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The effect of propranolol on the hyperaemic response of the hepatic artery to portal venous occlusion in the dog

B. Alexander, [1]L.H. Blumgart & [2]R.T. Mathie

Department of Surgery, Royal Postgraduate Medical School, London

1 It has been reported that activation of β-adrenoceptors may be responsible for the hyperaemic response of the hepatic artery to portal venous blood flow reduction.

2 The effect of β-adrenoceptor blockade on the hepatic arterial response to portal vein occlusion was investigated in 6 anaesthetized dogs. A side-to-side portacaval shunt was established to prevent loss of venous return and arterial blood pressure during periods of portal occlusion. Measurements of hepatic arterial and portal venous blood flows were made by use of electromagnetic flow probes.

3 Intravenous propranolol injection, at a dose sufficient to block the vasodilator effect of low doses of exogenous adrenaline, did not alter the magnitude of the hyperaemic response of the hepatic artery. Propranolol also produced no change in baseline portal venous pressure.

4 It is concluded that hepatic β-adrenoceptors are unlikely to be involved in the arterial response to portal occlusion. The absence of any reduction in basal portal venous pressure by propranolol is of interest in view of the current application of the drug in the treatment of patients with portal hypertension.

Introduction

A compensatory hyperaemic response of hepatic arterial (HA) blood flow occurs during periods of reduced portal venous (PV) flow (Greenway & Stark, 1971; Kock *et al.*, 1972; Mathie *et al.*, 1980). The mechanisms that control this hyperaemic response of the HA (the hepatic arterial 'buffer response': Lautt, 1981) remain poorly understood, though recent studies have implicated vasodilator metabolite involvement (Lautt, 1983; Mathie & Blumgart, 1983). Nevertheless, other mechanisms also postulated to control arterial blood flow have not been excluded. One such possible mechanism was investigated in a previous paper (Mathie *et al.*, 1980), which demonstrated that an extrinsic neurogenic phenomenon neither initiated nor modified the response. Another group has proposed the hypothesis that the mechanism involves activation of β-adrenoceptors through an intrinsic neurogenic vasodilator system or through circulating catecholamines (Fischer *et al.*, 1970).

The current study was carried out to determine if hepatic β-adrenoceptors are involved in the HA 'buffer response' to PV occlusion. The investigation provided an opportunity also to study the effect of propranolol on PV pressure in the normal dog, information relevant to discussions regarding the efficacy of the drug in the treatment of patients with portal hypertension (Conn, 1984).

Methods

Experiments were carried out in a total of 11 mongrel dogs of either sex, weighing 22.2–31.5 kg (mean 27.5 kg). The animals were deprived of food but not water for 24 h before the operation. Anaesthesia was induced with thiopentone (25 mg kg^{-1}, i.v.) and maintained with pentobarbitone (30 mg kg^{-1}, i.v.). After endotracheal intubation, the dogs were ventilated with a 3:1 mixture of nitrous oxide and oxygen using a Starling pump. The minute volume and the inspired oxygen concentration were adjusted to maintain the Po_2/Pco_2 at normal levels (approximately 100 mmHg [13.3 kPa] and 40 mmHg [5.3 kPa] respectively). The base deficit was maintained at 4 mmol l^{-1} by use of sodium bicarbonate i.v. as required. Fluid balance was achieved by infusion of 150 mM sodium chloride i.v.; haematocrit remained above 40% throughout each experiment. Body temperature remained at 36–38°C, maintained when necessary by means of radiant heat lamps.

[1] Present address: Klinik für Viszerale Chirurgie, Inselspital, Berne, Switzerland.

[2] Author for correspondence.

Operative procedures

The experimental model has been used extensively and is described in detail elsewhere (Mathie *et al.*, 1980; Mathie & Blumgart, 1983). After right femoral artery cannulation (for blood pressure measurement), a mid-line laparotomy was performed. A pre-calibrated electromagnetic flow probe (Statham) was applied to both the HA and the PV (3 mm and 6 mm diameter respectively). The HA probe was positioned about 2 cm from the coeliac axis while the PV probe was placed mid-way between the gastroduodenal and splenic veins (see Figure 1).

