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POSTPRANDIAL RESPONSES OF LIVER BLOOD FLOW PRIOR TO AND FOLLOWING HEPATECTOMY IN CONSCIOUS DOGS

（意識下犬における肝切除術前後の摂食後肝血流変化）

Running Title: Postprandial Liver Blood Flow in Conscious Dogs

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ABSTRACT

The responses of the portal and hepatic arterial blood flows to various diets and nutrients were measured simultaneously in conscious dogs prior to and following hepatic resection. Prior to hepatectomy, the increase in the portal blood flow was significantly larger in response to an elemental diet, fats or amino acids than to glucose or water. The peak increase was 60.2 ± 14.4 ml for water, 144.7 ± 22.1 ml for a 150 Cal elemental diet, 168.5 ± 16.1 ml for a 300 Cal elemental diet, 86.7 ± 14.0 ml for a glucose solution, 159.3 ± 16.7 ml for an amino acid meal and 188.5 ± 25.3 ml for a fat meal. Following partial hepatectomy, fats and amino acids induced an increase in the portal blood flow similar to that prior to hepatectomy. Glucose and the elemental diet, on the other hand, induced a significantly larger increase in portal blood flow following the surgery although water did not. The peak increase was 144.4 ± 27.8 ml for glucose (166% of the peak increase prior to hepatectomy) and 221.8 ± 32.5 ml for the 300 Cal elemental diet (132%). The postprandial response of the hepatic artery to every diet was quite different among the dogs and there were no significant changes both prior to and following surgery. The different response of the portal flow to intraluminal glucose following partial hepatectomy may be due to alterations in glucose metabolism following hepatectomy. We have shown that the postprandial response of the portal blood flow varies with the type of nutrient, and it can be altered by hepatectomy.

INTRODUCTION

With the recent advances in liver surgery, many patients have undergone a major liver resection for hepatobiliary malignancies [1,2]. The maintenance of liver blood flow is important for preventing liver failure following a liver resection [3]. Feeding is one of the most potent factors that modifies liver blood flow. The splanchnic and portal hemodynamic responses to feeding have been studied extensively in animals and humans [4-8]. The influence of nutrients on splanchnic circulation has been reported by many authors [9,10]. These data were obtained using an isolated jejunal loop under anesthesia and thus do not represent actual physiological conditions because liver blood flow is modified by anesthesia and surgical stress [11,12]. Hopkinson and Shenk, in 1968, first measured the changes in liver blood flow during feeding in conscious dogs using an electromagnetic flowmeter [13], and our colleagues have investigated the postprandial hemodynamic responses in the celiac, left gastric and superior mesenteric arteries in conscious dogs [14,15]. However, the portal and hepatic arterial hemodynamic responses in conscious animals to several nutrients have not yet been reported. Using an ultrasonic transit time blood flowmeter, we investigated the responses of the liver circulation to the intraluminal administration of three major nutrients and the influence of liver surgery on it.

MATERIALS AND METHODS

Animals and Instrumental Preparations.

Six adult beagle dogs, of both sexes, weighing 8.0-17.0 Kg, were used. Following laparotomy under general anesthesia, two transit time ultrasonic blood flow probes for chronic use (Transonic System Inc., Ithaca, NY, USA) were inserted around the common hepatic artery (3 mm in diameter) and portal vein (6 mm in diameter). The gastroduodenal artery and right gastric artery were ligated, if present, to assure that only the arterial blood flow to the liver was measured. A gastric fistula was created in each animal. The connecting wires from the probes were pulled out of the abdominal cavity via a subcutaneous tunnel and were fixed in the back of the neck. At least 1 week was allowed for recovery. The animals were treated

according to the 'Animal Experimental Guide, Nagoya University School of Medicine'. Each dog could move freely in its individual cage, and was allowed free access to water and food except during the experiments. All were in good health throughout the experimental period.

All of the flow probes were calibrated prior to surgery. The flow probes were connected to a transit time ultrasonic flow meter (T201, Transonic System Inc., Ithaca, NY, USA), with a zero stabilizing circuit system, and thus a reliable zero reference could be obtained without occlusion of the vessels. Zero calibration was confirmed when the probes were excised. Data were recorded on a polygraph system (A601, Nihon Koden, Tokyo, Japan) and a direct writing recorder (TI-250, Tokai Irika, Tokyo, Japan).

Responses to test meals prior to hepatectomy.

At least 1 week was allowed to elapse before the test meal experiments to permit the animals to recover from the first operation. The animals were restrained in Pavlov stands throughout the experiments following an 18 hr fast. Six types of test meals were given: 1) a commercially available elemental diet [Elental(R), Roussel Morishita, Osaka, Japan, that contains dextrin (79.4%), amino acids (17.6%), fat (0.7%)] 150 Cal/300 ml (380 mosmol/kg); 2) a two-fold higher concentration of the same elemental diet, 300 Cal/300 ml (760 mosmol/kg); 3) a fat emulsion [Venolipid(R), Roussel Morishita, Osaka, Japan, that contains 16.7 g of soybean oil and 1.8 g of refined soybean lecithin] 150 Cal/300 ml (280 mosmol/kg); 4) an amino acid solution [Aminic(R), Roussel Morishita, Osaka, Japan] 150 Cal/300 ml (1230 mosmol/kg); 5) a glucose solution 150 Cal/300 ml (700 mosmol/kg); and 6) water as a control. Each test was performed on a separate day in a random fashion and only one experiment was conducted per day for each animal. Following 18 hrs of fasting, the portal venous and hepatic arterial blood flows were measured for at least 30 min to allow for the quiescent period of the interdigestive cycle [16]. Three hundred milliliters of a test meal were then injected directly into the stomach within 1 min through the gastric fistula by irrigation from a height of 50 cm. The portal venous and hepatic arterial blood flows were measured simultaneously for 2 hrs following the test meal ingestion.

