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THE EFFECT OF FEEDING ON: I HEPATIC PLASMA FLOW IN ADULT NON-PREGNANT SHEEP

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Published August 1992

SUMMARY

Work was done on adult sheep to determine the effect of feeding per se on hepatic plasma flow. Continuous infusion of creatinine was used to determine the flow rate. Feeding increased hepatic plasma flow with maximum peak reached at 2 - 4 hours post-feeding. An increase of 53% and 27% of total hepatic plasma flow (THPF) and portal venous flow (PVF) respectively over the pre-feeding values was observed. In conclusion feeding is a stimulus on its own for increased hepatic-portal plasma flow.

INTRODUCTION

The liver is an important organ with regards to digestion. Besides secretion of bile and bile salts for lipid digestion, it is the key organ which receive digestion products from the gastro-intestinal tract through the portal vein. Bensadoun and Reid (1962) observed an increased blood flow 3-7 hours post feeding in sheep. Sellers *et al.* (1964) obtained similar response in adult cattle. Other workers using starved sheep observed an increased portal blood flow of 39% (Katz and Bergman, 1969a) and 2-56% (Webster and White, 1973) during feeding with maximum peak at 2-6 hours post-feeding. The present work was carried out to clarify further the importance of portal blood flow in relation to feeding as it acts as a medium for transporting nutrients and ions from the gut to the liver where these are re-synthesized, metabolized or secreted into the general circulation.

MATERIALS AND METHODS

Fifteen adult sheep were used. The sheep were kept indoors, fed on grass hay and water *ad libitum* and given 1.0kg/sheep/day of commercial sheep nuts. The sheep were cannulated as described by Leek (1976) and carotid artery loops prepared for easy access to arterial blood. The sheep were implanted with vinyl catheters of 1.5mm (internal diameter, No. 800/000/150/800, Portex LTD, Hythe Kent England) into the portal, hepatic and mesenteric veins, as described by Katz and Bergman (1969b) with modification by Kisauzi (1982). Heparinized saline (10ml heparin of 5000 i.u./ml to 500ml pyrogene free normal saline) was used to flush and maintain the catheters in working order. The mesenteric vein catheter was used for infusing while the hepatic vein and portal vein catheters were used for blood sampling. Arterial blood was sampled from the carotid artery. Hepatic venous catheterization has proved to be of major importance for measuring hepatic haemodynamic parameters. Accurate measurement of blood passing through the liver can be done using the Fick Principle in estimating the flow, hepatic clearance and dilution of isotopes with the splanchnic blood volume. In the Fick principle substances such as dyes which are cleared exclusively by the organ or tissue are used, e.g. bromosulphthalen (BSP), to measure accurately blood flow. Substances such as radioisotopes and radiomicrospheres have been successfuly used to measure hepatic blood flows in sheep (Barnes, Comline and Dobson, 1982 and 1983). Marker substances are also used. In this method a known quantity of a tracer or marker substance is infused into the hepatic circulation over an accurately measured time period. Marker substances used in sheep include paraaminohippuric acid (PAH) (Roe, Bergman and Kon, 1966); BSP (Katz and Bergman 1969a and 1969b); and creatinine (Kisauzi, 1982). Thermal dilution was employed by Fegler and Hill (1958), cited by Webster and White, (1973) and White (1973) revised this technique by injecting cold physiological saline into the blood stream.

In the present study creatinine continuous infusion was used to measure the total hepatic (TH) and portal venous (PVF) blood flows. The sheep were fasted 48 hours prior to commencement of experiment. Prior to infusion a priming dose of stronger concentration was injected through the mesenteric vein catheter. Thereafter continuous infusion of a 7.0mg/ml creatinine was done using a peristaltic pump at a rate of 1.0ml/min. Sampling took place at done 5 minutes before infusion, thereafter at 90, 110, 120, 130, 140, 150, 160, 170, 180, 190, 270 and 390 minutes. Feeding commenced at 110 to 150 minutes after start of infusion, (i.e. 40 minutes of feeding). For each blood sample the PCV% was measured using a haematocrit kit, it wasthen centrifuged, plasma harvested and stored frozen pending analysis. Plasma creatinine was analyzed using a commercial kit (Sigma Chemical, St. Louis Missouri USA). The plasma creatinine concentrations (mg/1) were used to calculate the plasma flows as follows:

(i) THPF (l/min) =i/{(CRT)h.v - (CRT)c.a}

(ii) PVPF (l/min) = i/{(CRT)p.v - (CRT)c.a}

(iii) HAPF (l/min) = (THPF - PVPF)

where:

i = infusion rate (1 ml/min of 7.0mg/ml)

(CRT)h.v. = Plasma creatinine concentration in hepatic vein.

