 1, 2 and 3 were significantly increased in the arterial blood compared to prehemorrhagic value. The increases at hrs. 2 and 3 were significantly greater than the corresponding sham-operated values. The value at hr. 3 was also significantly greater than the corresponding GOA value (Fig. 32). After blood transfusion the ratio in arterial blood showed a biphasic change: a decrease one hour after transfusion (hr 4) and then a marked increase one hour later, (i.e., at the terminal stage). In the venous blood (Fig. 33), the ratio progressively increased during the hypotensive period and following the transfusion in the untreated shock dogs. The values at hrs 1, 2, 3, 4,

Figure 32 Arterial TXB_2 to 6-keto-PGF_1 ratios in GOA-treated and untreated hemorrhagic shock dogs and sham- operated control dogs during the 5 hrs experimental period. Single and double asterisks and crosses denote significant differences relative to prehemorrhagic, corresponding control and GOA-treated shock values respectively $p < 0.05$. Each point represents mean ± SEM.

Figure 33 Intestinal venous TXB_2 to 6-keto-PGF_1 ratios in GOA-treated and untreated hemorrhagic shock dogs and sham-operated control dogs during the 5 hrs experimental period. Single and double asterisks and crosses denote significant differences relative to prehemorrhagic, corresponding control and GOA-treated shock values respectively $p < 0.05$. Each point represents mean ± SEM.

FIGURE 32

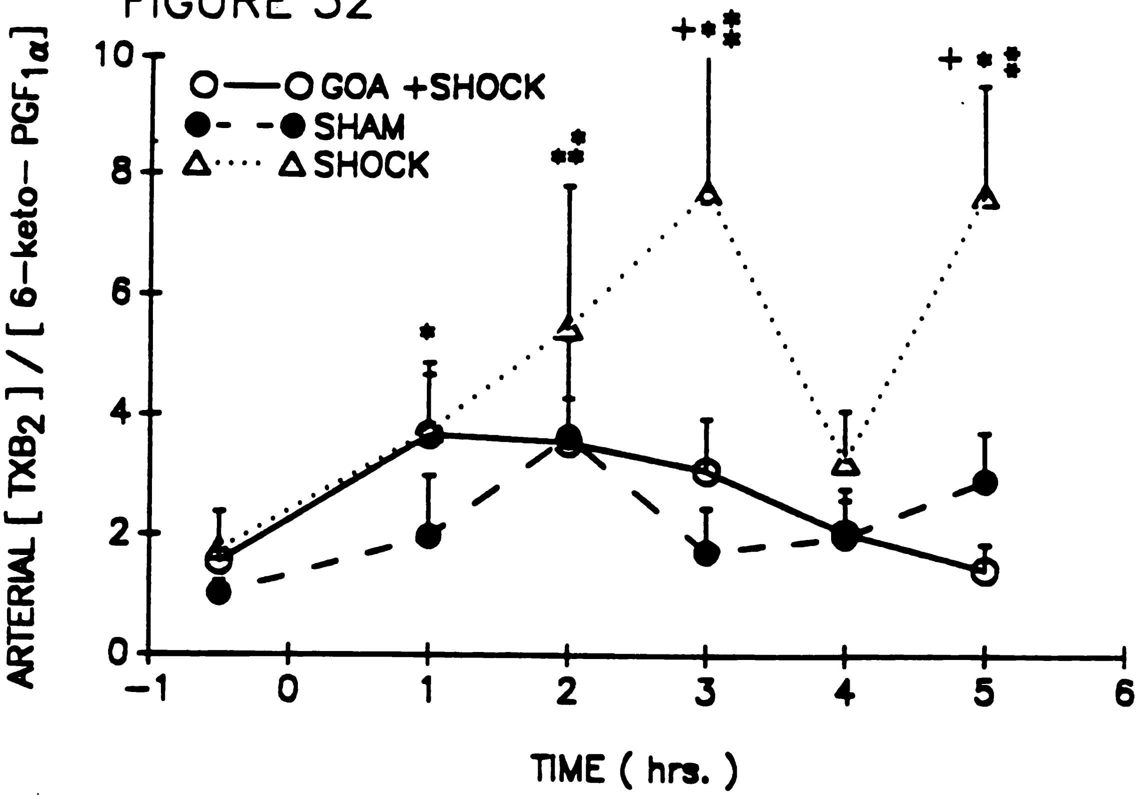


FIGURE 33

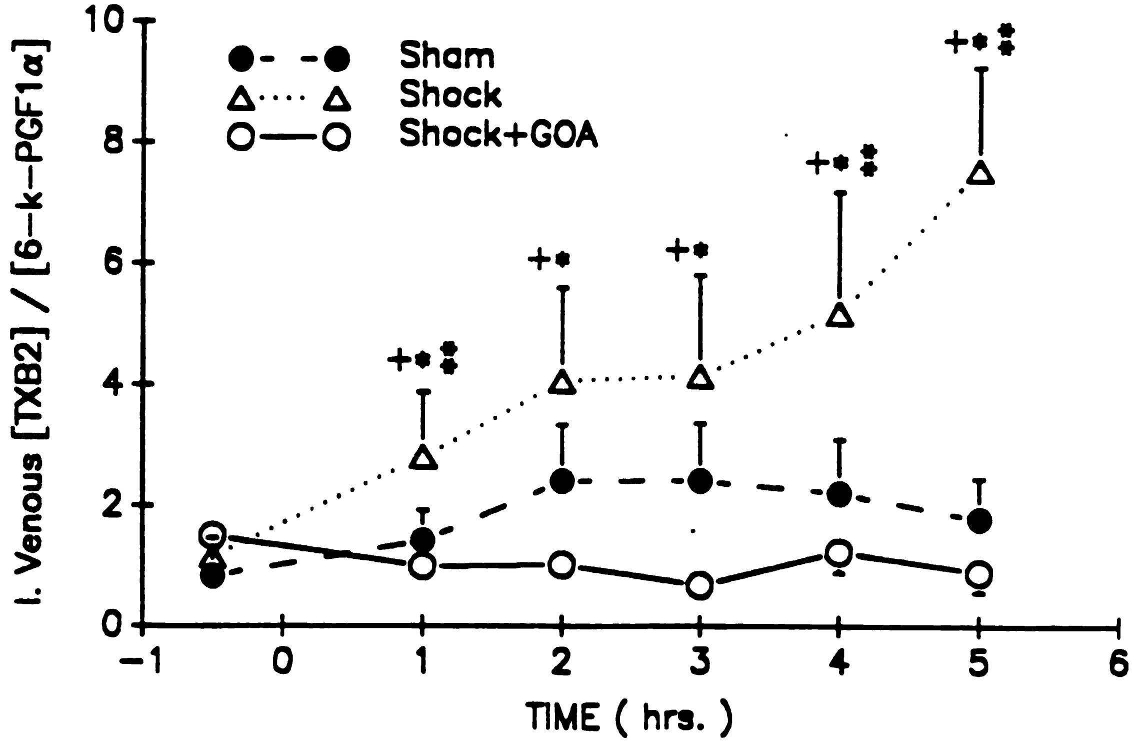


TABLE V: Intestinal TXB_2 release for GOA treated and untreated Hemorrhagic Shock and Sham-Operated Dogs (mean ± SEM)