Hepatectomy.

Following the measurement of the liver blood flow during both the fasting and postprandial states, a partial hepatectomy was scheduled several weeks after the first operation. Following laparotomy under general anesthesia, left medial and left lateral hepatic lobectomies (a 40% partial hepatic resection) were performed. The lobectomy was performed easily without any massive blood loss by ligating and cutting the pedicles. The dogs received 2 ml/min of physiologic saline during the operation, then antibiotics (CBPC 1g/body) and 500 ml of saline were administered on the first and second postoperative days. The animals were offered free access to food and water after the third postoperative day.

Responses to the test meals following hepatectomy.

The experiments were started at least 4 weeks following the hepatectomy to avoid any surgery-induced early hemodynamic changes. After following the records of the fasting blood flows for at least 30 min, the same test meals were given as mentioned previously. The liver blood flow was measured for 2 hrs to compare them with those prior to hepatectomy.

Gastric emptying.

The gastric emptying of each of the 6 test meals was measured in another series of dogs without blood flow probes. Polyethylene glycol 4000 (Katayama Chemical, Osaka, Japan) was used as a nonabsorbable marker. Each test meal (300 ml) containing 1.5 g of polyethylene glycol was given through a gastric fistula. The fistula was opened at 20, 40, 60, 80 and 120 min, and all gastric contents were collected by gravity drainage. The volume of the effluent was measured, and 3 ml were taken for the measurement of the polyethylene glycol concentration by spectrophotometry at a wavelength of 650 nm [17]. The effluent was then returned to the stomach via the gastric fistula.

Analysis.

All blood flow recordings were analyzed at 1 min intervals and the data are expressed as the difference (ml/min) from the basal value. The basal value of the blood flow was the mean value for the 30 min prior to each experiment. The peak response was determined from the maximal flow following the test meal irrigation. The integrated increase was calculated by

adding the increments above the base line from 1 to 120 min following the test meal ingestion. The gastric emptying curve for each animal was fitted by linear regression ($r=0.95$-0.99, $p<0.05$) following logarithmic transformation [18]; the gastric half-emptying time was obtained by calculation.

Statistics.

All the data are presented as the mean ± SE. Statistical analysis of the data was carried out by one-way factorial ANOVA to compare each test meal prior to hepatectomy, two-way repeated ANOVA to compare each test meal and hepatectomy status, and the paired t-test for paired data. A p value < 0.05 was considered to be statistically significant.

RESULTS

Fasting liver blood flow.

The preprandial control values of the portal blood flow and hepatic arterial blood flow are shown in Table 1. There were no significant differences in the portal blood flow among each test meal both prior to and following hepatectomy. There were no significant differences in the hepatic arterial blood flow among each test meal, but the hepatic arterial blood flow following hepatectomy was significantly lower than that prior to hepatectomy.

Responses to the test meals prior to hepatectomy.

Following feeding through the gastric fistula, the portal blood flow increased quickly above the base line in all test meals (Fig. 1). The increase remained significantly higher than the basal value for 2 hrs with the 150 Cal elemental diet, the 300 Cal elemental diet and the fat or amino acid meals. With glucose or water, however, the portal blood flow gradually decreased and returned to the basal value in 82 and 43 min, respectively. The peak increase of each test meal was 60.2 ± 14.4 ml for water, 144.7 ± 22.1 ml for the 150 Cal elemental diet, 168.5 ± 16.1 ml for the 300 Cal elemental diet, 86.7 ± 14.0 ml for the glucose solution, 159.3 ± 16.7 ml for the amino acid meal and 188.5 ± 25.3 ml for the fat meal. The peak increase was significantly smaller ($p<0.05$) with the glucose and water test meals than with the other four test meals. There were two peaks of portal blood flow increase in every diet. As

shown in Fig. 4, the first peak appeared soon after filling the stomach (within 10 min) and the second one appeared somewhat later (30-60 min after injection). The integrated increase observed with the 150 Cal elemental diet, the 300 Cal elemental diet, the fat diet or the amino acid diet was significantly larger than that with the glucose solution and/or water (Fig. 2A).

On the other hand, the hepatic arterial blood flow did not change significantly for 2 hrs following the ingestion of the test meal (Fig. 2B). The change in the total liver blood flow, calculated as the sum of the hepatic arterial blood flow and the portal blood flow, exhibited the same tendency as that of the portal blood flow because of the low hepatic arterial blood flow.

Responses to test meals following hepatectomy.

