

# Splenorenal reflex modulates renal blood flow in the rat

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We have previously shown that the splenorenal reflex controls renin release through splenic afferent and renal sympathetic nerves. We proposed that this reflex would also affect renal blood flow (RBF). RBF was measured in male Long Evans rats using transit-time flow probes. There were no significant differences between any of the experimental groups with respect to baseline values of RBF ( $8.9 \pm 0.4 \text{ ml min}^{-1}$ ,  $n = 25$ ) or mean arterial pressure (MAP,  $98.7 \pm 2.5 \text{ mmHg}$ ,  $n = 25$ ). Splenic venous pressure was selectively raised (from  $7.9 \pm 0.6$  to  $21.6 \pm 0.3 \text{ mmHg}$ ,  $n = 25$ ) in anaesthetized rats by partial ligation of the splenic vein. This caused an immediate fall in RBF ( $-2.1 \pm 0.2 \text{ ml min}^{-1}$ ,  $n = 7$ ) and in MAP ( $-12.4 \pm 2.8 \text{ mmHg}$ ,  $n = 7$ ). The fall in RBF, but not the fall in blood pressure, was attenuated by renal denervation ( $\Delta\text{RBF}$ :  $-0.7 \pm 0.1 \text{ ml min}^{-1}$ ,  $n = 6$ ), splenic denervation ( $\Delta\text{RBF}$ :  $-0.8 \pm 0.1 \text{ ml min}^{-1}$ ,  $n = 6$ ) and close renal arterial injection of the  $\alpha_1$ -adrenergic blocker phenoxybenzamine ( $12.5 \mu\text{g}$ ;  $\Delta\text{RBF}$ :  $-0.8 \pm 0.1 \text{ ml min}^{-1}$ ,  $n = 6$ ). Renal conductance fell only in the intact control group, i.e. the residual fall in RBF in the denervated and phenoxybenzamine-treated animals could be attributed to the fall in MAP. We also showed that splenic vein occlusion increased both splenic afferent (from  $3.0 \pm 0.3$  to  $6.6 \pm 0.6 \text{ spikes s}^{-1}$ ,  $n = 5$ ) and renal efferent (from  $24.8 \pm 2.0$  to  $50.2 \pm 4.9 \text{ spikes s}^{-1}$ ,  $n = 9$ ) nerve activity. We conclude that obstruction to splenic venous outflow, such as would occur in portal hypertension, initiates increased splenic afferent nerve activity and renal vasoconstriction through the splenorenal reflex, as well as a fall in blood pressure. We propose that this contributes to the renal and cardiovascular dysfunction observed in portal hypertension.

(Received 26 February 2004; accepted after revision 13 April 2004; first published online 16 April 2004)

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Portal hypertension is defined as a pathological increase in portal venous pressure to above 10 mmHg (Gupta *et al.* 1997; Henderson *et al.* 1998). Cirrhotic/portal hypertensive patients have elevated levels of noradrenaline in the renal venous blood (Henriksen *et al.* 1984), as well as significantly lower baseline mean renal blood flow levels compared to control subjects; this is indicative of increased renal sympathetic tone (Gatta *et al.* 1982). These changes in renal haemodynamics in cirrhotic patients appear to be functional, i.e. there is no intrinsic renal disease (Koppel *et al.* 1969). Several studies have investigated the hepatorenal reflex whereby elevation of portal venous pressure causes increased hepatic afferent nerve activity, reflex increases in renal and cardiopulmonary sympathetic efferent nerve activity (DiBona & Sawin, 1995; Kostreva *et al.* 1980) and decreased renal blood flow (Jalan *et al.* 1997). In addition, acute superior mesenteric vein occlusion has also been shown to reduce renal blood flow, suggesting possible involvement of an intestinal–

renal neural reflex (Miller *et al.* 1983). Thus, it has been proposed that altered neural reflexes mediate the abnormal renal haemodynamics observed in portal hypertension.

