Mesenteric blood pressure profile of conscious, freely moving rats

Jesper Fenger-Gron, Michael J. Mulvany and Kent L. Christensen

Department of Pharmacology, University of Aarhus, University Park 240, 8000 Aarhus C, Denmark

1. Blood pressure has been measured in the aorta and at four points in the mesenteric circulation of conscious, freely moving rats under physiological, resting conditions.

2. Using small polythene catheters, blood pressure was measured simultaneously in the aorta and either distally in the superior mesenteric artery (group A), at the base of a mesenteric arterial arcade (vessel diameter *ca* 100 μm) (group B), at the base of a mesenteric venous arcade (group C) or distally in the superior mesenteric vein (group D). Local blood flow distribution proximal and distal to the measurement point was restored after the cannulations through appropriate ligations.

3. In conscious animals 5–17 h after surgery, systemic mean blood pressure was 121 $\pm$ 2 mmHg. Local pressures at the four locations (as a percentage of systemic pressure) were: 95 $\pm$ 1% in group A, 64 $\pm$ 2% in group B, 13 $\pm$ 1% in group C and 7 $\pm$ 1% in group D. Thus, large arteries dissipated 5% of the total pressure drop, arcade small arteries 31%, the intramural circulation 51%, arcade veins 6% and the remaining veins plus the hepatic circulation 7%.

4. Immediately after surgery, the corresponding pressure drops were 4, 16, 66, 5 and 9%, respectively, thus emphasizing that the pressure profile can be profoundly affected by surgery and anaesthesia.

5. The data indicate that under resting conditions in conscious, freely moving rats, half the mesenteric vascular resistance resides outside the intramural circulation, primarily in the arcade small arteries.

Although it is now generally agreed that control of blood flow and capillary pressure is mediated not only by the arterioles but also by the more proximal small arteries (Segal & Duling, 1986; Segal, Damon & Duling, 1989; Mulvany & Aalkjær, 1990; Duling, 1991), direct evidence for this under conscious, physiological conditions is lacking (Williams & Segal, 1993). Apart from work using the wing of conscious but restrained bats (Wiederhelm & Weston, 1973; Slaaf, Reneman & Wiederhelm, 1987; Davis, 1988), current evidence is based almost entirely on investigations in anaesthetized animals during surgery, even though it is highly conceivable that necessary surgical procedures may compromise the physiological relevance of such data (Lindbom, Tuma & Arfors, 1982; Meininger, Fehr, Yates, Borders & Granger, 1986; Hill, Simpson & Meininger, 1990; Mulvany & Aalkjær, 1990; Williams & Segal, 1993; Christensen & Mulvany, 1993). Nevertheless, there is now a large body of literature concerned with the *in vitro* characteristics of small arteries (arteries proximal to the arterioles, with diameters < 500 μm; Mulvany & Aalkjær, 1990), the results of which have been interpreted on the basis that these function as resistance vessels (review by Mulvany & Aalkjær, 1990).

On this basis, it was suggested (Bohlen & Aukland, 1991) that efforts should be made to develop methods for measuring blood pressure in small arteries, so that their contribution to flow regulation could be assessed under conscious, physiological conditions. As a first step, we (Christensen & Mulvany, 1993) developed a technique for measuring blood pressure at the base of the mesenteric arterial arcade in conscious, freely moving rats. We found that about one-third of the peripheral resistance was located proximal to this point. The data could not, however, provide information about the distribution of the resistance proximal or distal to the measurement point. The data did not therefore give unequivocal evidence that the small arteries could be considered as resistance vessels.

The purpose of the present work was to obtain direct and more detailed evidence about the distribution of the mesenteric blood pressure drop, and thus to point out the main sites of resistance in the mesenteric circulation. In

particular, considering the widespread interest in the physiology of small arteries (Mulvany & Aalkjær, 1990), we wished to establish whether mesenteric arcade arteries contribute substantially to the peripheral resistance. To achieve this, we have extended our technique (Christensen & Mulvany, 1993, 1994) so that essentially undisturbed blood pressure can be measured at three further key positions of the mesenteric circulation. This has enabled us to establish the blood pressure drop over the superior mesenteric artery, the arcade small arteries, the intramural circulation, and the arcade veins in conscious, freely moving animals. The data indicate that the small arteries in the arcades can indeed be considered as resistance vessels.