The gastroduodenal artery and vein were then ligated and the latter vessel cannulated to allow PV pressure measurement. Hepatic vein (HV) cannulation was achieved via the right external jugular vein, the location of the catheter tip being confirmed by direct palpation; the catheter was withdrawn about 5 mm from a 'wedged' position for 'free' HV pressure measurement.

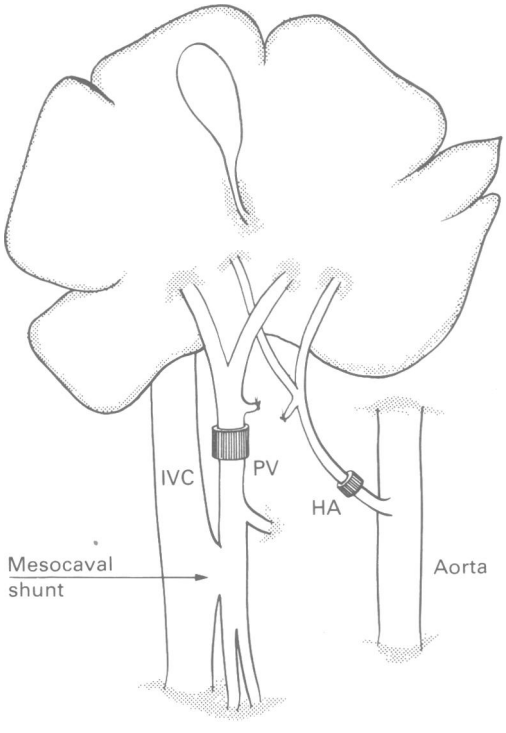

Figure 1 Diagrammatic illustration of experimental preparation, showing electromagnetic flow probes on hepatic artery (HA) and portal vein (PV), and position of the mesocaval shunt which allows diversion of PV blood into the inferior vena cava (IVC) during periods of PV occlusion. (Reproduced from Mathie *et al.*, 1980, by permission of Springer-Verlag).

A side-to-side mesocaval shunt was formed, using 5/0 silk suture, by the construction of an anastomosis between the inferior vena cava and the superior mesenteric vein, just below the entry of the splenic vein (Figure 1). After haemostasis had been obtained, the shunt was closed by means of a small bulldog clip placed along the suture line, thus restoring normal PV flow to the liver until the start of the experimental measurements.

Experimental protocol

The effect of PV flow interruption was investigated approximately 1 h following the operation. Measurements were made of the basal HA and PV blood flows and the pressures in the femoral artery, PV and HV, prior to any alterations in blood flow. The PV was then cross-clamped just proximal to the flow probe, and the shunt immediately opened. The PV occlusion was maintained for approximately 10 min, at which time blood flow and pressure measurements were repeated. PV flow was then restored by reclosing the shunt with the bulldog clip after release of the cross-clamp on the PV. These manoeuvres were repeated in order to obtain duplicate information on the magnitude of the 'buffer response'.

In 6 dogs the effect of intravenous adrenaline (Phoenix Pharmaceuticals) was then investigated to establish the normal response of the HA circulation to adrenergic stimulation. Doses in the vasodilator range (0.02–2.56 $\mu g\,kg^{-1}$, i.v.) were chosen. The peak of the hyperaemic response to adrenaline injection was plotted against the dose employed in each case.

Propranolol (ICI) was then administered at a loading dose of 0.3 $mg\,kg^{-1}$, i.v., followed by an infusion at 0.3 $mg\,kg^{-1}\,min^{-1}$ for the remainder of the experiment. After 30 min, two further 'buffer responses' were elicited for comparison with the control response. Potency of the β-blockade was confirmed immediately after the second 'buffer response' by the construction of a further adrenaline dose-response curve.