Blood from the splenic vein drains into the portal vein. Thus an increase in portal venous pressure causes a concomitant rise in splenic venous pressure. We wished to investigate whether changes in intrasplenic haemodynamics also alter renal function. There is both structural and functional evidence for a neural reflex pathway between the spleen and the kidneys (Herman *et al.* 1982; Calaresu *et al.* 1984; Meckler & Weaver, 1988; Deng & Kaufman, 2001). We proposed, therefore, that derangement of renal function in portal hypertension may be mediated by a splenorenal neurogenic reflex, whereby elevated portal and splenic venous pressure would increase splenic afferent nerve activity, which would induce an increase in efferent renal sympathetic nerve activity and decrease renal blood flow. In order to isolate the spleen as the initiator of the

splenorenal reflex, we partly occluded the splenic vein to elevate splenic venous pressure to the degree observed in portal hypertension; this did not cause any obstruction to portal venous flow. The effects of renal denervation, splenic denervation, and pharmacological blockade of intrarenal  $\alpha_1$ -adrenergic receptors were studied. In addition, we measured the changes in splenic afferent and renal efferent nerve activity elicited by splenic venous occlusion.

## Methods

The experimental procedures were approved by the local Animal Welfare Committee in accordance with the guidelines issued by the Canada Council on Animal Care. All animals were killed with an anaesthetic overdose of pentobarbitone sodium (96 mg, i.v., MTC Pharmaceuticals, Cambridge, Ontario, Canada) at the completion of each experiment. All data were recorded online (DATAQ Instruments, Akron, Ohio, USA) and analysed using WINDAQ software (DATAQ Instruments).

## Animals

Male Long-Evans rats (350–600 g, Charles River, Montreal, Quebec, Canada) were housed in the University of Alberta Animal Facility for at least 1 week before experiments started. They were exposed to a 12 h–12 h light–dark cycle in a temperature- and humidity-controlled room. All rats were fed standard 0.3% sodium rat chow and water *ad libitum*. There were four experimental groups: intact control rats ( $n = 7$ ), renal denervated rats ( $n = 6$ ), splenic denervated rats ( $n = 6$ ) and phenoxybenzamine-treated rats ( $n = 6$ ).

## Surgery

Anaesthesia was induced with pentobarbitone sodium ( $60 \text{ mg (kg body weight)}^{-1}$ , i.p.), followed 1 h later by Inactin (Sigma, Canada; ethyl-(methyl-propyl)-malonyl-thio-urea,  $80 \text{ mg (kg body weight)}^{-1}$ , s.c.). Body temperature was maintained at  $37^\circ\text{C}$  with a homeothermic blanket (Harvard Apparatus).

The femoral vein and artery were cannulated with Silastic™ (Dow Corning, 0.51 mm i.d., 0.94 mm o.d.) and polyethylene tubing (VWR International, Mississauga, Ontario, Canada, PE 50, 0.58 mm i.d., 0.97 mm o.d.) for administration of isotonic saline ( $3 \text{ ml h}^{-1}$ ) and monitoring of systemic blood pressure, respectively. Through a mid-line laparotomy, the gastric and renal vessels were exposed. A Silastic™ cannula (Dow Corning, 0.30 mm i.d., 0.64 mm o.d.) was inserted occlusively into the gastric vein, advanced until the tip lay at the junction with the splenic vein, and

secured with a drop of Vetbond tissue glue (3M Animal Care Products, St. Paul, MN, USA). This cannula was connected to a pressure transducer for online monitoring of splenic venous pressure.

A Prolene 0.7 loop (Ethicon, USA) was placed loosely around the splenic vein at its junction with the portal vein; this allowed for controlled partial occlusion of the splenic vein. Similarly, a loose ligature (Prolene 1.5) was placed around the hepatic portal vein (rostral to the junction with the splenic vein), to induce portal hypertension; in this case, a cannula (polyethylene, 0.58 mm i.d., 0.97 mm o.d.) was inserted non-occlusively into the portal vein, and secured with tissue adhesive (3M Vetbond, Animal Care Products) to monitor portal venous pressure.