The responses of the portal blood flow to each test meal except glucose, the 150 Cal elemental diet and the 300 Cal elemental diet exhibited the same patterns as those observed prior to hepatectomy (Figs. 1,2A). The peak increases were 65.6 ± 12.8 ml for the water diet, 162.2 ± 33.0 ml for the amino acid diet and 183.8 ± 34.3 ml for the fat diet. On the other hand, the responses to the glucose and the 300 Cal elemental diets following hepatectomy were significantly larger than those observed prior to hepatectomy. The peak increases in response to glucose and the 300 Cal elemental diet were 144.4 ± 27.8 ml and 221.8 ± 32.5 ml (166 and 132% of the peak increase prior to hepatectomy), respectively, and the integrated increase also was significantly larger (168 and 135%, respectively) than that prior to hepatectomy (Fig. 2A). The peak increase in response to the 150 Cal elemental diet was 181.1 ± 29.7 ml (125% of that prior to hepatectomy), but the integrated increase did not change significantly following hepatectomy (Fig. 2A). A biphasic increase also was seen in every diet. The response of the hepatic arterial blood flow to each test meal was not altered significantly following hepatectomy (Fig. 2B).

Gastric Emptying.

No differences were seen in gastric emptying among the 150 Cal elemental diet, glucose, amino acid or fat diets (Fig. 3A and 3B). The half-emptying time, i.e., the time required for the initial volume of the test meal in the stomach to decrease by one half, was 33.2 ± 2.0 min for the 150 Cal elemental diet, 31.4 ± 3.7 min for the glucose diet, 34.9 ± 3.7 min for the amino

acid diet and 38.8 ± 5.5 min for the fat diet. The emptying of water was significantly faster (half time; 8.3 ± 1.0 min) than that of the other four test meals, while the emptying of the 300 Cal elemental diet was significantly slower (half time 53.5 ± 5.2 min) than that of the other four.

DISCUSSION

The present study has shown that different diets can cause differences in hepatic blood flow in conscious dogs. Prior to hepatectomy, a fat or amino acid diet induced a greater response in portal blood flow than did a diet of glucose despite the same amount of gastric emptying, whereas the type of diet had no consistent influence on the hepatic arterial blood flow. Following hepatectomy, the response of the portal blood flow to glucose increased significantly compared with that prior to hepatectomy, even though the other nutrients induced the same responses as those prior to surgery.

An amino acid or fat diet increased the portal blood flow more than glucose did under physiologic conditions prior to liver surgery while the gastric emptying of these three nutrients were similar. It has been reported that a high-fat and high-protein meal (peanut butter and milk) produced a more profound and sustained intestinal hyperemia than did a carbohydrate meal (fruit) in primates [19]. It also has been reported that glucose feeding in humans does not alter splanchnic blood flow [20]. One likely mechanism for this difference in responses is difference in the release of one or more gut hormones from the gastrointestinal tract. Several candidates of gut hormones which may increase splanchnic circulation include: cholecystokinin, secretin, gastrin, glucagon, vasoactive intestinal polypeptide, somatostatin, neurotensin, substance P, gastric inhibitory polypeptide, and opiates [21]. Of these peptides, only cholecystokinin and neurotensin are released by intraluminal fat or amino acids and are not released by glucose [22]. Moreover, these have been postulated to be the most important physiologic mediators of intestinal postprandial hyperemia [23]. Even though they had an effect on the intestinal blood flow only in pharmacologic doses, the quantity of nutrients in the diets used in this study was

greater than physiologic quantities. Therefore, these two hormones might be released in higher concentrations than those with ordinary meals.

It has been observed previously that the higher the osmolarity of the nutrients, the greater the increase in the liver blood flow [24]. The osmolarity of the nutrients used here was 700 mosmol/kg for the glucose diet, 1230 mosmol/kg for the amino acid diet and 280 mosmol/kg for the fat diet. In spite of the higher osmolarity of the amino acid diet and the lower osmolarity of the fat diet than the glucose diet, the amino acids and fat diet induced a greater increase in the portal blood flow than did glucose. The osmolarity of the 300 Cal elemental diet was twice as high as that of the 150 Cal elemental diet, but these two test meals produced about the same effect on changes in the portal blood flow. The contribution of the osmolarity of food on portal blood flow seemed to be rather small when the meals were given intraluminally.

The changes in the portal blood flow showed biphasic increases following feeding with every diet. Takagi et al.[14] and Kato et al.[15] have reported sharp increases in the celiac and left gastric arterial blood flows and a slow gradual increase in the superior mesenteric arterial flow following feeding. Since the portal blood flow consists of the outflow from the gut, the spleen and the pancreas [25], the biphasic changes observed in the portal blood flow following feeding are likely to be the result of a combination of the responses seen in the celiac and superior mesenteric arteries.

There have been many reports concerning hepatic blood flow following a partial hepatectomy. Kahn et al.[26] have reported that the total liver blood flow increased immediately following a partial hepatectomy and remained elevated until the sixth postoperative day. They also noted that the cardiac output of pigs increased for a couple of days following a hepatectomy. We also observed a significant increase in the hepatic blood flow shortly after a partial hepatectomy and found a second peak of increased portal blood flow on the seventh postoperative day (Sato et al. unpublished observation, November 1990). In this study, therefore, the responses of the liver blood flow to food ingestion were examined at least 4 weeks after a partial hepatectomy.