Calculations

Blood flows were recorded on the flowmeters in $ml\,min^{-1}$ and subsequently recalculated in ml $100\,g^{-1}\,min^{-1}$ by relating the readings to the wet weight of the liver, determined at the end of each experiment. Total liver blood flow was calculated by addition of the individual HA and PV flows.

The 'buffer capacity' (or 'buffering efficiency') of the HA was calculated as the increase in HA flow/decrease in PV flow and expressed as a percentage.

Vascular resistance for the HA, PV and mesenteric vasculature were calculated in the normal manner (Hughes *et al.*, 1979).

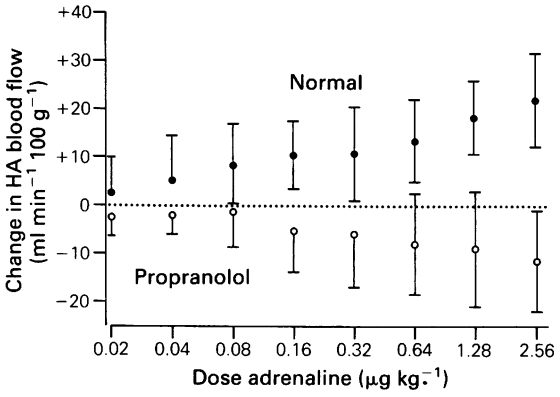

Figure 2 Hepatic arterial (HA) blood flow response to increasing doses of adrenaline i.v. before (●) and after (○) propranolol in 6 dogs.

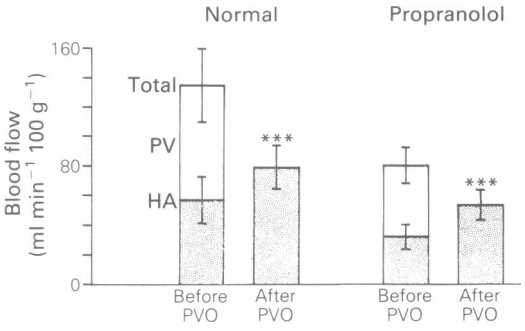

Figure 3 Effect of portal venous (PV) occlusion on liver blood flow before and after propranolol in 6 dogs. Before PV occlusion (PVO), total liver blood flow comprises both PV and hepatic arterial (HA) components; during PVO there remains only HA blood flow (shaded areas). *** Significant difference from baseline HA flow ($P < 0.001$).

Statistics and presentation of data

Student's paired t test was used to test the significance of (a) the differences in measured parameters before and after PV occlusion, and (b) the differences in the magnitude of responses before and after propranolol administration. All results are quoted as mean ± s.e.mean.

Results

Dose-response to adrenaline

The changes in HA blood flow produced by adrenaline in 6 dogs before and after propranolol are illustrated in Figure 2. It is evident that increasing doses of adrenaline caused increasing dilatation of the HA, and that propranolol inhibited the flow increase, thus indicating effective β-adrenoceptor blockade. This is confirmed by the systemic arterial blood pressure changes due to adrenaline. Before propranolol these showed a 10–20 mmHg decrease at each adrenaline dose up to 0.32 $\mu g\,kg^{-1}$ followed by a 10–30 mmHg increase at the three highest doses, whereas after propranolol there was an increase in pressure at every dose of adrenaline used, implying absence of β-mediated vasodilatation.

Hepatic artery 'buffer response'