In renal denervation experiments, the renal nerves were stripped from the left renal artery and vein as previously described (Kaufman & Stelfox, 1987). Similarly, in splenic denervation experiments, the splenic nerves were stripped from the splenic artery and vein, distal to branching of the vessels toward the spleen (Andrew *et al.* 2001).

## Renal blood flow (RBF)

A factory-calibrated flow probe (1RB series, Transonic Systems, Ithaca, NY, USA) was placed around the left renal artery and covered in conducting jelly. A 35–40 min stabilization time was allowed, during which time body temperature, mean arterial pressure (MAP) and RBF were monitored. Baseline values of RBF, MAP and splenic venous pressure were then recorded for 20 min, after which tension was applied to the splenic venous ligature to raise splenic venous pressure to 20–24 mmHg. Splenic venous pressure, MAP and RBF were recorded for a further 20 min.

Phenoxybenzamine ( $12.5 \mu\text{g}$  in  $150 \mu\text{l}$  heparinized isotonic saline, Sigma, Canada) was administered over 30 s into the renal artery with application of vibration to ensure even distribution throughout the kidney (Hamza & Kaufman, 2004). After a stabilization period of 20–25 min, the effect of splenic venous occlusion on RBF was measured as described above. At the end of each experiment, it was confirmed that the phenoxybenzamine had completely blocked intrarenal  $\alpha_1$ -adrenergic receptors; the  $\alpha_1$ -adrenergic agonist phenylephrine ( $0.15 \mu\text{g}$  in  $150 \mu\text{l}$  heparinized isotonic saline, Sabex, Boucherville, Quebec, Canada) did not cause any change in RBF.

## Extracellular nerve recording

Separate groups of rats were used for these experiments. Nerve recordings were performed as previously described (Kaufman & Levasseur, 2003). The abdominal cavity was

filled with mineral oil, and the splenic nerve isolated and cut. Splenic sensory afferent nerve activity was measured by placing the distal end of a small nerve fibre (closer to the spleen) onto bipolar platinum recording electrodes, and covering them with Kwik-Cast (WPI, Sarasota, FL, USA). The nerve signal was amplified and filtered between 100 and 1000 Hz (Leaf Electronics Ltd QT-B; WPI LPF-30, Sarasota, FL, USA). Output from the amplifier was fed to a loudspeaker and displayed on a PC (sampling rate between 3 and 10 kHz, WINDAQ, DATAQ Instruments, Akron, OH, USA). After stabilization (20 min), afferent nerve activity was recorded online. Twenty minutes later, the splenic venous ligature was tightened until splenic venous pressure measured between 20 and 24 mmHg. Nerve recording continued for a further 20 min. A similar procedure was used to measure renal efferent nerve activity except that, in this case, the *proximal* end (closer to the spinal cord) of a small severed nerve fibre was placed on the recording electrodes. The analysis of nerve discharge was based on average discharge rate (spikes  $s^{-1}$ ) of visually identified action potentials in the raw filtered recordings (Fig. 1).

### Drugs

Phenoxybenzamine (Sigma, Canada) was dissolved in heparinized isotonic saline (heparin 10 000 IU  $l^{-1}$ ) at a concentration of 12.5  $\mu g$  in 150  $\mu l$ . This dose of phenoxybenzamine has previously been shown to block intrarenal  $\alpha$ -adrenergic receptors (Smyth *et al.* 1984). Phenylephrine hydrochloride (Sabex, Canada; 10 mg  $ml^{-1}$ ) was diluted with heparinized isotonic saline (heparin 10 000 IU  $l^{-1}$ ) to a final concentration of 0.15  $\mu g$  in a 150  $\mu l$  volume.

### Data analysis

Results are based on the last 10 min of each 20 min recording period described above. The data were analysed using Student's paired *t* test, or ANOVA followed by Student–Newman–Keuls *post hoc* test. Significance was accepted at  $P < 0.05$ .