The changes the liver blood flow following a meal after hepatectomy have not been reported yet, nor have there been reports regarding the effects of each type of nutrient. We demonstrated in this study that glucose and a 300 Cal elemental diet (including 61.5 g of dextrin) induced a more pronounced increase in the portal blood flow following a hepatectomy compared with that prior to hepatectomy. Cohen et al.[27] have indicated that the serum insulin, glucagon and pancreatic polypeptide levels became significantly higher during the 15-day period following a hepatectomy but that the plasma glucose levels remained normal throughout this period. Ida et al.[28] have examined the glucose tolerance test following hepatectomy and have reported that the blood glucose levels did not change at 24 hrs following a hepatectomy, but gradually increased by 48 hrs following surgery. Nonetheless, the glucose tolerance test returned to the normal range at 6 weeks after a hepatectomy. The different response of portal blood flow to intraluminal glucose may be due to these changes in glucose metabolism following hepatectomy. The more delayed and prolonged increase in the portal blood flow induced by a 300 Cal elemental diet compared with that of glucose may be due to the fact that the carbohydrate included in the elemental diet was dextrin, and it needs to be digested in the intestine and metabolized in the liver.

Liver regeneration after hepatic resection has been documented in association with liver blood flow [3,26]. Portal blood flow is thought to be a particularly important determinant of hepatic regeneration [29]. Thus, it is important to maintain liver blood flow after liver surgery. Our data suggest that an amino acid or fat diet would be more favorable clinically for enteral feeding after a hepatectomy than would a carbohydrate meal. An mixed elemental diet is also available and may be useful.

The responses of the hepatic arterial blood flow to the various diets did not demonstrate a consistent pattern both prior to and following hepatectomy, presumably because of the different responses of the hepatic arterial blood flow in each animal. In some dogs, the hepatic arterial blood flow increased following food ingestion, while it did not change in other dogs and even decreased in the remaining dogs (Fig. 4). The term 'buffer response' of the hepatic artery is used to describe the hyperemic response of the hepatic artery to portal vein occlusion [30]. One

of the most likely mediators of this response is thought to be adenosine [31,32], and the local concentration of adenosine at the site of the hepatic arterial resistance vessels is determined by its washout into the portal blood vessels [31]. Adenosine also has been proposed to be a mediator of postprandial splanchnic hyperemia [33]. It is hypothesized that the different responses of the hepatic arterial blood flow to food ingestion is induced by differences in the local adenosine concentration which is determined by increases in the concentration of adenosine due to splanchnic hyperemia and decreases in the concentration due to increased washout by the increased portal blood flow following feeding.

We have not measured the cardiac output in our series because of the technical difficulties in measuring the cardiac output in conscious dogs, and the redistribution of blood to the liver following feeding has not been determined. Hawley et al. investigated the changes in cardiac output after eating four types of proprietary liquid diets in healthy human adults [34]. In contrast to our data, they reported that a protein, a carbohydrate and a balanced meal diet induced a significant rise in cardiac output but that a fat diet did not. Thus, it is likely that the postprandial increase in portal blood flow is a result not only of intestinal hyperemia and an associated increase in cardiac output, but also of a redistribution of blood flow to the liver and intestine.

Further studies, including the measurement of cardiac output and humoral factors, are needed to clarify the mechanisms of the different responses of the liver circulation to each nutrient and the hemodynamic changes following hepatectomy.

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Table 1
Basal value of portal blood flow and hepatic arterial blood flow before ingesting each test meal

	Test meal ingested						
	water	ed150[a]	ed300[b]	glucose	a.a.[c]	fat	Total
PBF[d] (ml/min)							
Pre[e]	353±40	304±37	370±32	395±29	348±28	398±33	361±16
Post[f]	364±30	327±24	300±28	344±31	313±25	333±28	330±13
HABF[g] (ml/min)							
Pre	84±11	56±8	71±20	54±9	36±8	53±8	59±6
Post	44±4	43±8	41±6	44±4	40±4	40±3	42±2

Note. [a] ed150, 150 Cal elementary diet. [b] ed300, 300 Cal elementary diet.
[c] a.a., amino acid. [d] PBF, Portal blood flow.
[e] Pre, prior to hepatectomy. [f] Post, following hepatectomy.
[g] HABF, hepatic arterial blood flow.
Values are means±SE, n=6 dogs.

FIGURE LEGENDS

Figure 1

Changes in the portal blood flow following the intragastric administration of various test meals prior to hepatectomy (●) and following hepatectomy(○).

A: Water, B: 150 Cal elemental diet, C: 300 Cal elemental diet, D: Glucose, E: Anino acids and F: Fat was given at time 0 (arrow).

*indicates significant increase ($P<0.05$) from preprandial control. Means±SE are given. n = 6 dogs.

Figure 2

Integrated increase (1-120min) in the portal blood flow (A) and hepatic arterial blood flow (B) following the intragastric ingestion of water, 150 Cal elemental diet (ed150), 300 Cal elemental diet (ed300), glucose, amino acid (a.a.) and fat. The left bar (hatched) indicates the value prior to hepatectomy and the right bar (stippled) indicates the value following hepatectomy.

* indicates significant difference between the pre- and post-hepatectomy values ($P<0.05$). Means±SE are given. n = 6 dogs.

Figure 3

A: Gastric emptying of 300 ml of water (○), 150 Cal elemental diet (●) and 300 Cal elemental diet (□).

* indicates a significant difference ($P<0.05$).

B: Gastric emptying of 300 ml of glucose (○), amino acid (●) and fat(□). Means±SE are given. n = 6 dogs.