TABLE VI: Intestinal 6-keto-PGF_1 release for GOA treated and untreated Hemorrhagic Shock and Sham-Operated Dogs (mean ± SEM)

TABLE V

Intestinal TXB_2 Release (ng/min/100gm)

Time (h)	GOA ± Shock	Shock	Sham
-0.5	11 ± 3	14 ± 11	21 ± 19
1	-7 ± 8	11 ± 7	38 ± 18
2	-5 ± $4^{\#+}$	24 ± 8	22 ± 13
3	-10 ± $7^{\#+}$	17 ± 5	47 ± 19
4	13 ± $14^{\#+}$	69 ± 36^{*+}	24 ± 13
5	10 ± $7^{\#+}$	86 ± 44^{*+}	15 ± 19

* $p<0.05$ relative to -0.5 value
\# relative to untreated shock
\+ relative to sham operated control

TABLE VI

Intestinal 6-keto-PGF_1 Release (ng/min/100gm)

Time (h)	GOA ± Shock	Shock	Sham
-0.5	13 ± 3	34 ± 7	34 ± 11
1	11 ± 7	6 ± 2 *+	36 ± 11
2	40 ± 12 *#	9 ± 3 *+	27 ± 7
3	16 ± 9	5 ± 1 *+	27 ± 8
4	47 ± 18 *#	2 ± 6 *+	27 ± 10
5	37 ± 13 *#	8 ± 4 *+	28 ± 8

* $p<0.05$ relative to -0.5 value
\# relative to untreated shock
\+ relative to sham operated control

and 5 were significantly greater than the pre-hemorrhagic, corresponding sham operated, and GOA-treated shock values ($P < 0.05$).

After a transient increase (1 hr) in the arterial blood ratio, the values in GOA-treated hemorrhagic shock group returned back to the pre-hemorrhagic value. However, the ratio in venous blood did not increase during the whole experimental period and the values at 1, 2, 3, 4, and 5 hrs were significantly lower than the corresponding untreated shock values.

Table V and Table VI, respectively, show the rate of TXB_2 and 6-keto-PGF_1 release from the intestine, as calculated from the product of blood flow and arteriovenous concentration difference. The intestinal release of TXB_2 and 6-keto-PGF_1 did not significantly change throughout the experimental period in control sham-operated dogs. In untreated hemorrhagic shock dogs, TXB_2 release did not change significantly until after blood transfusion when a marked and significant increase in release occurred. The release of 6- keto-PGF_1 , however, significantly decreased throughout the hemorrhagic hypotensive period and after blood transfusion. In GOA-treated hemorrhagic shock dogs, a significant decrease in TXB_2 release at 2, 3, 4, and 5 hrs was noticed compared to the untreated group. The values at 2 and 3 hrs were significantly lower than the corresponding sham-operated values. However, GOA treatment has significantly increased 6-keto-PGF_1 release at 2, 4, and 5 hrs as compared to prehemorrhagic values and corresponding untreated shock values. If all TXA_2 and prostacyclin produced in the intestinal tissue is released into the venous effluent, the rate of release can be considered as the rate of intestinal production.

At the end of the experiment, intestinal tissue samples were collected to determine if any morphological changes had occured during the experimental procedure from GOA perfused ileal segment and non-perfused adjacent gut (n=8). According to the classification of the degree of intestinal lesions used by Chiu et al.

(page 33), the non- perfused segment showed mucosal lesions ranging from Grade 3 to Grade 5 in all eight dogs. The major abnormalities detected were epithelial cell ulceration and necrosis, mixed inflamatory infiltrates with severe congestion, and hemorrhage extending into the submucosa. The GOA-treated segment showed no apparent mucosal loss (Grade 0 to Grade 2). The morphological findings were some mild vascular congestion with focal minor surface blebbing and small petechial hemorrhages. The findings in the untreated segment are consistent with necrotizing and hemorrhagic enteropathy of small intestine . In comparison to the untreated group , the group with GOA-treated segment had significantly fewer severe mucosal abnormalities.

DISCUSSION

Recent studies have shown that metabolites of arachidonic acid may play a role in regulation of intestinal blood flow, capillary exchange capacity, and oxygen uptake under resting and postprandial conditions (52,102,103,104, 117) as well as in shock-induced intestinal ischemia (12,111). However, there are still many unanswered questions. The present study addressed some of these questions.

In the first series of experiments, jejunal production of PGE_2, PGI_2, PGF_2, and TXA_2 was determined under four experimental conditions. These four prostanoids are most commonly found in the gastrointestinal tract (2,6,91,124,150,152) and have well-defined vasoactivity (1,22,38,49,56).