Part of the work has been presented previously in abstract form (Fenger-Gron, Mulvany & Christensen, 1995*a*, *b*).

METHODS

Animals

All rats were bred locally from a strain of Wistar rats originating from Moellegaard Breeding Laboratories (Lille Skensved, Denmark) and used at age 14–16 weeks. Prior to experiments, the animals were housed in pairs with a 12 h–12 h light–dark cycle. During experiments, animals were kept in individual cages, and the light–dark cycle was maintained. The experiments were approved by the Danish Committee for Research Animals.

Main experiment

Twenty rats were assigned into four groups (A–D) and then instrumented with two separate polythene catheters for simultaneous measurements of systemic and peripheral blood pressure. These groups did not differ significantly in body weight (A, 374 ± 11 g; B, 385 ± 10 g; C, 380 ± 13 g; D, 362 ± 9 g) or systemic blood pressure (see Results). For surgical procedures, rats were anaesthetized with intraperitoneal methohexital (a barbiturate; 75 mg kg^{-1} + 20 mg kg^{-1} per 20 min of surgery). Ampicillin, (30 mg kg^{-1} intraperitoneally) was given to prevent infection, the wounds were closed and then the rats were allowed to recover. During the measurements, the rats were conscious, free to move and with unlimited access to food pellets and water. After regaining consciousness, the rats were kept under close observation and repetitively examined for signs of disease or discomfort (Svendsen, 1995). Towards the end of the experiments, two rats (one from group C and one from group D) did not appear healthy, and in these animals, the measurements were stopped at 17 h. However, in these two animals as well as in the remaining eighteen, there were no signs of intraperitoneal bleeding or other irregularities at autopsy, performed when the rats had been killed by excision of the heart in deep methohexital anaesthesia immediately after terminating the experiments. Also, at the same time, all catheters were checked and verified as being patent and correctly positioned.

Control experiments

Experiments were performed using other Wistar rats to assess the effect of laparotomy on systemic blood pressure.

First, six rats (average body weight, 358 ± 22 g) had aortic catheters implanted and systemic blood pressure, monitored 5–12 h after surgery, was stable in all rats, with an average value of 122 ± 2 mmHg. Then the entire procedure for distal arcade blood pressure measurements including catheterization and all other preparation procedures (see below) was performed. Systemic blood pressure measured over the period 5–17 h after this second operation was 123 ± 4 mmHg, and thus not different from that measured after the first operation.

Second, in twelve further rats (body weight, 368 ± 13 g) in which only the femoral artery had been cannulated, systemic blood pressure measured during the period from 5–17 h postoperatively was 116 ± 3 mmHg. This was not significantly different from the systemic blood pressure measured during this period in the twenty rats from the main experiment (121 ± 2 mmHg; see below).

Thus, the abdominal surgery did not appear to affect the level at which systemic blood pressure stabilized.

Blood pressure measurements

Blood pressures were measured simultaneously in the aorta and at one of the four mesenteric locations shown in Fig. 1, as described below. After implantation, the two polythene catheters were taken subcutaneously to the nape of the neck where they were extruded together through a dual-channel liquid swivel (375/D20, Scandidact, Denmark), allowing free movement of the rat including rotation around the swivel axis, and connected to separate pressure transducers (Medex Novatrans 2, Simonsen & Weel, Aarhus, Denmark). The transducer signal was preamplified (Hypart Quadramp 10/100, Hypart Biomedical Engineering, Aarhus, Denmark) and recorded on chart paper (Thermal Arraycorder, WR 7730-4, Paratron, Denmark). To keep catheters open, sterile saline containing 20 IU ml^{-1} of heparin was continuously infused at a rate of about 10 $\mu l\ min^{-1}$ in the aortic catheter and 3·5 $\mu l\ min^{-1}$ in the mesenteric catheter. Occasionally, catheters clotted despite the perfusion, and a small bolus injection was given. When tested before and after the experiments, the pressure drop between the transducer membrane and the tip of the catheters never exceeded 1 mmHg at normal infusion rates. All catheters were damped so that mean blood pressure could be recorded directly (Christensen, Mulvany & Jespersen, 1990).