Figure 4

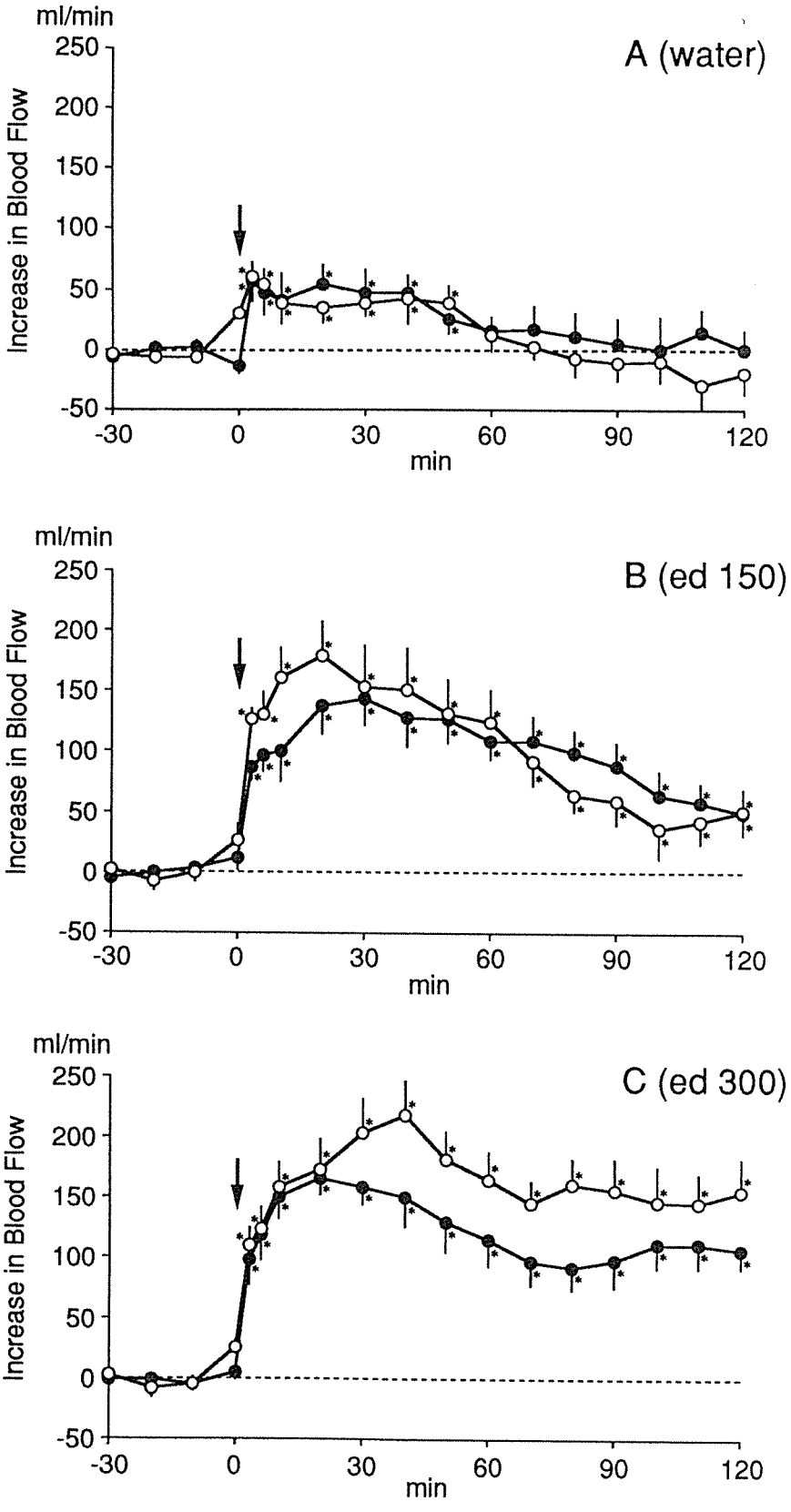
Three typical patterns of the changes in the hepatic arterial blood flow (●) and portal blood flow (○) following feeding.

A: The portal and hepatic arterial blood flow both increase. (Dog #6)

B: The hepatic arterial blood flow does not change while the portal blood flow increases. (Dog #4)

C: The hepatic arterial blood flow decreases while the portal blood flow increases ('buffer response'). (Dog #3)

150Cal/300ml of amino acid was given at time 0 (arrow) prior to hepatectomy.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A (water)
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min

Figure 1(A-C)