As shown in Figs. 5 and 6, the jejunum produces and releases PGI_2 (measured as its metabolite 6-keto-PGF_1), PGE_2, and TXA_2 (measured as its metabolite TXB_2), and an insignificant amount of PGF_2 under resting conditions (i.e., normal saline in the lumen). This finding is in agreement with other studies (91,152). The relative magnitude of the production (release) in the present study is PGI_2 (44.4%) > PGE_2 (31.9%) > TXA_2 (21.2%) > PGF_2 (2.5%). Bennett et al. (6) found in the human small intestinal mucosa or muscle that these four prostanoids are formed in amounts greater than 80 $ng.g^{-1}$, tissue wt, while only trace amounts of the lipooxygenase product 12-HETE, eicosatrienoic acid metabolites, and eicosapentaenoic acid metabolites are formed. Le Duc et al. (91) found that PGI_2 is the major product (81%) of the muscularis tissue. In mucosal tissue, they found TXB_2 (15%), PGI_2 (14%), PGE_2 (10%), PGF_2 (5%) and PGD_2 (4%) are the major prostanoids (with 51% of unspecific hydroxy-fatty acids). In canine jejunal muscle the relative magnitude of prostanoid synthesis is: PGI_2 (43%) > PGF_2 (20%) = PGE_2 (17%) > PGA_2 (10%) = PGD_2 (7%) > TXB_2 (trace) (124). The production rate measured in the present study is from the whole gut wall and is comparable with the above studies. Series I experiments shows that under resting conditions, the vasodilator prostanoids, PGI_2 and PGE_2, comprise 76% of the four common vasoactive prostanoids produced in the jejunum. Thus, in the resting gut, prostanoid synthesis favors vasodilators, and the mechanism by which cyclooxygenase inhibitors decrease blood flow in resting gut (22,38,52,56,98) may be due to inhibition of the synthesis of these vasodilators.

Introduction of food containing 10% gallbladder bile increased the venous concentrations and releases of all four prostanoids without significantly altering their arterial concentrations (Fig. 5 and 6). If all the prostanoids produced in the gut were released into the venous outflow, one can assume that release rate is the same as production rate. Thus, the presence of digested food in the jejunal lumen indeed stimulates synthesis of all four prostanoids, particularly PGE_2 and PGF_2, which increase 4- fold and 8-fold, respectively. Could the food-induced increases in prostanoid concenterations be responsible for the changes in blood flow by their direct vascular actions ? In order to assess this possibility, the effects of local i.a. infusions of these prostanoids, individually and in combination, were studied in the next series of experiments.

As shown in Fig. 8A, infusions of the four prostanoids, to simulate the increase in blood concentrations over a range 0.5 to 20 times that occurring when luminal content was changed from saline to food, did not significantly alter jejunal vascular resistance. However, as other investigators have reported (52,38,43,49,56), when these prostanoids were infused individually, they produced either vasoconstriction or vasodilation (Fig. 7). At concentrations above 1000 pg/ml, both PGI_2 and U-44069 produced significant vasodilation and vasoconstriction, respectively, whereas PGE_2 and PGF_2 required concentrations greater than 10^4 pg/ml to produce significant vasoactivity (Fig. 7). The local blood PGI_2, U-44069, PGE_2, and PGF_2 concentrations achieved during infusion of the mixture at 10 to 20 times that of

[PGs]F-NS were 823 to 1646, 717 to 1434, 2593 to 5186, and 470 to 941 pg/ml, respectively. The failure of the mixture to produce significant vasoactivity is most likely due to the antagonistic vasodilator action of PGI_2 and vasoconstrictor action of U-44069. The close agreement between the predicted and observed data shown in Fig. 8A supports the above possibility.

However, a similar antagonism between PGI_2 and TXA_2 might not occur during food placement for the following reasons. The jejunum is composed of three tissue layers and the major prostanoids produced in each layer are different. The two potent vasoactive prostanoids, TXA_2 and PGI_2, are produced primarily in the mucosa and muscularis, respectively (91,124), and that villus epithelial cells produce significant amounts of TXA_2 and PGF_2 (3). These prostanoids, which are released during food placement, act only on the vasculature in the vicinity of the site of their releases. As a result, vasoconstriction could occur in the mucosa, while vasodilation could occur in the muscularis. In contrast, i.a. infusion delivers these prostanoids to both the mucosa and muscularis evenly, resulting in no significant change in total vascular resistance, as shown in Fig. 8A. In the interpretation of Fig. 8A, one must, therefore, consider the difference in the events occuring in the mucosa during food placement and during i.a. infusion of the prostanoid mixture. This is important because postprandial intestinal hyperemia occurs mainly in the mucosa.

It must be concluded from the data of Fig. 8A that the increases in prostanoid release and concentration during food placement do not act directly on the vasculature to alter blood flow. The inhibitory effect of endogenous prostanoids as indicated by the studies utilizing cyclooxygenase inhibitors (52,117), therefore, must be mediated by other mechanisms. The most likely mechanism is the action of prostanoids on intestinal functions and oxidative metabolism. Several pieces of evidence support this hypothesis. Cyclooxygenase inhibitors affect food-induced changes in both blood flow and oxygen uptake in parallel fashion. Some prostanoids have been shown to alter intestinal absorption, secretion, and motility (34,44,152). In our experimental setting, mefenamic acid increases carbohydrate absorption and metabolism (54). Alteration in these intestinal functions by endogenous prostanoids could indirectly alter blood flow via changes in oxidative metabolism and motility (25,53) In the present study, an attempt was made to measure oxygen uptake during i.a. infusions of prostanoids. Unfortunately, the infusions alter the reading of the A-V oxygen content difference analyzer, making it impossible to analyze accurately the oxygen uptake data.

Addition of arachidonate to normal saline did not significantly alter jejunal blood flow nor oxygen uptake, and increased only the venous PGF_2 concentrations as compared to normal saline in the lumen (Figs. 4-5). In contrast, addition of arachidonate to food attenuated the food-induced increases in blood flow and oxygen consumption, and produced higher venous TXB_2 and PGF_2 than did food alone (Figs. 4-5). Thus, food in the presence of arachidonate appears to shift arachidonate metabolism in favor of TXA_2 synthesis. The reasons for the effects of arachidonate on jejunal blood flow, oxygen uptake, and the relative synthesis of vasodilator and vasoconstrictor prostanoids during nutrient absorption, but not during luminal placement of normal saline, are not known. The metabolic activities accompanying nutrient absorption seem to play a significant role in the observed arachidonate actions. Could the alterations in TXA_2 and PGF_2 act directly on vasculature to inhibit food-induced hyperemia? In order to assess this possibilty NS or food was placed in the lumen; then prostanoids were infused at concentrations which mimicked the situation when lumen content was changed from NS or food to food plus AA.