Systemic blood pressure

Systemic blood pressure was measured using a polythene catheter (Non-sterile polythene tubing: 580 μm o.d., 280 μm i.d.; Scandidact, Denmark) introduced retrogradely into the femoral artery so that the tip was located in the aorta just proximal to the bifurcation.

Local blood pressures in the mesentery

A small laparotomy was performed and the distal end of the superior mesenteric artery was identified. Local blood pressures were measured at the locations shown in Fig. 1 using polythene catheters (Kospan Spinal Catheter 28 G, Kendall, Denmark (300 μm o.d., 150 μm i.d.)) as follows.

Group A rats. One of the most distal arcade small arteries was cannulated in retrograde direction to provide a measure of the undisturbed pressure at the distal end of the superior mesenteric artery (A in Fig. 1). The measurement is believed to be valid, since the superior mesenteric artery gives rise to about twenty arcades (Hebel & Stromberg, 1976) and, given the extensive collateral circulation in the arcades, the blood flow in the superior mesenteric artery will hardly be affected by the intervention. Catheter orientation was maintained by stitching it to the perivascular tissue and to the intestinal wall, and finally securing it to the abdominal wall at the caudal end of the laparotomy (not shown in figure).

Group B rats. This method has been described in detail earlier (Christensen & Mulvany, 1993, 1994). In brief, the method is based on the recognition that the net blood flow at the base of the arcades must be close to zero, and that this will also be true for the juxtaposing part of the intestinal wall. Following any intervention it must therefore be ensured that this situation is re-established. After introducing the catheter anterogradely into one of the most distal arcade arteries, we ligated all side branches between the catheter and the base of the arcade, and placed twelve to fifteen small ligatures in the circumference of the juxtaposing intestinal wall. The vein accompanying the cannulated artery then had to be closed to avoid this extra drainage route. Under these conditions, the pressure at the catheter tip should equal the pressure at the base of the arcade under normal haemodynamic conditions (B in Fig. 1). Finally, a small piece of polythene tube was looped around the intestine and attached to the catheter. In this way, the distance from the catheter tip to the intestinal wall could be kept constant, and at the same time, rotation and vertical kinking of the catheter could be prevented.

Group C rats. In a manner analogous to group B, a distal arcade vein was cannulated, and the side branches, the intestinal wall and the accompanying arcade artery were ligated. For the same reasons as for the arcade artery measurement, the catheter should then provide undisturbed blood pressure at the base of the venous arcades (C in Fig. 1).

Group D rats. In a manner analogous to group A, a catheter was introduced into one of the distal arcade veins and fixed as described above. As for group A, this catheter provided a measure of the undisturbed pressure at the distal end of the superior mesenteric vein (D in Fig. 1).

Drugs

The following drugs were used: methohexital (Lilly Denmark A/S, Copenhagen), heparin (LEO A/S, Ballerup, Denmark) and ampicillin (Gist-Brocades, Glostrup, Denmark).

Data analysis

Every 30 min, systemic and local blood pressures were read. Fractional local blood pressures were calculated as percentages of the systemic blood pressure. The twenty-five values obtained for each of these parameters 5–17 h postoperatively were averaged to one value per rat and used for group values. Likewise, group values were calculated 0–2 h after surgery. Blood pressures from these two periods were assessed statistically by two-way ANOVA (using the statistical programme SPSS). Other comparisons were made by