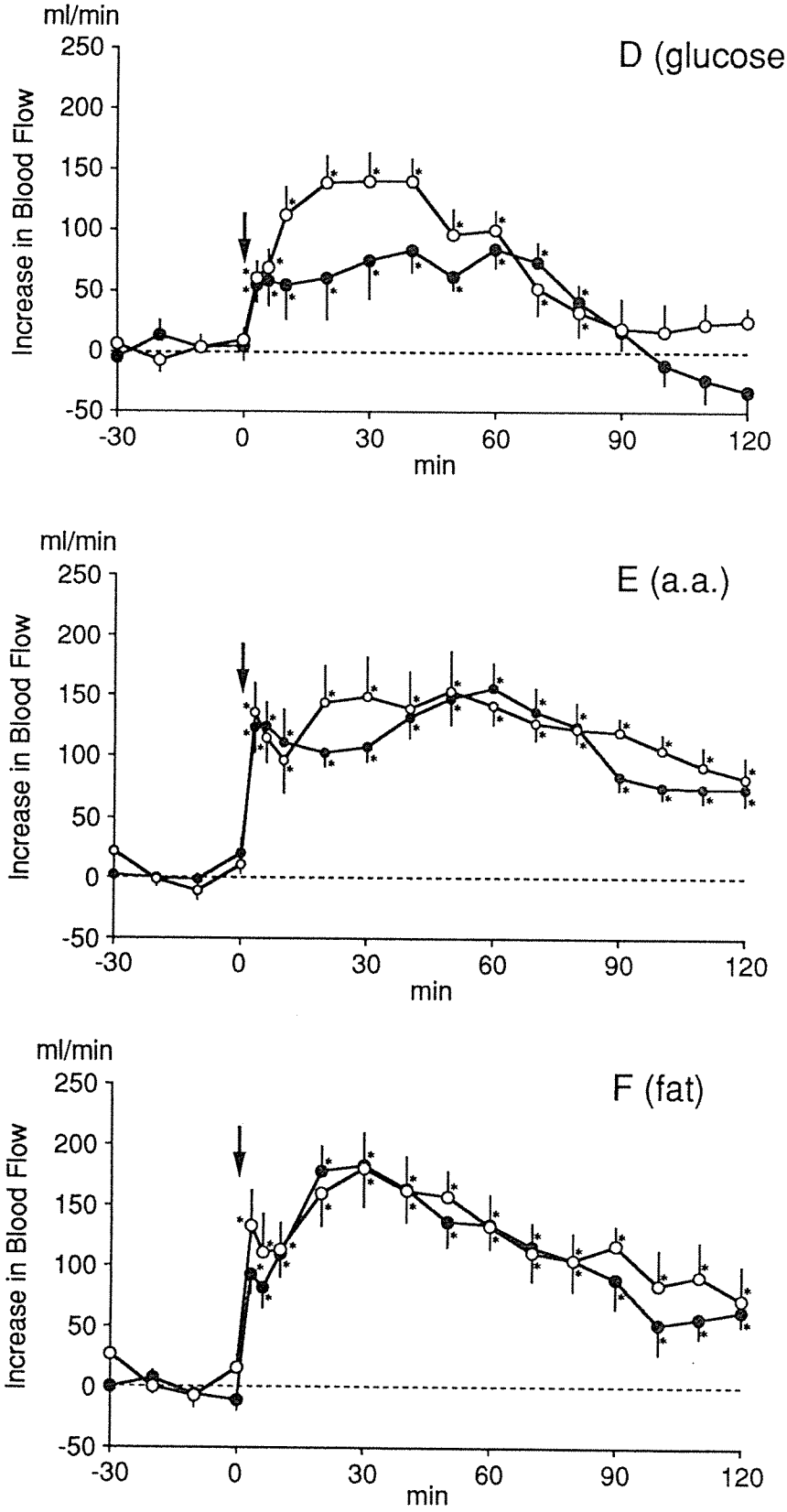
ml/min
D (glucose)
Increase in Blood Flow
250
200
150
100
50
0
-50
-30
0
30
60
90
120
min
ml/min
E (a.a.)
Increase in Blood Flow
250
200
150
100
50
0
-50
-30
0
30
60
90
120
min
ml/min
F (fat)
Increase in Blood Flow
250
200
150
100
50
0
-50
-30
0
30
60
90
120
min

Figure 1(D-F)