As shown in Fig. 8B and 9, i.a. infusion of the prostanoid mixture at concentrations 0.5 to 20 times those occurring when luminal content is changed from NS or food to food plus AA increased jejunal vascular resisitance in a dose-dependent fashion. At concentrations 0.5 to 2 times those occurring when luminal content was changed from food to food plus AA, abolished the food induced decrease in vascular resistance (Fig. 9). This finding is similar to that shown in Fig. 4, when arachidonate was added to food in the lumen. This study therefore suggests that the inhibitory action of arachidonate on food-induced hyperemia shown in Fig. 4 and observed in a previous study (103) was at least in part due to the direct vasoconstrictor action of endogenous TXA_2 and PGF_2. The parallel change in blood flow and oxygen uptake shown in Fig. 4, however, may suggest involvement of the metabolic mechanism described in the previous paragraph. Regardless of what the actual mechanism is, the effect of luminal arachidonate has its physiological significance. Since arachidonate is a natural food constituent, the amount of arachidonate ingested might influence postprandial intestinal blood flow and oxygen uptake.

TXA_2 is a much more potent vasoconstrictor than PGF_2 (56,150) and quantitatively venous TXA_2 concentration and production during luminal placement of food plus arachidonate were 2- to 3-fold greater than those of PGF_2 (Figs. 5 and 6). In order to determine the contribution of TXA_2 in vascular and metabolic responses, we infused a TXA_2/endoperoxide receptor antagonist, SQ-29548, when the lumen still contained food plus arachidonate. As shown in Fig. 4, this infusion increased blood flow and oxygen uptake to levels similar to those observed with food alone in the lumen (Fig. 4). Thus, the inhibitory action of arachidonate on food-induced change in blood flow and oxygen uptake appears to be, at least in part, due to the action of TXA_2 /endoperoxide which decreased intestinal blood flow as well as capillary filtration coefficient (56,103).

In conclusion, the present study in Series I, II and III has addressed some of the many questions in regard to the involvement of the cyclooxygenase products, prostanoids, in the regulation of blood flow and oxygen uptake of the jejunum, particularly the regulation during nutrient absorption. By utilizing radioimmunoassay the arterial and venous concentrations of four commonly found prostanoids (PGI_2, PGE_2, TXA_2 and PGF_2) were measured and the findings are as follows: Under resting conditions, the jejunum produces and releases the first three prostanoids, and digested products of food in the gut lumen enhance the production of all four. The relative magnitude of releases are PGE_2 (46%) > PGI_2 (32%) > TXA_2 (16%) > PGF_2 (6.4%). Addition of arachidonate into the food inhibits food-induced increases in blood flow and oxygen uptake, decreases the release of two vasodilators PGI_2 and PGE_2, and increases the release of two vasoconstrictors, TXA_2 and PGF_2 . SQ-29548, a TXA_2/endoperoxide receptor antagonist, reverses the inhibitory action of arachidonate on blood flow and oxygen uptake. Intra-arterial infusion of the mixture of the above four prostanoids at blood concentrations similar to the increases observed when lumen content was changed from saline to food did not signficantly alter jejunal vascular resistance (JVR). However, at concentration similar to the increases observed when arachidonate was added to the luminal food, the mixture increased JVR and abolished the food- induced decrease in JVR. The vascular effects of a prostanoid mixture was similar to the algebraic sum of each individual prostanoid effect. These studies indicate that jejunal productions of PGI_2, PGE_2, TXA_2, and PGF_2 increase during nutrient absorption. Addition of arachidonate to food attenuates the former two and enhances the latter two releases, which act to attenuate food-induced jejunal hyperemia and oxygenation.

In Series 1 it has been shown that placement of food into the jejunal lumen enhanced prostanoid release. However, which of the constituents of food, and/or events accompanying food absorption increased prostanoid release is/are unknown. In Series IV, V, VI, and VII jejunal prostanoid production was measured during luminal placement of normal saline, 10% bile and air and during pump-induced mechanical hyperemia. Normal saline and 10% bile were used in preparing the food mixture, air was used to simulate the intestinal wall distension during food placement, and the pump induced hyperemia was used to simulate the food-induced hyperemia. As shown in Figures 10 , 11 and 12, luminal placement of normal saline, air and 10% bile, respectively, did not significantly alter jejunal venous prostanoid concenteration. However, previous study (82) have shown that bile per se in the jejunal lumen, does not alter local blood flow. However, it significantly enhanced the hyperemic and metabolic effect of digested food. The augmenting effect of bile is probably due to its facilitating effect on digestion and absorption of lipids. This facilitatory effect of bile on nutrient absorption might also have an indirect effect on prostanoid production. The distension of the intestinal wall has been known to induce various response patterns from the visceral musculature at intraluminal pressure greater than 25mm.Hg (25,28). However, repeated placement of solutions in the lumen have been shown to induce receptive relaxation. (25,32,83,102). In the present study, the intraluminal pressure was less than 5 mmHg. Therefore, the absence of changes on blood flow and prostanoid production with luminal placement of air suggest that intestinal distension per se observed during luminal placement of solutions might not be responsible for the food-induced increases in prostanoid production. This is further supported by the data obtained during NS and bile placement.

The effect of pump induced hyperemia on jejunal prostanoid release is shown in Fig 15. The jejunal releases of PGE_2, PGI_2 and TXA_2 were enhanced while PGF_2 release was not altered by the hyperemia. During nutrient absorption, an increase in jejunal blood flow is a well-documented observation (30,53,55). It is possible that part of the food-induced increases in jejunal prostanoid releases might be mediated through the food-induced increases in jejunal blood flow.

In conclusion the studies in Series IV-VII showed that normal saline and bile added to the food mixture did not directly contribute to the food-induced increases in jejunal prostanoid production. Similarly, distension of the intestinal lumen with an equivalent volume of air as the food placement, did not alter jejunal prostanoid release. However, pump-induced jejunal hyperemia to simulate the postprandial hyperemia has significantly increased the jejunal releases of PGE_2, PGI_2 and TXA_2 while PGF_2 release was not altered. Part of the food-induced jejunal prostanoid release might be secondary to the food-induced hyperemia.

In the next Series of experiments an attempt was made to determine the physiological role of jejunal TXA_2 during resting conditions and nutrient absorption. Previous studies performed utilizing cyclooxygenase inhibitors suggested that vasoconstrictor prostanoids might play a predominant role during nutrient absorption (52,117). TXA_2 is the most potent vasoconstrictor prostanoid and is primarly synthesized by the jejunal mucosal layer (3,6,91). It is possible that it plays a significant role in the regulation of jejunal blood flow, oxygen consumption, and capillary exchange capacity. As shown in Fig. 18, 19, and 20 administration of a TXA_2/endoperoxide receptor blocker did not alter resting jejunal blood flow, oxygen consumption, and capillary exchange capacity. These results agree with previous studies performed utilizing thromboxane synthetase inhibitors (imidazole and U-63557A). In the resting gut, TXA_2 seems not to play a significant regulatory role in the jejunum. However, in the presence of nutrients in the lumen the TXA_2/endoperoxide receptor blocker significantly enhanced the food induced increases in oxygen consumption (Fig. 19) and capillary exchange capacity (Fig 20) without altering the magnitude of the hyperemia (Fig 18). A similar finding was observed utilizing TXA_2 synthetase inhibitors (103,104). Therefore, TXA_2 seems to regulate effective jejunal capillary exchange capacity and oxygen extraction during nutrient absorption.