## Results

### Splenic venous pressure

Preliminary experiments revealed that, when portal venous pressure was increased from  $3.9 \pm 0.4$  to  $13.6 \pm 0.3$  mmHg, there was an accompanying increase in splenic venous pressure from  $10.1 \pm 0.8$  to  $23.0 \pm 0.7$  mmHg ( $n = 5$ ). In the subsequent series

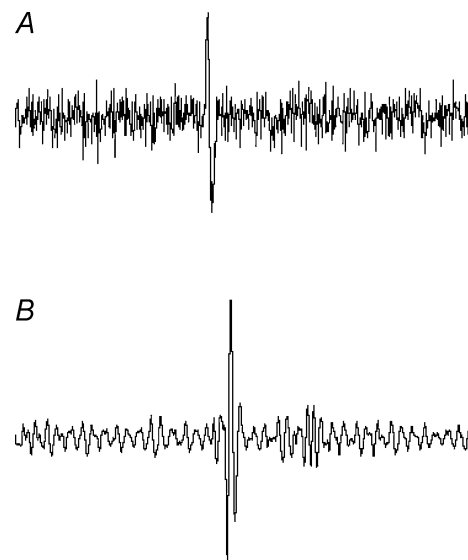
of experiments, mean baseline splenic venous pressure for all the animals was  $7.9 \pm 0.6$  mmHg ( $n = 25$ ). This was increased to 20–24 mmHg (mean,  $21.6 \pm 0.3$  mmHg,  $n = 25$ ) by partial occlusion of the splenic vein, i.e. to that pressure which would be associated with a portal venous pressure of 12–15 mmHg. There were no significant differences between the four experimental groups with regard to the baseline or experimental splenic venous pressures.

### Renal blood flow

Mean baseline RBF for all the animals was  $8.9 \pm 0.4$  ml  $min^{-1}$  ( $n = 25$ ). There were no significant differences between the baseline renal blood flows for any of the four experimental groups (Fig. 2). When splenic venous pressure was increased, there was an immediate decrease in RBF in the intact animals ( $-2.1 \pm 0.2$  ml  $min^{-1}$ ,  $n = 7$ ; Fig. 2). This response was greatly attenuated after renal denervation ( $-0.7 \pm 0.1$  ml  $min^{-1}$ ,  $n = 6$ ), after splenic denervation ( $-0.8 \pm 0.1$  ml  $min^{-1}$ ,  $n = 6$ ) and after intrarenal administration of phenoxybenzamine ( $-0.8 \pm 0.1$  ml  $min^{-1}$ ,  $n = 6$ ; Fig. 2).

### Mean arterial pressure

Mean baseline MAP for all the animals was  $98.7 \pm 2.5$  mmHg ( $n = 25$ ). There were no significant differences between the baseline values for any of the four experimental groups (Fig. 3). Moreover, the fall



**Figure 1. Raw recordings of action potentials**

A, recordings from splenic afferent nerves (sampling rate, 10 kHz). B, recordings from renal efferent nerves (sampling rate, 3.3 kHz).

in MAP during splenic vein occlusion did not differ significantly between the intact ( $-12.4 \pm 2.8$  mmHg,  $n = 7$ ), renal denervated ( $-8.3 \pm 1.9$  mmHg,  $n = 6$ ), splenic denervated ( $-8.2 \pm 1.5$  mmHg,  $n = 6$ ) and phenoxybenzamine-treated animals ( $-5.0 \pm 0.33$  mmHg,  $n = 6$ ; Fig. 3). Although the baseline MAP and the fall in pressure tended to be lower in the phenoxybenzamine-treated animals, this did not reach significance (baseline MAP,  $P = 0.306$ ; change in MAP,  $P = 0.133$ ).