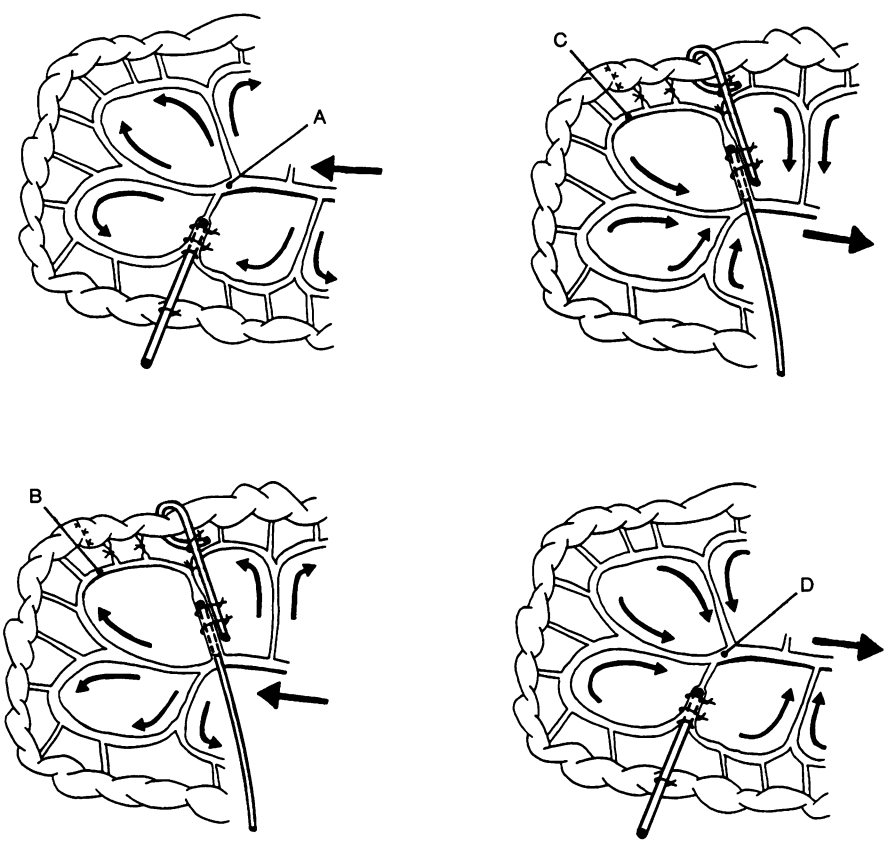

Figure 1. Measurement of local blood pressures

The sketches indicate the methods used to measure local blood pressure at the distal end of the superior mesenteric artery (A), at the base of a mesenteric arterial arcade (B), at the base of a mesenteric venous arcade (C) and at the distal end of the mesenteric vein (D). The sketches show the directions of cannulation, the fixation of the catheters and the direction of the blood flow after the interventions (arrows). For further details see text.