The mechanism by which endogenous TXA_2 limits the magnitude of food-induced increases in jejunal oxygen extraction is unknown. One possible way might be through direct action on oxidative metabolism. In general, vasoactive agents may affect oxygen uptake in accord with their action on oxidative metabolism (83,112,113,114). Gallavan and Chou (54) reported that inhibition of cyclooxygenase during nutrient absorption significantly enhanced the rate of glucose utilization and absorption in canine jejunum. However, there are very few studies performed on the effect of endogenous TXA_2 on jejunal oxidative metabolism. These studies showed that TXA_2 did not alter jejunal glucose absorption (103), and colonic chloride (35) and duodenal bicarbonate (58) secretion. Since the effect of thromboxane A_2 on other energy-dependent intestinal functions is not well known, one cannot rule out the possible role that thromboxane A_2 might have on jejunal oxidative metabolism.

In the present study, infusion of vasoactive chemicals during nutrient absorption has altered the magnitude of food induced changes in jejunal capillary filtration coefficient (Series XI) in parallel to the blood flow changes. Other studies also have shown that all vasoconstrictor chemicals attenuate and vasodilator chemicals (except adenosine) enhance capillary filtration coefficient by altering intestinal blood flow (121,134). However, the findings with thromboxane receptor blocker and synthtase inhibitors during nutrient absorption seem to lack the parallelism between blood flow changes and capillary exchange capacity. A similar finding was previously observed during infusion of cholecystokinin, secretin and 5HT where an increase in capillary filtration coefficient was noticed at dosages lower than those needed to produce changes in intestinal blood flow (8,48). These investigators concluded that capillary filtration coefficient reflects in most cases the tone of the pre-capillary sphincter section. The contribution by pre-capillary sphincters to the total jejunal resistance to blood flow is slight, so net changes in resistance or blood flow do not necessarily correspond to any capillary filtration coefficient changes (48). Therefore, it is possible that the predominant effect of TXA_2 might be on the precapillary sphincter tone which could possibly limit the capillary density without altering jejunal blood flow through a redistribution of blood between different layers of the jejunum.

In conclusion, the present study in Series VIII, IX, and X indicated that a thromoxane A_2 analog (U-44069) is a potent vasoconstrictor in the jejunal vascular bed. During nutrient absorption thromboxane A_2 receptor antagonist (SQ- 29548) potentiated the food-induced increases in jejunal oxygen consumption and capillary filtration rate. There was no change in blood flow. Endogenous TXA_2 might limit the food-induced changes in jejunal capillary density and oxygen extraction.

In the next Series of experiments the effect of TXA_2 on blood flow distribution between mucosal and muscularis layers of the jejunal wall was determined utilizing radioactive microspheres. As shown in Fig. 22 with a free-flow jejunal preparation, local intra-arterial infusion of a thromboxane A_2 analog decreased blood flow to both layers of the jejunal wall. However, the magnitude of decrease in mucosal plus submucosal blood flow was significantly greater than the muscularis plus serosal. This finding might indicate the presence of a difference in response between the two layers of the jejunal wall to the action of thromboxane A_2 analog. The data obtained in a constant flow jejunal preparation (Fig 23) presents additional evidence indicating a greater sensitivity of the mucosal-submucosal vascular bed to the actions of the thromboxane A_2 analog. Furthermore, Figs. 22 and 23 showed that a thromboxane A_2 receptor antagonist inhibited the TXA_2 analog-induced decreases in jejunal blood flow in both layers of the intestinal wall. However, the percent increase in mucosal plus submucosal blood flow was significantly greater than the muscularis plus serosal. These findings might indicate that endogenous thromboxane A_2 could possibly elicit a variable degree of vascular response in the mucosal- submucosal and muscularis-serosal vascular bed.

In the intestine where the mucosal-submucosal and muscularis-serosal blood vessels are arranged in parallel (77), a redistribution of blood between the two layers has been previously reported during sympathetic stimulation (48), adenosine infusion (65,137), reactive hyperemia (136) and isoproterenol infusion (135,137). The present study suggests that thromboxane A_2 redistributes intestinal blood flow. This might indicate that the enhancement of the food-induced increases in jejunal capillary exchange capacity by thromboxane receptor blocker shown in Fig. 20 and by thromboxane synthetase inhibitors observed in the previous study (104) was at least in part due to a redistribution of blood away from the muscularis plus serosal layer to the mucosal plus submucosal layer. Since, thromboxane A_2 is primarly produced by the intestinal mucosal layer (3,91), it is likely that a true redistribution of flow takes place in such a way that the blood supply to the mucosal-submucosal layer becomes limited. One possible physiological advantage of this TXA_2 action might be to regulate the rate of nutrient absorption.

The hyperreactivity of the mucosal layer to thromboxane A_2 may have serious consequences in certain pathophysiological situations associated with increased thromboxane A_2 production. During intestinal ischemia secondary to hemorrhagic shock (Fig. 30, Fig. 31 and Table V), superior mesenteric artery occlusion (111) and endotoxemia (45), an increase in TXA_2 production and severe intestinal mucosal damage have been reported. The intestinal muscle layer is minimally affected under these conditions. One of the pathophysiological mechanisms contributing to mucosal damage might be a higher sensitivity of the intestinal mucosa to thromboxane A_2. This may constrict the vessels and further aggravate the degree of mucosal ischemia to the extent of producing necrotic lesions.