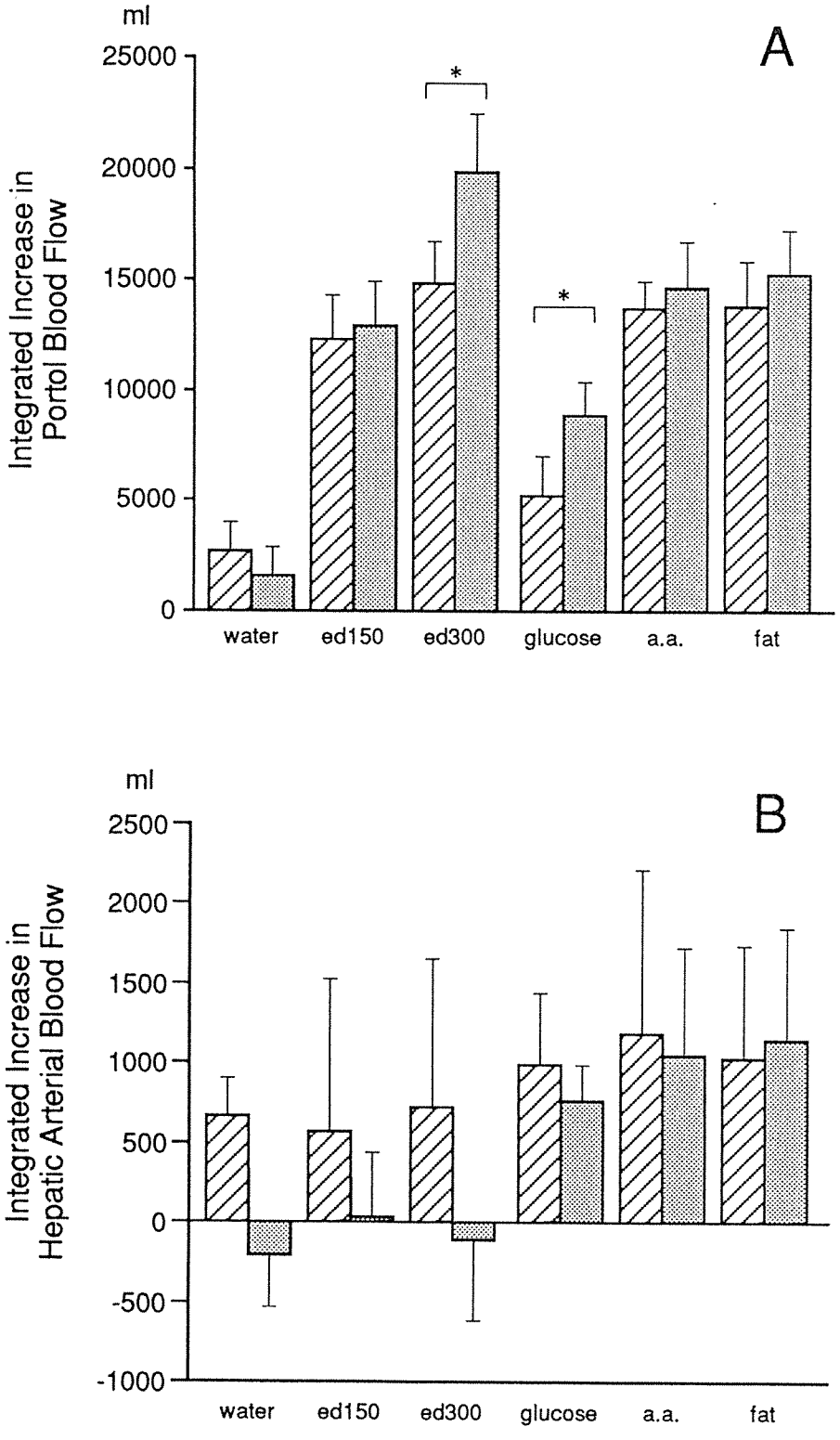
ml
A
25000
20000
15000
10000
5000
0
Integrated Increase in Portol Blood Flow
*
*
water
ed150
ed300
glucose
a.a.
fat
ml
B
2500
2000
1500
1000
500
0
-500
-1000
Integrated Increase in Hepatic Arterial Blood Flow
water
ed150
ed300
glucose
a.a.
fat

Figure 2

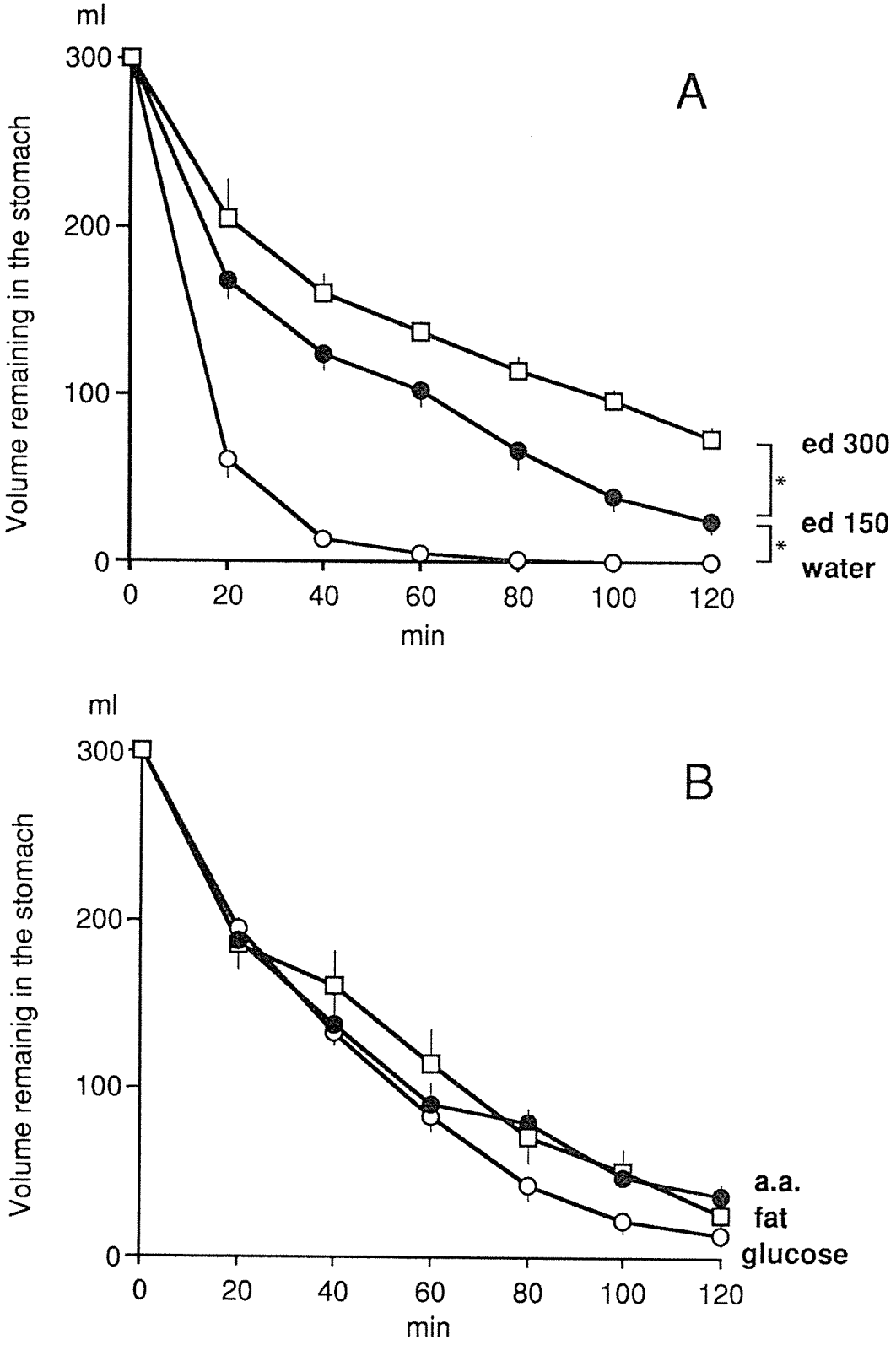
ml
300
200
100
0
Volume remaining in the stomach
A
0
20
40
60
80
100
120
min
ed 300
ed 150
water
*
*
ml
300
200
100
0
Volume remainig in the stomach
B
0
20
40
60
80
100
120
min
a.a.
fat
glucose