In the normal situation, PV occlusion caused HA blood flow to increase by 22.0 ± 1.9 ml $100\,g^{-1}\,min^{-1}$; after propranolol, the increase remained essentially unchanged at 21.0 ± 1.8 ml $100\,g^{-1}\,min^{-1}$ (Figure 3). In both instances, the increase was statistically significant ($P < 0.001$). However, the basal HA flow was significantly different in the two groups (57.5 ± 15.4 and 31.7 ± 7.5 ml $100\,g^{-1}\,min^{-1}$ respectively). Baseline PV blood flow was significantly reduced by propranolol from 77.4 ± 9.9 to 47.5 ± 6.4 ml $100\,g^{-1}\,min^{-1}$ ($P < 0.05$). Total liver blood flow was also significantly reduced by propranolol (134.9 ± 25.0 cf. 79.2 ± 13.1 ml $100\,g^{-1}\,min^{-1}$; $P < 0.05$); the magnitude of decrease caused by PV occlusion was smaller after propranolol (55.4 ± 10.5 cf. 26.5 ± 5.6 ml $100\,g^{-1}\,min^{-1}$; $P < 0.05$) due to the smaller baseline PV flow in the latter situation. Interestingly, the 'buffer capacity' of the HA increased from 31.1 ± 5.0% in the normal situation to 50.1 ± 8.6% after propranolol, but this increase was not statistically significant; the difference from normal was primarily due to the smaller baseline PV flow following propranolol infusion.

Mean arterial blood pressure did not change significantly from baseline levels during PV occlusion with or without propranolol infusion. However, there was a small, non-significant decrease in baseline arterial pressure (Table 1), attributable to the systemic actions of propranolol. HV pressure remained unaltered by any procedure (Table 1). Similarly, basal PV pressure was not affected by propranolol administration (Table 1). The effects of PV occlusion on prehepatic venous pressure could not be assessed due to the absence of a recording catheter below the cross-clamp.

The changes in HA vascular resistance were reciprocal to those of HA blood flow (Table 1). There was a significant increase in basal HA resistance due to propranolol ($P < 0.05$). Propranolol also caused an increase in both portal and mesenteric baseline vascular resistances, though only the latter was statistically significant (Table 1); mesenteric vascular resistance was not calculated during the

Table 1 Pressure and vascular resistance measurements during hepatic artery (HA) 'buffer response' before and after propranolol in 6 dogs

	Normal		*Propranolol*	
	Before PV occlusion	*During PV occlusion*	*Before PV occlusion*	*During PV occlusion*
Blood pressure (mmHg)	123.2 ± 8.4	123.8 ± 8.7	109.8 ± 5.4	109.7 ± 5.9
PV pressure† (mmHg)	6.3 ± 0.5	(4.1) ± (0.6)	6.9 ± 0.7	(5.2) ± (0.7)
HV pressure (mmHg)	4.0 ± 0.4	3.7 ± 0.3	4.7 ± 0.4	4.8 ± 0.4
HA resistance ($mmHg\,ml^{-1}\,100\,g^{-1}\,min^{-1}$)	3.4 ± 1.2	1.8 ± 0.3	5.2 ± 1.5*	2.2 ± 0.3
PV resistance ($mmHg\,ml^{-1}\,100\,g^{-1}\,min^{-1}$) × 10^{-2}	3.1 ± 0.9	—	4.7 ± 1.8	—
Mesenteric vascular resistance§ ($mmHg\,ml^{-1}\,min^{-1}$)	0.31 ± 0.03	—	0.45 ± 0.03*	—

PV: portal vein; HV: hepatic vein.
* Significant difference from normal baseline value ($P < 0.05$).
† PV pressure measurements after PV occlusion do not represent prehepatic pressure readings, due to the position of the recording catheter (see text).
§ Mesenteric resistance calculations after PV occlusion were not possible because flow through the anastomosis was not measured (see also text).
All values are mean ± s.e.mean.

'buffer response' since PV flow through the anastomosis was not measured.

Effect of controlled hypotension on hepatic artery 'buffer response'

In another series of experiments the effect of haemorrhagic hypotension on the magnitude of the HA 'buffer response' was examined in 5 mongrel dogs. The animals were bled from the femoral artery until arterial blood pressure remained steady at 75% of control values. Results showed that the 'buffer response' remained at a normal magnitude ($17.5\,ml\,100\,g^{-1}\,min^{-1}$) despite the reduction in blood pressure; hypotension *per se* did not diminish HA blood flow (see Table 2).