(CRT)p.v. = Plasma creatinine concentration in portal vein.

(CRT)c.a. = Plasma creatinine concentration in carotid artery.

RESULTS

Feeding increased hepatic plasma flows. THPF, PVPF and HAPF were 1.75 ± 0.05, 1.23 ± 0.04 and 0.52 ± 0.05 l/min respectively the fasted state. During feeding both THPF and HAPF increased to 2.03 ± 0.11 and 0.89 ± 0.13 1ml/min respectively while PVPF decreased to 1.14 ± 0.09 1 mil/min. At half hour post feeding all i.e. THPF, PVPF and HAPF increased with maximum peaks at 2-4 hours post feeding with values of 3.79 ± 0.42, 1.68 ± 0.18 and 2 11 ± 0.41 l/min respectively. The trend of increase is as shown in Figure 1 and Table 1.

DISCUSSION AND CONCLUSION

Estimation of hepatic plasma flows by the marker-dilution principle in this study was feasible. The sheep were easily trained to stay in individual metabolic cages and gave no difficulties while the experiments were being performed.

The marker dilution technique for the estimation of hepatic blood flows was used and creatinine was used as the marker substance. Creatinine was found suitable as a marker substance in a previous study by Kisauzi (1982) and gave comparable results to other substances such as BSP, PAH and thermal dilution (cold physiological saline) as used by

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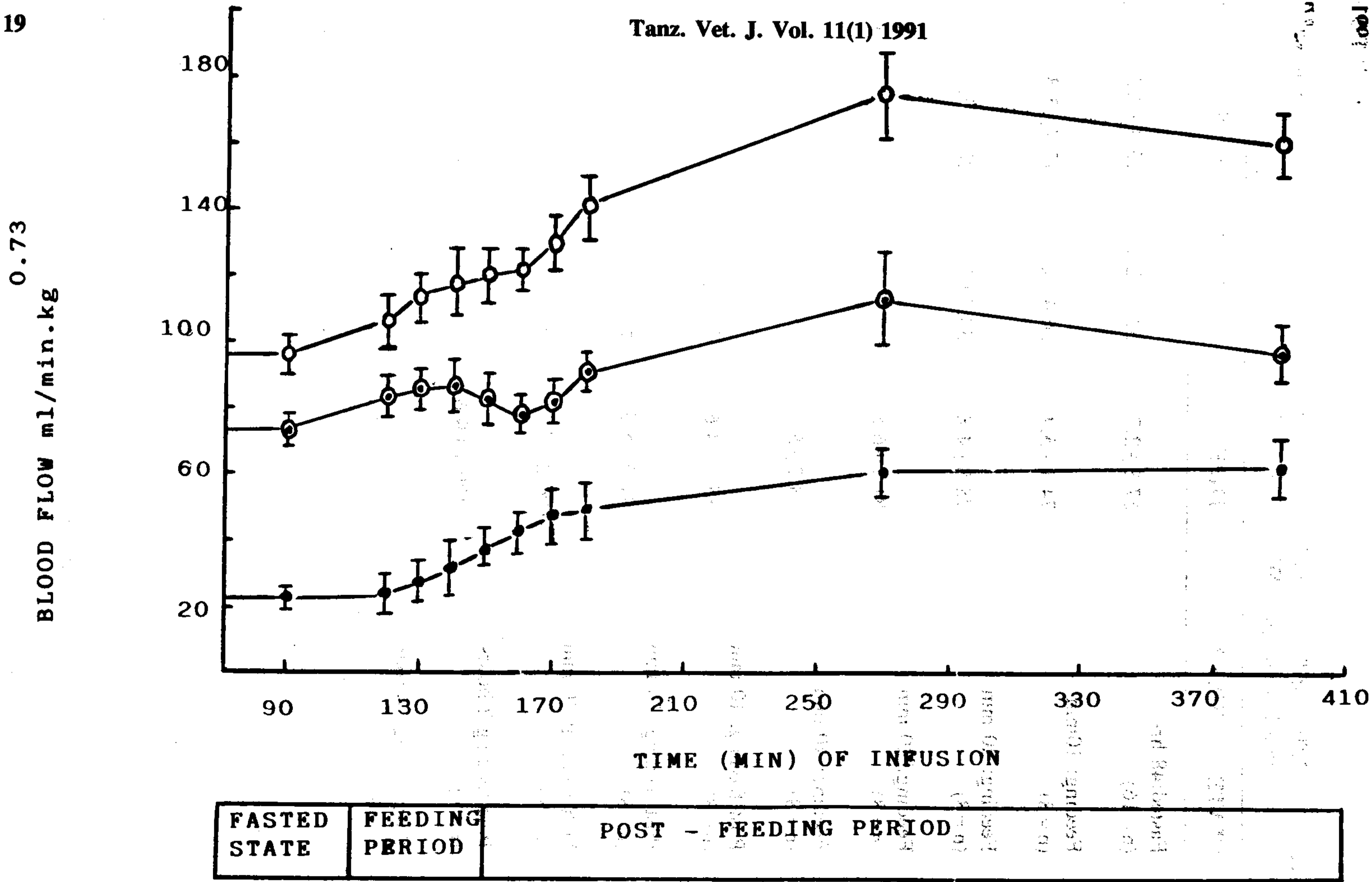