In conclusion, the study in Series XII and XIII showed that a thromboxane A_2 analog (U-44069) decreased mucosal plus submucosal and muscularis plus serosal blood flow. The percent decrease in blood flow was significantly higher in the mucosal plus submucosal layer than in muscularis plus serosal. The U-44069-induced decreases in blood flow were reversed by administration of a thromboxane

A_2 receptor antagonist (SQ-29548). These actions of U-44069 and SQ-29548 suggest that the intestinal mucosal vascular bed has a greater reactivity to the action of thromboxane A_2 than the muscle. The greater reactivity of the mucosal vascular bed to the actions of thromboxane A_2 may play a significant role in various physiological (nutrient absorption) and pathological (shock) conditions.

The next Series of experiments was designed to determine the role of endogenous prostanoids, particularly TXA_2 and PGI_2 released from the small intestine on the progress and development of irreversible hemorrhagic shock and intestinal mucosal damage. Furthermore, the effects of intraluminal instillation of a diet, particularly a glucose oleic acid (GOA) solution, on the magnitude and proportion of hemorrhagic shock-induced intestinal PGI2 and TXA2 releases and the degree of intestinal mucosal damage were determined.

Previous studies have shown that prostanoids, particularly thromboxane A_2 and prostacyclin, may play a role in the development and progress of a variety of shock conditions (12,17,18,20,37,40,45,70,73,111,149). Evidences for their involvement is derived from experiments utilizing synthetase or receptor inhibitors (12,17,20,40,70,111) and those measuring the concentration of these two prostanoids in systemic blood (17,18,20,37,45,70, 73,111, 149). The studies which measure prostanoids show that both TXB_2 and 6-keto-PGF_1 increase in septic shock (20,153), endotoxic shock (73,45), and after splanchnic artery occlusion (111). There is, however, no study which measures these two eicosanoids during the course of severe irreversible hemorrhagic shock. Furthermore, most studies have measured their concentrations in systemic blood rather than in venous blood draining specific organs. In order to determine the relative contribution of TXA_2 and prostacyclin and the contribution of the intestine in the development of irreversible hemorrhagic shock, arterial and intestinal venous blood concentrations of TXB_2 and 6-keto-PGF_1 and the rate of release of these two prostanoids from the intestine were measured during severe hemorrhagic hypotension and after blood transfusion. Although there are species differences in the blood concentration of TXB_2 and 6-keto-PGF_1 in shock conditions (153), the resting and experimental values obtained in the present study are comparable to those obtained in anesthetized dogs subjected to splanchnic arterial ischemia (12).

The result shows that prostacyclin and TXA_2 productions are affected differently at different stages of hemorrhagic shock. Intestinal venous 6-keto-PGF_1 increased at hrs. 2 and 3 during the hypotensive period, then fell sharply after retransfusion of the shed blood in untreated shock group (Fig. 29). The increases in venous concentrations during the hypotensive period were not significantly different from the corresponding values of the sham-operated control dogs, but the decreased venous concentration values after reinfusion were significantly lower than the corresponding control values (Fig. 29). The three-fold decrease in intestinal venous 6-keto-PGF_1 concentration after reinfusion (Fig. 29) may be misleading because there was a concurrent six-fold increase in blood flow. Indeed, 6-keto-PGF_1 output (venous concentration x blood flow) significantly increased from 8.5 ± 2.0 ng/min at hr 3 to 31.4 ± 7.9 ng/min (one hour after reinfusion (hr 4)) ($p < 0.05$). The increase, however, was primarily due to an increase in arterial 6-keto-PGF_1 concentration. As shown in Table VI, intestinal 6-keto-PGF_1 production remained low at hr 4 and 5. Other investigators have shown that arterial or systemic venous 6-keto-PGF_1 concentration increases in septic shock in rats and pigs (20,153,142), in endotoxin shock in piglets (126), and following 3-hour splanchnic arterial ischemia in dogs (111). However, septic shock in dogs (153) and endotoxin shock in piglets (149) did not significantly alter arterial and systemic venous 6-keto- PGF_1 . The response of prostacyclin production to stress therefore appears to vary with species and types of shock.

Conversely, perfusion of a GOA solution into an isolated intestinal segment significantly increased intestinal venous 6-keto-PGF_1 concentration when compared to that observed in the untreated hemorrhagic shock and sham- operated control groups (Fig. 29). As shown in table VI, intestinal 6-keto-PGF1 release in the GOA perfused segment significantly increased at 2, 4, and 5 hrs compared to prehemorrhagic values and corresponding untreated shock values. This indicates that GOA treatment during hemorrhagic shock stimulates prostacyclin production from the perfused ileal segment.

In contrast to no change or a decrease in intestinal venous 6-keto-PGF_1 (as compared to sham-operated control and GOA-treated hemorrhagic shock dogs) (Fig. 28 and Fig. 29), TXB_2 concentration significantly and progresively increased during hypotensive (hr 0-3) and post-transfusion (hr 4 and 5) periods in the untreated shock groups (Fig. 30, and Fig. 31). Furthermore, TXB_2 concentration in the intestinal venous blood samples was significantly higher than that in the arterial samples obtained at the corresponding time. This indicates that thromboxane production increases in the intestine, and the increased production may contribute at least in part, to the increased arterial thromboxane concentration during these periods. A recent study shows that the gastrointestinal tract contains high activities of thromboxane synthetase (130). In the GOA-treated shock dogs, the arterial TXA2 concentration significantly increases in a similar way to the untreated shock dogs. Other investigators have also found that arterial TXB_2 increases in septic shock in pig (153,142), rat, and dog (153) and that the systemic venous TXB_2 concentration increases in endotoxic shock in piglets (149, 126) and splanchnic arterial ischemia in dogs (111). The increased arterial and systemic venous TXB_2 levels under these conditions may also, at least in part, be due to the increased thromboxane production in the intestine, particularly in the case of splanchnic ischemia. As shown in Fig. 26 and Fig. 27, respectively , intestinal blood flow decreases and intestinal vascular resistance increases markedly during hemorrhagic hypotension.

However, GOA treatment significantly lowered the shock-induced increases in intestinal venous TXB2 concentrations at 2, 3, and 5 hrs compared to the corresponding untreated shock values. Thus, GOA treatment increases prostacyclin and decreases thromboxane A_2 production from the perfused ileum during hemorrhagic shock.