Discussion

This study has demonstrated the absence of any significant change in the magnitude of the HA hyperaemic response to PV occlusion following β-adrenoceptor blockade. We can therefore conclude it is unlikely that activation of hepatic β-receptors is of any significance in the normal 'buffer response' of the HA, either through an intrinsic neural vasodilator mechanism or by circulating catecholamines. This conclusion is in contrast to that proposed by Fischer *et al.* (1970), who suggested that β-receptor stimulation played an important, though not exclusive role. However, these authors observed a reduction in the response after propranolol in only 5 out of 11 dogs studied; the remaining animals did not show any change in response from controls

Table 2 Effect of portal vein (PV) occlusion in 5 dogs subjected to haemorrhagic hypotension

	Control	*Hypotension alone*	*Hypotension + PV occlusion*
Blood pressure (mmHg)	121.0 ± 6.9	91.6 ± 5.1*	87.4 ± 3.7*
HA blood flow ($ml\,100\,g^{-1}\,min^{-1}$)	29.6 ± 7.2	28.3 ± 5.1	45.8 ± 5.7†*
PV blood flow ($ml\,100\,g^{-1}\,min^{-1}$)	62.0 ± 10.7	32.0 ± 6.6*	—
HA resistance ($mmHg\,ml^{-1}\,100\,g^{-1}\,min^{-1}$)	3.8 ± 0.9	2.8 ± 0.5	1.5 ± 0.2†*
PV resistance ($mmHg\,ml^{-1}\,100\,g^{-1}\,min^{-1}$) × 10^{-2}	8.4 ± 3.0	19.6 ± 8.5	—

For abbreviations see Table 1, except: * significant difference from control ($P < 0.05$); † significant difference from hypotension alone ($P < 0.05$).

although greater doses of propranolol were administered. The standard dose administered in Fischer's investigations was identical to that used in the present study, but the experimental model differed: diversion of PV blood was achieved via a portofemoral shunt and it is not clear from their published description if the degree of diversion was controlled in a reproducible way. We suggest, therefore, that the report did not conclusively demonstrate the partial involvement of β-adrenoceptors as claimed by the authors. The relatively high dose of propranolol used in the present study conformed with that employed by Fischer and demonstrated that β-adrenoceptors play little or no part in the response. Indeed, this dose of propranolol transformed the HA response to exogenous adrenaline from vasodilatation to vasoconstriction.

The experimental model used in the present work has been employed in several previous studies by our group: it achieves complete PV occlusion in a repeatable manner without loss of systemic venous return or development of arterial hypotension (Mathie *et al.*, 1980; Mathie & Blumgart, 1983; 1987). The magnitude of the HA 'buffer response' is also highly reproducible with repeat observations in individual animals: in a series of 17 normal dogs, a repeat 'buffer response' was only 1.1% smaller than the first measurement (18.6 ± 1.8 ml $100\,g^{-1}\,min^{-1}$ and 18.8 ± 1.8 ml $100\,g^{-1}\,min^{-1}$ respectively; R.T. Mathie and B. Alexander, unpublished observations).

Propranolol infusion resulted in a small decrease in arterial blood pressure, an increase in HA, PV and mesenteric vascular resistance and a decrease in HA and PV blood flow. If it is assumed that the drug produced a generalised peripheral vasoconstriction, it may be surmised that the slight drop in mean blood pressure was the result of a significant fall in cardiac output, a noted action of propranolol (Lebrec *et al.*, 1982). The reduced values of basal HA and PV blood flow after propranolol administration did not influence the absolute magnitude of the HA flow increase during PV occlusion. We believe that such basal haemodynamic conditions do not compromise our conclusions regarding the absence of β-receptor involvement, since the results of our other experiments demonstrated a normal 'buffer response' of 17.5 ml $100\,g^{-1}\,min^{-1}$ even after 25% reduction of mean arterial blood pressure by controlled haemorrhage.

Propranolol administration in our experiments caused a substantial increase in the 'buffer capacity' of the HA from 31% to 50%. This was felt to be a feature solely of the reduced basal PV blood flow and was not taken to imply an increased hyperaemic response of the HA *per se*. The figures may, nevertheless, be advanced as supportive evidence for the conclusion that the response is not diminished by propranolol.