Figure 1: Hepatic blood flows (ml/min.kg$^{0.73}$ normal adult sheep fasted 48 hours, during feeding and 2-4 hours post feeding (mean±SE)

Table 1: Effect of feeding on hepatic plasma flow rate, mean + SE, ml/min. $kg^{0.73}$ in adult sheep. $BW^{0.73}$ = 78.3 ±3.2kg (n=8).

STATE OF SHEEP	THPF	PVPF	HAPF
Fasted:48 hrs (n=16)	67.8±2.7	52.0±2.1	15.8±2.2
Feeding: 10min (n=8)	74.1±5.4	56.4±2.7	17.7±3.8
Feeding: 20 min (n=8)	78.8±4.8	58.7±3.8	20.2±3.1
Feeding: 30 min (n=8)	81.1±6.8	59.4±5.0	21.7±4.3
Feeding: 40 min (n=8)	83.7±5.1	75.6±4.7	26.1±2.9
Post feeding: 10 min (n=8)	85.3±4.6	55.3±2.7	30.0±3.3
Post feeding: 20 min (n=8)	91.0±5.5	58.3±3.5	32.7±5.3
Post feeding: 30 min (n=8)	96.2±7.1	63.9±3.8	32.3±6.3
Post feeding 2 hours (n=8)	120.1±9.6	77.7±8.3	42.4±5.5
Post feeding: 4 hours (n=8)	112.9±9.2	69.4±6.5	43.6±5.9

other workers.

In the present study the THBF in 24 hours fasted normal adult sheep was 104 ± 5ml/min.$kg^{0.73}$ and 123 ± 14ml/min.$kg^{0.73}$ in ad lib fed normal adult sheep. This was not significantly different from that of 108 ± 3ml/min. $kg^{0.73}$ in fasted sheep (Kisauzi, 1982) using creatinine as a marker substance. Also it was not significantly different from those obtained using PAH which were 126±13 ml/min.$kg^{0.73}$ in fasted sheep (Katz and Bergman, 1969a) and 113±8ml/min.$kg^{0.73}$ in fed sheep (Harrison and Leat, 1972).

The PVF obtained in the present study was 83±1 (in 24h fasted sheep) and 85±5 (in ad lib fed sheep) ml/min. $kg^{0.73}$. These were not significantly different from that of 82±4ml/min. $kg^{0.73}$. obtained using creatinine as a marker substance in fasted sheep (Kisauzi, 1982). Also they were not significantly different from those of 97±12 or 81±4ml/min. $kg^{0.73}$ in fasted sheep using the thermal dilution method (Webster *et al.*, 1975).