### Renal conductance

Renal conductance ( $K$ ) was calculated as the ratio of flow ( $\dot{Q}$ ) to renal perfusion pressure ( $P$ ):  $K = \dot{Q}/P$ . There was a significant fall in renal conductance (from  $0.088 \pm 0.011$  to  $0.079 \pm 0.014$  ml min<sup>-1</sup> mmHg<sup>-1</sup>,  $n = 7$ ) in intact

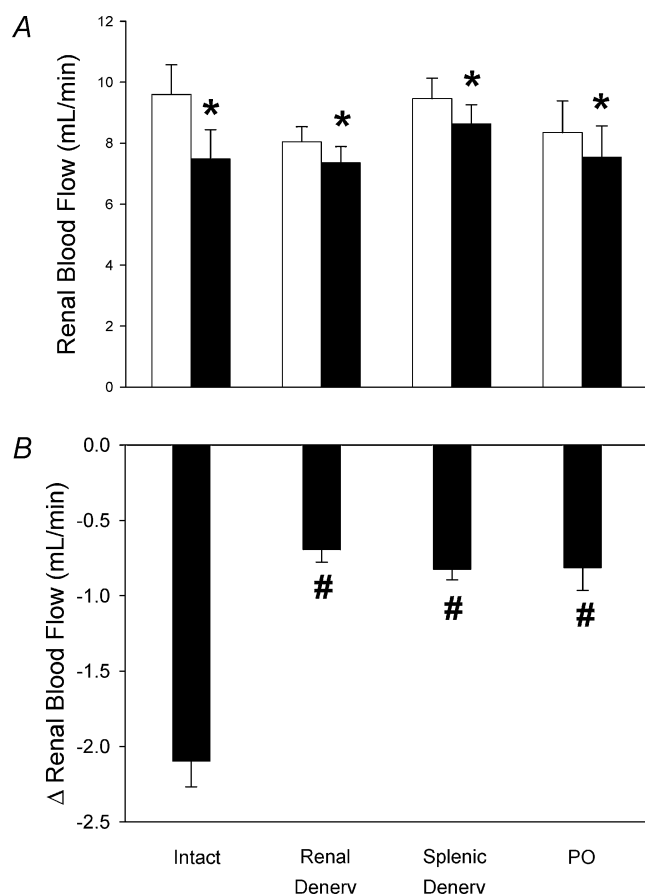
animals during splenic vein occlusion. However, there was no such change in the renal denervated (from  $0.086 \pm 0.011$  to  $0.086 \pm 0.012$  ml min<sup>-1</sup> mmHg<sup>-1</sup>,  $n = 6$ ), splenic denervated (from  $0.094 \pm 0.008$  to  $0.094 \pm 0.009$  ml min<sup>-1</sup> mmHg<sup>-1</sup>,  $n = 6$ ), or phenoxybenzamine-treated animals (from  $0.092 \pm 0.012$  to  $0.088 \pm 0.013$  ml min<sup>-1</sup> mmHg<sup>-1</sup>,  $n = 6$ ).

### Nerve activity

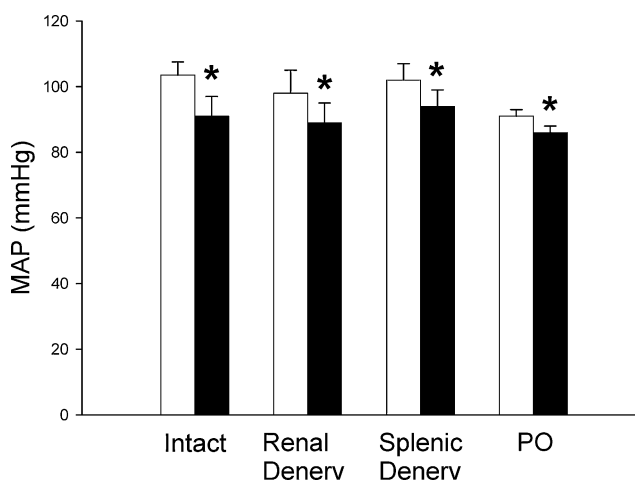
Increased splenic venous pressure (partial splenic vein occlusion) caused an immediate and significant increase both in splenic afferent (from  $3.0 \pm 0.3$  to  $6.6 \pm 0.6$  spikes s<sup>-1</sup>,  $n = 5$ ) and renal efferent nerve activity (from  $24.8 \pm 2.0$  to  $50.2 \pm 4.9$  spikes s<sup>-1</sup>,  $n = 9$ ; Fig. 4).