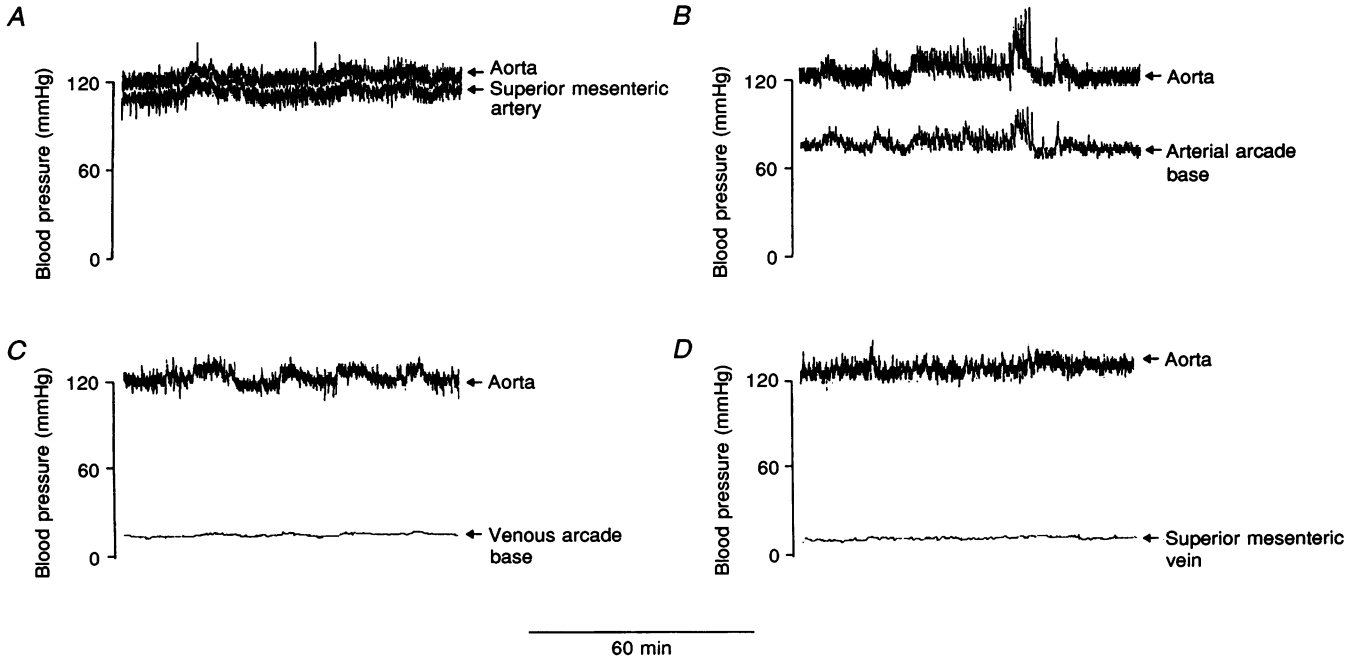

Figure 2. Blood pressure traces

A–D, representative traces from conscious, freely moving rats showing simultaneously measured systemic blood pressure (upper trace in each panel) and local blood pressure (lower trace in each panel) at the corresponding points A–D indicated on Fig. 1. The traces were obtained 7, 7, 10 and 11 h postoperatively in four different rats.