The suitability of creatinine as a marker substance was further established by studying its clearance from the body. Creatinine being one of the nitrogenous metabolites produced in the body is excreted through the kidneys. The rate of creatinine formation and its concentration in plasma usually remain relatively constant (Swenson, 1984). Also its excretion through the kidney is fairly constant from day to day. In the present study the recovery of the exogenous creatinine (intravenously infused through the jugular vein) was found to be 118±8% in ad lib fed sheep and 101±4% in fasted sheep (in the latter creatinine was infused through the mesenteric vein)within 24h after start of the exogenous creatinine infusion. The high average value in the ad lib fed sheep was entirely attributable to unexpectedly high values from one sheep. This means creatinine is a safe substance to use as a marker as the body does not retain it or metabolize it. Also creatinine has an advantage of being easily assayed in plasma as well as in urine. Thus the present study further supports Kisauzi's (1982) conclusion that creatinine gives comparable results to other substances with the advantage of being a natural substance in plasma with no risk of interfering with the animal's metabolic functions.

In this study feeding increased the hepatic plasma flows as observed by other workers. THPF increased as soon as feeding started. The increase was gradual during feeding but became more rapid after the food was withdrawn from the sheep. Maximum values were obtained at 2 hours post-feeding being in accordance with observations made by Katz and Bergman (1969a), Bergman *et al.* (1970) and Bergman and Wolff (1971). At peak value THPF was 52.6% above the pre-feeding values. This observation was higher than those of 45% (Katz and Bergman, 1969a), 28% (Bergman *et al.*, 1970) and 34% (Bergman and Wolff, 1971). The difference could be due to the difference in actual sampling time after feeding, duration of feeding and type of feed given to the sheep during the experiment.

Feeding caused a biphasic increase of PVPF in the sheep. Initially there was an increase observed for a short period (20 min) followed by a transient decrease where levels weren't reaching pre-feeding values. Such a decrease could have been attributed to the fact that when sheep (and other ruminants) eat dry feed a decrease in plasma volume is observed. In the present study a decrease of 6.7% in PVF was observed during feeding which was higher than that of 2.01% recorded by Barnes *et al.* (1983). The difference could, again still be in the nature of the feed and duration of feeding during the experiment. After the transient decrease there was a gradual increase in PVF with an overall increase of 27.2% above the pre-feeding values. This is consistent with those of 26% (Bensadoun and Reid, 1962), 27.3% (Roe *et al.*, 1966) but are lower than those of 39% (Katz and Bergman 1969) 33% (Bergman *et al.* 1970). Also the increase by 27.2% in this study was higher than those of 18% (Webster and White, 1973) and 19% (Barnes *et al.*, 1983). The inconsistence being perhaps due to experimental design up, type of feed used, duration of feed and even factors like environmental temperatures which could cause an increase of up to 2-56% (Webster and White, 1973).

HAPF increased very gradually with feeding, maximum values were observed between 2 - 4 hours post-feeding.

These results support the view that feeding per se (regardless of feed type) increases the hepatic flow with PVF contributing more to THPF than HAPF. The maximum plasma flow at 2-4 hours post-feeding coincided with the increased levels of reticulo-rumen fermentation products thereby stimulating tension and chemo-receptors which excites the cardiovascular centres in the brain so as to increase blood supply to the splanchnic organs and tissues. In this respect increased blood supply would facilitate the removal of carbon dioxide and most of all the fermentation products from the gastro-intestinal tract. The portal flow increases most as this provides major drainage of the splanchnic organs and tissues.

ACKNOWLEDGEMENT

This paper is an extract from M.V.M. Thesis work entitled:
Trans-hepatic plasma lipids movement in normal adult sheep and pregnant sheep. by Pereka A.E. (1985) University College Dublin, Ireland.

The author is indebted to HEDCO Ireland who sponsored the study, Prof. B.F. Leek who supervised the work tirelessly and the staff of The Department of Veterinary Physiology and Biochemistry, UCD Ireland for all the help rendered.

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