### Discussion

Splenic venous occlusion caused an immediate fall in RBF, which was attenuated by renal denervation, splenic denervation and close renal arterial injection of the  $\alpha_1$ -adrenergic blocker phenoxybenzamine. This was accompanied, in all groups, by a fall in MAP. Renal conductance fell only in the intact group. We also showed that splenic vein occlusion increased both splenic sensory afferent and renal efferent nerve activity. We conclude that obstruction to splenic venous outflow, such as would occur in portal hypertension, increases splenic sensory afferent nerve activity and renal sympathetic nerve activity through the *spleno renal* reflex. This causes renal vasoconstriction



**Figure 2.** Effect of partial splenic vein ligation on RBF of intact ( $n = 7$ ), renal denervated (Renal Denerv,  $n = 6$ ), splenic denervated (Splenic Denerv,  $n = 6$ ) and intrarenal phenoxybenzamine-treated (PO,  $12.5 \mu\text{g}$ ,  $n = 6$ ) rats. A, RBF before (■) and after (□) partial splenic venous occlusion. B, change in RBF during partial splenic venous occlusion. Data are presented as means  $\pm$  s.e.m. \*Significant change in renal blood flow,  $P < 0.05$ . #Significant difference compared with intact group,  $P < 0.05$ .



**Figure 3.** Effect of partial splenic vein ligation on MAP of intact ( $n = 7$ ), renal denervated (Renal Denerv,  $n = 6$ ), splenic denervated (Splenic Denerv,  $n = 6$ ) and intrarenal phenoxybenzamine-treated (PO,  $12.5 \mu\text{g}$ ,  $n = 6$ ) rats. □, baseline values; ■, values during partial splenic venous occlusion. The data are presented as means  $\pm$  s.e.m. \*Significant difference between baseline MAP and MAP during partial splenic vein ligation,  $P < 0.05$ .

and a fall in RBF. There is also a fall in systemic blood pressure.

Portal hypertension is associated with perturbations of renal function which are mediated, at least in part, through the renal sympathetic nerves (Anderson *et al.* 1976). There is evidence that several neurogenic pathways are involved. The *hepatorenal* reflex has been shown to regulate RBF (Jalan *et al.* 1997; Kew *et al.* 1972); portal vein occlusion increases hepatic sensory afferent nerve activity and induces reflex increases in renal sympathetic nerve activity (Kostreva *et al.* 1980). It has also been shown that, in dogs, acute occlusion of the superior mesenteric vein causes a reduction in renal arterial blood flow (Miller *et al.* 1983). The authors concluded that increased mesenteric outflow pressure, as would be associated with portal hypertension, initiates an *intestinal-renal* neural reflex. The model used in the present study, ligation of the splenic vein, does not cause any changes in portal venous pressure or mesenteric vascular pressure. The reflex changes we observed in RBF were thus initiated by the spleen, there being no direct contribution from the liver or intestines.

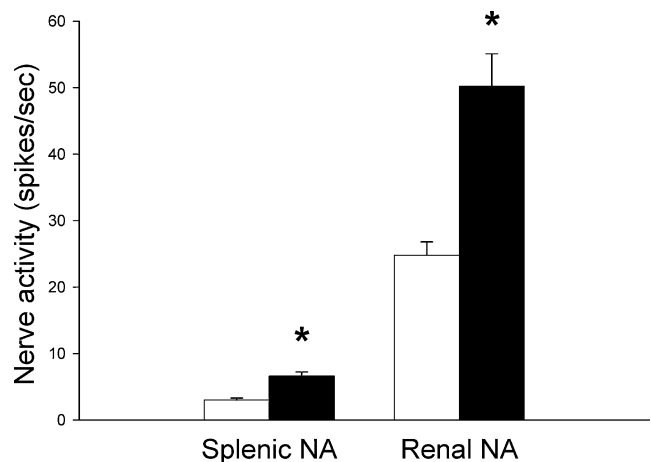
$\alpha_1$ -Adrenergic receptors mediate renal vasoconstriction (Schmitz *et al.* 1981). The dose of phenoxybenzamine (12.5  $\mu\text{g}$ ), an irreversibly binding receptor antagonist, was chosen to completely block renal  $\alpha_1$ -adrenergic receptors, but to have minimal systemic effects (Harvey & Nickerson, 1954; Smyth *et al.* 1984). We verified that the intrarenal  $\alpha_1$ -adrenergic receptors were indeed blocked, by administering intrarenal phenylephrine at a dose (0.15  $\mu\text{g}$ ) known normally to cause significant renal vasoconstriction (Hamza & Kaufman, 2004). However, there was probably some phenoxybenzamine spillover into the systemic circulation. Although baseline MAP tended to be lower in the phenoxybenzamine-treated animals, this did not reach significance (which may reflect the limited sample size rather than lack of any systemic effect). This does not, however, detract from our finding that, in the phenoxybenzamine-treated animals, there was still a significant fall in blood pressure in response to splenic vein ligation.