Figure 3

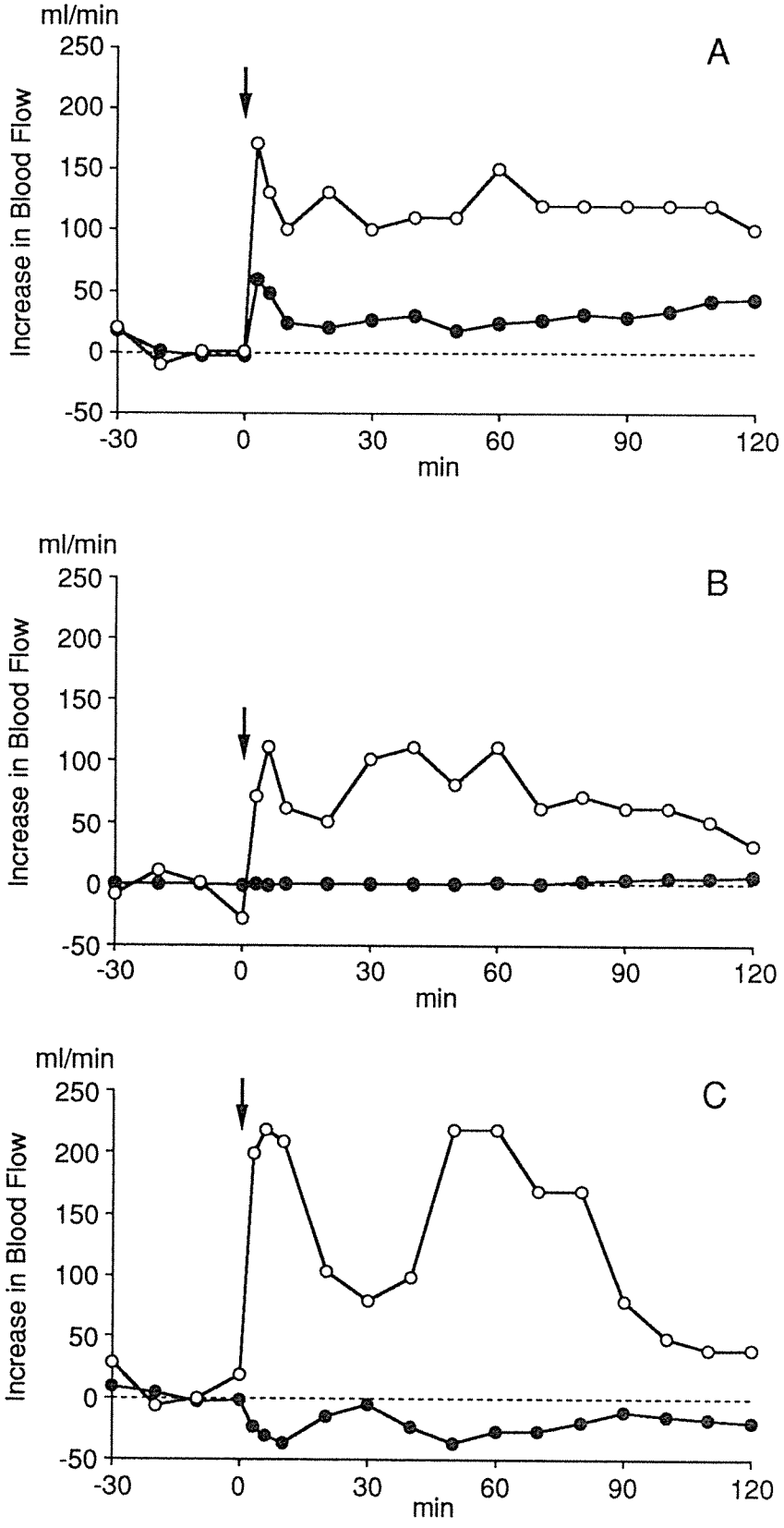
ml/min
A
Increase in Blood Flow
250
200
150
100
50
0
-50
-30
0
30
60
90
120
min
ml/min
B
Increase in Blood Flow
250
200
150
100
50
0
-50
-30
0
30
60
90
120
min
ml/min
C
Increase in Blood Flow
250
200
150
100
50
0
-50
-30
0
30
60
90
120
min

Figure 4