Because of their opposite actions, it has been proposed that TXA_2 and PGI_2 play opposite roles in their contribution to the progress of shock states. TXA_2 is generally considered to be destructive (12,92,93,111), whereas PGI_2 is considered to be beneficial (45,93,95). However, PGI_2 has also been implicated as responsible for the terminal hypotension in endotoxic shock (17,18,73). One way to evaluate their relative contribution is to calculate the relative concentration in the blood and relative amount of production in the intestine of these two eicosanoids. It must be noted here that although various actions of PGI_2 are in opposition to those of TXA_2, the concentrations at which the former (e.g. vasodilation) will effectively cancel the latter action (e.g. vasoconstriction) are unknown. The concentration ratio, therefore, can provide only a general idea of the balance in their actions.

As shown in Fig. 32, the TXB_2/6-keto-PGF_1 ratio in the arterial blood was increased, particularly at hr 3 and 5 in the untreated shock groups. A comparison of the present result was made with the changes in arterial TXB_2/6-keto- PGF_1 ratio as reported in septic shock (153) and as calculated based on the data presented in endotoxic (126) and septic (142) shock. In all of the four conditions the ratio increased. However, the time of onset and the magnitude of increase in the ratio is variable. The sources for the variations might be the difference in species and the type, severity, and duration of shock under study. This data seems to suggest that the imbalance in the change of arterial thromboxane and prostacyclin concentration, and thus the production, may be a contributing factor for the progression of these shock states. In the untreated shock group, the intestinal venous concentration ratio of TXB_2 and 6-keto- PGF_1 increased progressively (i.e. four-fold at hr 3 and seven-fold at 2 hours after blood transfusion (hr 5) (Fig. 33)). Table V and Table VI further show that while 6-keto- PGF_1 release from the intestine decreased significantly, TXB_2 release increased significantly, five- to six-fold 1-2 hours after blood transfusion. If the rate of release reflects fairly the rate of production in the intestine, the data indicates that the influence of thromboxane in the intestine increases while that of prostacyclin decreases.

In the GOA-treated segment the intestinal venous concentration ratio of TXB_2 and 6-keto- PGF_1 tended to decrease during the hypotensive period (Fig. 33). Table V and Vl further show that while intestinal TXB_2 release significantly decreased, 6-keto-PGF_1 increased, particularly during the post-transfusion period. The data indicates that the hemorrhagic shock-induced increased influence of thromobxane in the intestine is significantly abolished by luminal perfusion of GOA.

The imbalance of influence of these two prostanoids may contribute to the development of irreversible shock as well as reperfusion injury of the intestine. Though reperfusion of ischemic intestine has the beneficial effect of salvaging the organ, it is also associated with tissue damage (61). The finding in the untreated shock group that thromboxane production in the intestine markedly increases after reperfusion, seems to suggest that thromboxane may be a factor contributing to this damage. In support of this thesis, GOA perfusion has significantly attenuated the degree of shock-induced intestinal mucosal damage and TXA_2 production. Recent studies have also shown that administration of a TXA_2 receptor blocker or synthetase inhibitor attenuates the rise in a proteolytic enzyme activity that occurs after reperfusion in splanchnic artery occlusion (111) or hemorrhagic shock (12).

The intestine has been shown to play a significant role in the development of irreversible shock. One possible involvement is the release of myocardial depressant factor (MDF) from the intestine (69,94,115). In a previous study (115), a significant release of MDF occurred two hours after blood transfusion in dogs subjected to 3-hour severe hemorrhagic hypotension. The time of MDF release coincides with the maximum increase in thromboxane release shown in Fig. 31 and Table V in untreated shock dogs. This appears to suggest that in addition to other harmful actions, such as platelet aggregation, an increase in intestinal TXA_2 production may be related to intestinal MDF production and release. Bitterman et al. (12) have shown that a TXA_2 receptor antagonist reduced the rise in plasma cathepsin D and MDF activities and amino-nitrogen concentration in cats subjected to severe hemorrhagic shock. In another study (111), the rise in the beta-glucuronidase activity that occurred after the release of splanchnic artery occlusion was attenuated by a thromboxane synthetase inhibitor. Instillation of GOA into the intestinal lumen of dogs subjected to irreversible hemorrhagic shock has been shown to prevent the release of cardiodepressants from the splanchnic region (71,72). In the present study (Fig. 31 and Table V), it has been shown that GOA treatment significantly attenuated the hemorrhagic shock-induced increases in intestinal TXA_2 production and mucosal damage. Furthermore, the degree of mucosal damage was significantly correlated with mortality (68,69). Part of the mechanism by which GOA treatment prevented irreversible hemorrhagic shock and increased survival rate (67% for 26 - 41 hrs) (71,72) might be through enhancement of a beneficial prostanoid (prostacyclin) and inhibition of a destructive prostanoid (thromboxane A_2) from the intestine.

In 1982, Halper et al. (71,72) perfused GOA throughout the lumen of the small intestine during severe hemorrhagic shock. The perfusion prevented the terminal hypoglycemia and prolonged survival. In the present study, the GOA treatment through a very small segment of the small intestine has also prevented the terminal hypoglycemia (Fig. 25). An additional mechanism by which GOA prevented the severity of irreversible hemorrhagic shock is by making available an adequate level of substrate for oxidative metabolism. Strawitz and Hiff (143), Moffat et al. (106), and Hinshaw et al. (75) have reported a similar salutatory effect of exogenous glucose administration in different types of shock. Moreover, Gump et al. (67) and Lang et al. (88) reported that fat metabolism may represent a more effective energy substrate than glucose in hypovolemic or endotoxic shock.

In conclusion, the study in series XIV shows that arterial and intestinal venous TXB_2 concentration increased progressively during severe hemorrhagic hypotension and after blood transfusion. The 6-keto-PGF_1 concentration in the blood increased during hypotension and decreased during the post-transfusion period. Thromboxane production in the intestine increased, whereas prostacyclin production decreased during the course of hypotension and reperfusion. GOA treatment during the development and progress of shock inhibits the shock-induced increases in intestinal TXA_2 production and enhances the shock-induced decreases in PGI_2 production. This GOA effect on prostanoid production might be related to the saluatory effect that GOA perfusion has been shown to have during shock. The imbalance in the production and release from the intestine of these two eicosanoids, which act in opposition to each other, may be a factor contributing to the development of irreversible hemorrhagic shock and reperfusion injury of the intestine.