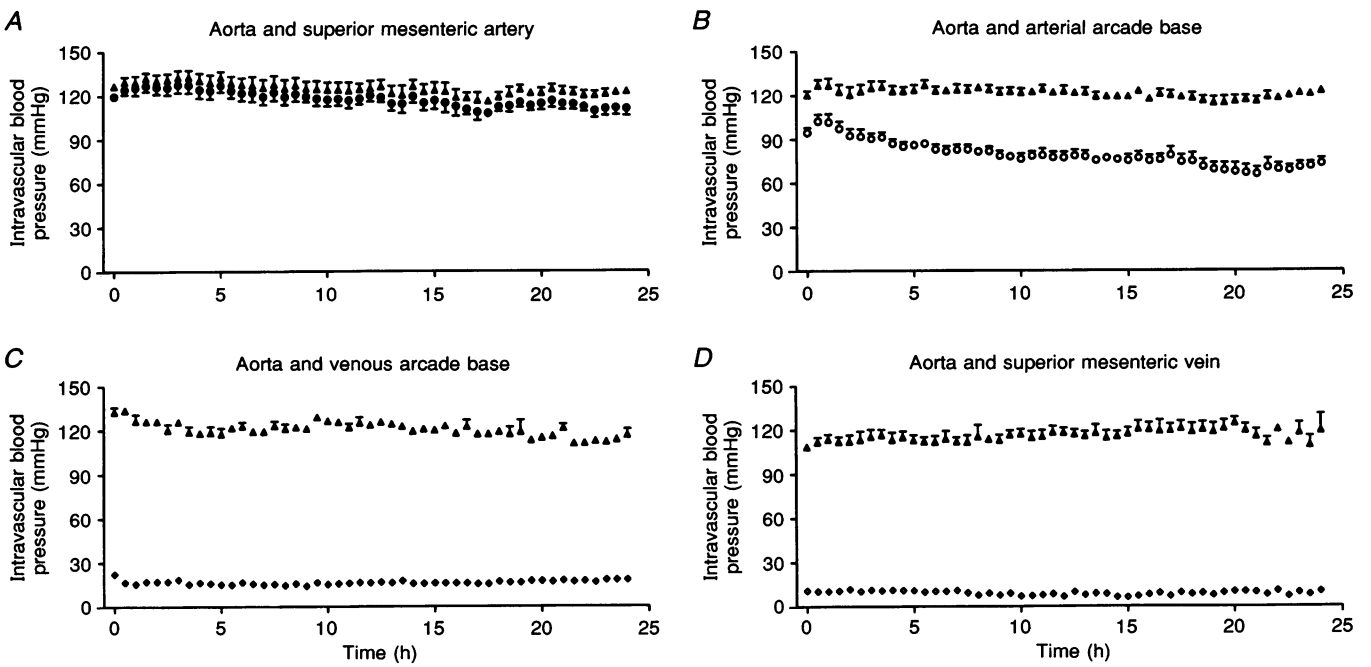

Figure 3. Time course of undisturbed blood pressures

Blood pressure in conscious, freely moving rats measured simultaneously in the abdominal aorta (△) and at one of four peripheral locations: at the distal end of the superior mesenteric artery (●; $n = 6$), at the arterial arcade base (○; $n = 6$), at the venous arcade base (◆; $n = 4$) or at the distal end of the superior mesenteric vein (◇; $n = 4$). Symbols show mean values, and error bars show S.E.M. values where these exceed the size of the symbols. After 17 h, n values were 6, 6, 3 and 3, respectively (see Methods).

Table 1. Two-way analysis of variance comparing fractional local blood pressures 0–2 h and 5–17 h postoperatively

Data				ANOVA			
Location	0–2 h	5–17 h	*n*		*F*	*n*	*P*
A	96·2 ± 0·9	95·1 ± 0·9	6	Time	33	1	< 0·001
B	80·1 ± 1·5	64·9 ± 2·2*	6	Location	1991	3	< 0·001
C	13·9 ± 0·9	13·1 ± 0·6	4	Interaction	15	3	< 0·001
D	9·6 ± 0·5	7·4 ± 1·0	4				

Values are given as mean percentages of systemic blood pressure ± S.E.M. A, distal end of superior mesenteric artery; B, base of arterial arcade; C, base of venous arcade; D, distal end of mesenteric vein. * $P < 0·05$, Student's *t* test performed on the basis that the two-way analysis of variance gave interaction.

Student's *t* test (grouped or paired, as appropriate). Results are given as means ± S.E.M. and *P* values of less than 0·05 were considered significant (see Table 1).

RESULTS

Local mesenteric blood pressures

All twenty rats investigated were in good health, all catheters were patent and all four groups A–D showed little variation in blood pressures for the whole of the 5–17 h postoperative period. However, as discussed in Methods, two rats had to be taken out of the experiment 17 h postoperatively. Furthermore, two additional rats from group B did not have stable blood pressures in the period from 17 to 24 h. We have therefore taken the period 5–17 h postoperatively as the main measurement period.

Figure 2 shows representative traces for systemic blood pressure and for the local blood pressures at each of the four measurement points (group A, distal end of the superior mesenteric artery; group B, base of the mesenteric arterial arcade; group C, base of the mesenteric venous arcade; group D, distal end of the superior mesenteric vein; see Fig. 1). Note that at the two arterial locations there was close parallelism between local and systemic blood pressure fluctuations.

Figure 3 shows group means of systemic and local blood pressures in the four groups for 24 h postoperatively. For all groups, systemic blood pressure was stable for the period 5–17 h postoperatively. For groups A, C and D, local blood pressures stabilized shortly after surgery and anaesthesia (Fig. 3*A*, *C* and *D*). For group B, fractional local blood pressure (at the arterial arcade base) fell markedly during the first 5 h postoperatively. This was tested by two-way analysis of variance (see Table 1), where we found interaction between 'time' (0–2 h after surgery compared with 5–17 h after surgery) and 'location'. This interaction was almost entirely due to the effect of surgery and anaesthesia on local blood pressure in the arterial arcade base.

The difference between the immediate postoperative period (0–2 h) and the measurement period 5–17 h postoperatively