We had hypothesized that phenoxybenzamine would block the effects of the renal sympathetic nerves on the renal arterioles, and prevent the drop in RBF seen after splenic venous occlusion. While it has previously been shown that phenoxybenzamine administration completely inhibits renal nerve-stimulated vasoconstriction (Chapman *et al.* 1982), administration of phenoxybenzamine in our study attenuated, but did not abolish, the decrease in RBF during splenic venous occlusion. However, given that MAP fell during splenic

venous occlusion, we reasoned that the residual drop in RBF seen in the denervated and phenoxybenzamine-treated animals might have been secondary to the fall in blood pressure. Calculation of renal arterial conductance confirmed that, while conductance fell in the intact animals, there was no such change in the denervated and phenoxybenzamine-treated animals, i.e. the residual decrease in RBF after interruption of the spleno-renal reflex could indeed be accounted for by the fall in renal perfusion pressure. One might question why autoregulation did not prevent the fall in renal perfusion pressure from inducing a fall in RBF, given that MAP was within the normal autoregulatory range of the kidney. However, it has been shown that moderate sympathetic activation, such as would have been induced by splenic vein occlusion, raises the lower limit of autoregulatory control of RBF (Persson *et al.* 1990). As such, the fall in MAP could indeed have reduced renal blood flow, without changing renal vascular conductance.

Portal hypertension, induced either by cirrhosis or by portal vein ligation, is associated with a fall in MAP (Albillos *et al.* 1992; Bomzon *et al.* 1993; Kaufman & Levasseur, 2003), which is not blocked by renal denervation (Anderson *et al.* 1976). This is consistent with our observation that the fall in MAP induced by partial splenic vein ligation was likewise not blocked by splenic or renal denervation.

In conclusion, we have demonstrated that obstruction to splenic venous outflow, such as would be associated with portal hypertension, causes a reduction in RBF and a



**Figure 4. Effect of partial splenic vein ligation on splenic afferent (Splenic NA,  $n = 5$ ) and renal efferent (Renal NA,  $n = 9$ ) nerve activity**

□, baseline values; ■, values during partial splenic venous occlusion. Data are presented as means  $\pm$  S.E.M. \*Significant difference between baseline nerve activity and nerve activity during partial splenic vein ligation,  $P < 0.05$ .

fall in MAP. While the change in RBF is neurally mediated through the splenorenal reflex, the fall in systemic blood pressure is unaltered by either splenic or renal denervation. It has previously been established that, in portal hypertension, renal function is influenced by both hepatorenal and intestinal–renal reflex pathways (Jalan *et al.* 1997; Miller *et al.* 1983). We now propose that, in addition, concomitant changes in intrasplenic haemodynamics also initiate splenorenal reflex pathways which contribute to the perturbations in renal and cardiovascular function associated with the condition.

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## Acknowledgements

This research was supported by grants from the Heart and Stroke Foundation of Alberta, NWT and Nunavut. We gratefully acknowledge the technical assistance of Jody Levasseur and Siu Lin Tam for measuring splenic and renal nerve activity.