It is known that both α- and β-adrenoceptors exist in the HA (Richardson & Withrington, 1981). The effect of adrenaline is complicated by the dose-dependency of its action on α- and β-receptors: at low blood concentrations, vasodilatation predominates, whereas at higher concentrations vasoconstriction occurs. Only dilatation was observed at the concentrations used in the present study (below $10\,\mu g\,kg^{-1}$, i.v.), which ensured a valid basis for comparison of the haemodynamic response before and after β-blockade and for assessment of its potency. By contrast, Richardson & Withrington (1977) found predominantly vasoconstriction of the HA, but at a higher effective dose than in the present experiment since the adrenaline was injected intra-arterially. However, their observation that propranolol potentiated the basal vasoconstrictor response supports the present findings. We used adrenaline in preference to the more selective β-agonist isoprenaline in our study because of the more profound effects of the latter on systemic haemodynamics: it produces generalised vasodilatation and causes a fall in blood pressure coupled with a marked increase in heart rate (Bowman *et al.*, 1975). In addition, the dilator action of adrenaline on the HA has been more extensively documented than isoprenaline (Richardson & Withrington, 1981). The selection of adrenaline was vindicated by the modest changes in blood pressure observed at the doses used and by the unequivocal effect of propranolol on the dose-response curve.

The current study has also provided further data relating to the effect of propranolol on PV pressure and blood flow. Propranolol has recently been used as a means of decreasing PV pressure in order to reduce the risk of variceal bleeding in patients with portal hypertension (Lebrec *et al.*, 1980; Bercoff *et al.*, 1984; Ohnishi *et al.*, 1985), though not with universal success (Burroughs *et al.*, 1983; Anderberg *et al.*, 1984). One mode of action is thought to be related to its vasoconstrictor action on the mesenteric vascular bed, caused by β_2-adrenoceptor blockade, which results in a fall in PV blood flow and pressure (Kroeger & Groszmann, 1985; Jenkins *et al.*, 1985). However, in the current series of investigations PV (and HV) pressure remained unaltered despite a decrease in PV flow. This effect may be a result of the increase in intrahepatic PV resistance; it is widely believed that the PV vascular bed contains α- but not β-adrenoceptors (Richardson & Withrington, 1981), and therefore it is not evident why PV resistance should have increased during β-blockade in this preparation.

Propranolol can also produce a decrease in PV pressure by a reduction in PV flow as a result of a fall in cardiac output (Lebrec *et al.*, 1982), due to

β_1-adrenoceptor blockade (Ohnishi *et al.*, 1985). Most authors now conclude that propranolol achieves its reduction in PV flow and pressure through a combination of β_1-adrenoceptor blockade (causing a reduction in cardiac output) and β_2-adrenoceptor blockade (causing a reduction in mesenteric blood flow) (Hillon *et al.*, 1982; Kroeger & Groszmann, 1985; Jenkins *et al.*, 1985).

It is probable that blood flow in the normal canine liver behaves in a quite different manner from the human cirrhotic hepatic circulation, but our results do indicate some caution in the administration of propranolol during treatment of portal hypertension in man. Recent haemodynamic studies in dogs with chronic bile duct ligation and portal hypertension have demonstrated minimal hepatic circulatory or pressure effects of propranolol despite significant systemic responses (Willems *et al.*, 1986). As these authors stated, 'the factors responsible for the discrepancy between man and dog are not known.' It is of interest that other authors have demonstrated a significant reduction in PV pressure with propranolol in cirrhotic rats (Jenkins *et al.*, 1985), and it is therefore possible that differences between the dog and other species may be explained by the relative absence of potential portal-systemic collateral vessels in the canine circulation.

This investigation has demonstrated that hepatic β-adrenoceptors have little or no role in the vasodilator response of the HA to PV occlusion. Further studies are currently under way in an attempt to discover the possible mechanisms. The present study has indicated an absence of PV pressure reduction in response to intravenous propranolol injection in the normal dog.

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