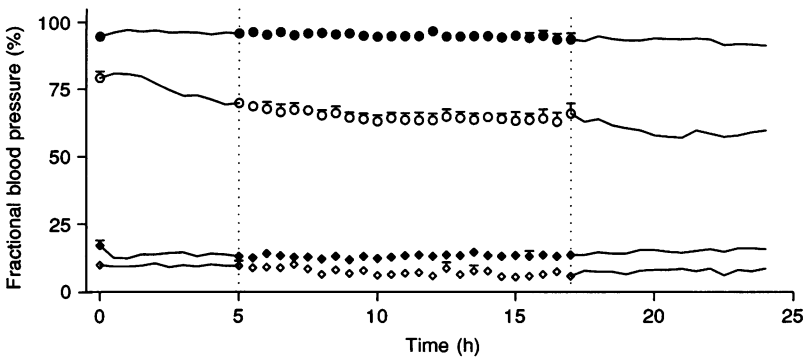

Figure 4. Time course of fractional blood pressures

Local blood pressures shown in Fig. 3 expressed as a percentage of systemic blood pressure in conscious, freely moving rats either at the distal end of the superior mesenteric artery (●), at the arterial arcade base (○), at the venous arcade base (◆) or at the distal end of the superior mesenteric vein (◇). Symbols show mean values, and error bars show S.E.M. values where these exceed the size of the symbols. Data obtained 5–17 h postoperatively (period between dotted lines) were used for group averages. The trends outside this period are indicated by continuous lines.

is emphasized in Fig. 4, which shows the fractional local blood pressures during these times. Figure 4 also indicates that in all cases local blood pressures were rather constant 5–17 h postoperatively. During this period, systemic blood pressure did not differ between the four groups (group A, 124 ± 5 mmHg; group B, 122 ± 3 mmHg; group C, 122 ± 2 mmHg; group D, 116 ± 4 mmHg). Fractional blood pressures are given in Table 1.

Figure 5 shows the resulting blood pressure profile and the calculated segmental pressure drops. Pressure drops were 5% (*ca* 6 mmHg) over the superior mesenteric artery, 31% (*ca* 37 mmHg) over the arcade small arteries, 51% (*ca* 61 mmHg) over the intramural circulation, and 6% (*ca* 7 mmHg) over the venous arcades, leaving 7% (*ca* 8 mmHg) of systemic blood pressure to drive the blood through the liver back to the heart. As can be calculated from Table 1, the corresponding pressure drops 0–2 h postoperatively were 4, 16, 66, 5 and 9%, respectively.

Observed variations in blood pressure (see, for example, traces in Fig. 2) were generally associated with movement, eating or drinking. We also noted a close parallelism between fluctuations in systemic and local blood pressures at the arterial locations, and the fractional blood pressures were rather constant. At the venous locations, the fluctuations in systemic blood pressure had little effect on local blood pressure.

DISCUSSION

The main finding of this work is that under physiological conditions, the mesenteric arterial arcades provide a substantial fraction of the mesenteric resistance. We have therefore concluded that the small arteries of which the arcades are composed may be considered as resistance vessels.

Previous measurements of the vascular pressure profile have been made almost entirely in anaesthetized animals. In general, these have indicated that the fractional blood pressure in vessels of diameter 100 μm is in the range 60–95% (Mulvany & Aalkjær, 1990; DeLano, Schmid-Schönbein, Skalak & Zweifach, 1991; Bohlen & Aukland, 1991), thus indicating that vessels proximal to these contribute 5–40% of the resistance. On the basis that most of this resistance is borne by the small arteries, the available literature is therefore compatible with the small arteries playing either a minor (Prewitt & Wang, 1991) or a major (Hébert & Marshall, 1988; Mulvany & Aalkjær, 1990; Williams & Segal, 1993) role in resistance regulation.

Part of the discrepancy may be due to the difference in vascular beds which have been studied, in that in general the fractional blood pressures in skeletal muscle small arteries are reported to be higher than those in intestinal small arteries of similar size (Fronek & Zweifach, 1975; Davis, Ferrer & Gore, 1986; Prewitt & Wang, 1991).