SUMMARY AND CONCLUSION

Recent studies suggest that endogenous intestinal prostanoids play a role in the regulation of jejunal blood flow and oxygen uptake at rest, during nutrient absorption, and during the progress of severe hemorrhagic shock. In the present study which of the intestinal prostanoids that play a regulatory role was determined. The main findings of the study are:

1. During luminal placement of normal saline (NS), the jejunum releases PGI_2, PGE_2 and TXA_2.

2. During nutrient absorption:

A. Food (F) produced a significantly higher blood flow and oxygen uptake.

B. Food significantly increased the jejunal production and releases of PGE_2, PGI_2, TXA_2 and PGF_2. Infusions of a mixture of the four prostanoids to mimic a situation of changing luminal content from NS to F did not significantly alter the jejunal vascuar resistance (JVR). However, local intra-arterial infusion of U-44069 (a TXA_2 analog), and PGF_2 increased, while PGI_2 and PGE_2 decreased JVR in a dose dependent fashion.

3. Effect of substrate loading with arachidonate:

A. Addition of arachidonate to food (F+AA) abolished food- induced increases in blood flow and oxygen uptake.

B. Addition of arachidonate to food signficantly increased PGE_2, TXB_2 and PGF_2 releases.

C. As compared to F in the lumen, F+AA significantly increased venous TXA_2 and PGF_2 releases.

D. Infusion of the four prostanoids, to mimic a situation of changing luminal content from NS to F+AA increased the JVR in a dose dependent fashion.

E. Placement of F per se significantly decreased JVR, which was abolished and reversed by prostanoid mixture, infused to mimic a situation of changing luminal content from F to F+AA.

F. Local intra-arterial infusion of SQ-29548, a TXA_2/ Endoperoxide receptor antagonist abolished the arachidonate inhibition on blood flow and oxygen uptake during food placement.

4. Effects of individual constituent of food and events associated with nutrient absorption on jejunal prostanoid production.

A. Jejunal blood flow was not altered by luminal placement of NS, air, or 10% bile compared to an empty lumen.

B. Jejunal venous concentrations of 6-keto-PGF_1 and TXB_2 were not significantly altered by luminal placement of NS, air, or 10% bile.

C. Jejunal venous concentrations of 6-keto-PGF_1 and TXB_2 tended to decrease and PGE_2 tended to increase during pump-induced jejunal hyperemia, whereas, the PGF_2 concentration significantly decreased.

D. Pump-induced jejunal hyperemia significantly increased the rate of PGI_2, TXA_2 and PGE_2 releases from the jejunum. However, PGF_2 release did not change.

5. Role of enodgenous TXA_2 on the regulation of intestinal vascular and metabolic changes.

A. Local intra-arterial infusion of U-44069, a TXA_2/ Endoperoxide agonist, increased JVR in a dose dependent fashion. SQ-29548, a TXA_2/Endoperoxide receptor blocker, reversed the U-44069-induced JVR changes to control levels.

B. Local intra-arterial infusion of SQ-29548 potentiated the magnitude of post-prandial jejunal oxygen uptake and capillary filtration coefficient without altering the magnitude of hyperemia.

C. Local intra-arterial infusion of U-44069 decreased jejunal mucosal-submucosal and muscularis-serosal blood flow in a free-flow jejunal preparation. However, the magnitude of decrease in blood flow was significantly greater in the mucosal-submucosal layer than the muscularis-serosal layer. SQ-29548 reversed the U-44069-induced blood flow changes to control levels.

D. Local intra-arterial infusion of U-44069 decreased jejunal mucosal-submucosal and increased muscularis- serosal blood flow in a jejunal preparation perfused at a constant flow rate. SQ-29548 restored the U-44069-induced blood flow changes to control levels.

6. Hemorrhagic shock and intestinal prostanoids:

A. Intestinal vascular resistance (IVR) increases during the hypotensive period of severe hemorrhagic shock. Perfusion of a glucose oleic acid (GOA) solution through the intestinal lumen abolished the shock-induced increase in IVR.

B. GOA perfusion prevented the hemorrhagic shock-induced terminal hypoglycemia .

C. Intestinal venous concentrations of TXB_2 progressively increased during hypotensive and reperfusion periods of severe hemorrhagic shock, while the 6-keto-PGF_1 concentration decreased. Conversely, GOA perfusion abolished the shock-induced increases in intestinal venous TXB_2 concentration, whereas the 6-keto-PGF_1 concentrations significantly increased.

D. Intestinal rate of TXA_2 release significantly increased following reperfusion of the shed blood in severe hemorrhagic shock dogs. However, the PGI_2 release significantly decreased during hypotensive and reperfusion periods. Conversely, GOA perfusion abolished the shock- induced increases in intestinal TXA2 release, whereas, the PGI_2 release was significantly increased.

E. Perfusion of GOA solution during severe hemorrhagic shock reduced the magnitude of intestinal damage.

The data indicates resting gut produces a significant amount of PGI_2, PGE_2, and TXA_2. Nutrient absorption significantly increased the release of PGI_2, PGE_2, TXA_2 and PGF_2 from the gut. Substrate loading with arachidonate significantly enhanced the formation of vasoconstrictor prostanoids, which in turn abolished the postprandial intestinal hyperemia and oxygen consumption. Intra-arterial infusion studies suggest that prostanoid action on the gut might be a direct or an indirect vascular action through alteration of the parenchymal cell metabolism. Part of the stimulus for the food-induced increase in intestinal prostanoid release might be to the food-induced increase in blood flow.

Endogenous TXA_2 limits intestinal oxygen consumption and capillary exchange capacity during nutrient absorption. The TXA_2 action seems to be primarly localized to pre-capillary sphincter. Among the intestinal layers, the mucosal vascular bed seems to have a significantly greater senstivity to TXA_2 than the muscle. This enhanced mucosal senstivity to TXA_2 might be the mechanism by which endogenous TXA_2 limits the rate of oxygen uptake and capillary exchange capacity without altering the total intestinal blood flow during nutrient absorption. Furthermore, the greater mucosal sensitivity to TXA_2 might play a significant role in pathophysiological conditions associated with intestinal mucosal damage.

During severe hemorrhagic shock, intestinal production of TXA_2 progressively increases, whereas PGI_2 production decreases, indicating a possible pathophysiologic role TXA_2 might play in the progress and development of irreversible hemorrhagic shock, particularly in the development of intestinal mucosal damage. The deleterious effects of TXA_2 during shock conditions were significantly attenuated by perfusion of GOA solution through the intestinal lumen. GOA significantly decreased the shock- induced increase in intestinal TXA_2 release, enhanced intestinal PGI_2 release, and reduced the magnitude of intestinal mucosal damage.

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