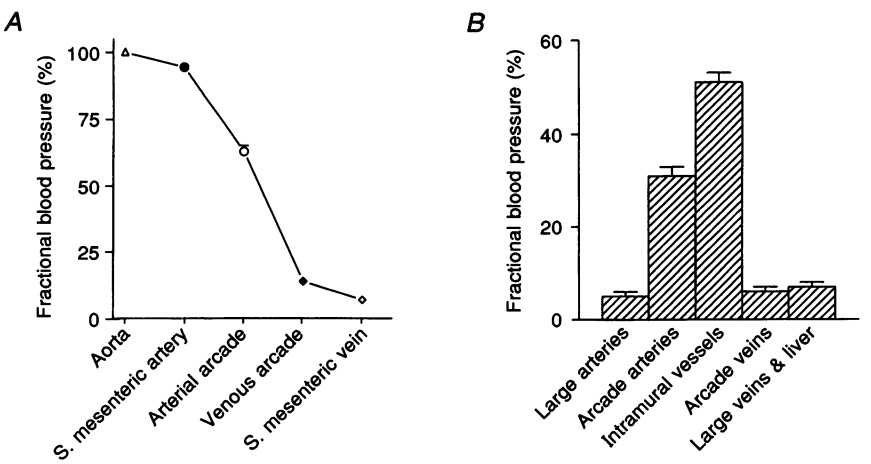

Figure 5. Mesenteric fractional blood pressure profile (*A*) and segmental, fractional blood pressure drops (*B*)

A, based on the average fractional blood pressure measurements 5–17 h postoperatively shown in Fig. 4, the figure shows the blood pressure profile in conscious, freely moving rats obtained at the following locations: aorta (△), distal end of the superior mesenteric artery (●; $n = 6$), arterial arcade base (○; $n = 6$), venous arcade base (◆; $n = 4$) and distal end of the superior mesenteric vein (◇; $n = 4$). Values are expressed as percentages of systemic blood pressure. Error bars show S.E.M. values where these exceed size of symbols. *B*, the figure shows mean fractional blood pressure drops over the sections indicated. These were calculated by subtracting group values shown in the left panel from each other. Bars show S.E.M. calculated as: $(\text{S.E.M.})^2 = (\text{S.E.M.}_1)^2 + (\text{S.E.M.}_2)^2$, where S.E.M._1 and S.E.M._2 are the S.E.M. of the fractional pressures at points 1 and 2.

However, the discrepancies may also be attributable to the different anaesthetics and procedures which have been used. Thus, in 6-week-old Sprague–Dawley rats under urethane/chloralose anaesthesia, Gore & Bohlen (1977) measured fractional mesenteric pressures of 43% in '1A' small arteries and 10% in '1V' small veins. In contrast, using the same anaesthetic – but at a lower dose – in 8-week-old Sprague–Dawley rats, Meininger *et al.* (1986) measured fractional blood pressures of 77% in '1A' small arteries and 16% in '1V' small veins of the mesentery. In a third study, using 18- to 21-week-old WKY rats anaesthetized with inactin, Bohlen (1983) measured fractional mesenteric blood pressures of 60% in '1A' small arteries and 17% in '1V' small veins, very similar to our findings at neighbouring locations in the conscious state. In the present study, the role of the arcade small arteries and the intramural vessels seemed markedly different immediately after surgery and anaesthesia, compared with 5–17 h postoperatively, when the rats had regained consciousness and normal activity. This variability points to the importance of performing experiments under conscious, resting conditions, if the physiological role of small arteries is to be established.

In the methods described in the present paper, the main advantage is that the rats were conscious and freely moving, not under the influence of anaesthetics, and haemodynamically stable for the 12 h measurement period. Furthermore, although the interventions are substantial, they are such that the haemodynamic situation at the point of the measurement should be normal. The importance of haemodynamic control has been shown convincingly in skeletal muscle vasculature (Hill *et al.* 1990; DeLano *et al.* 1991; Hill, Trippe, Li & Meininger, 1992) where blood pressures in the microcirculation were crucially dependent on whether or not the feeding arteries had been ligated. Other advantages are that the rats are not handled or disturbed during the measurements, that the vascular bed studied could be kept in its natural environment, and that the polythene catheters were remote from the point of the measurement and thus did not produce local irritation.

The main disadvantage compared with previous methods is that the technique depends on the peculiar architecture of the mesenteric circulation, and it is hardly applicable to other vascular beds. It may therefore prove difficult to determine if the present results are relevant to other vascular beds. Nevertheless, the intestinal circulation is interesting in its own right, since it receives a large percentage of the cardiac output at rest and has impressive potential for demand related up- or downregulation of the blood flow (Mitchell & Blomqvist, 1971).

It could be argued that the large pressure drop which we have found in the arcade vasculature may only reflect the relatively long length of the arcade arteries and may not necessarily indicate regulatory potential (Davis, Ferrer & Gore, 1986). In this respect, our finding that in the first 5 h postoperatively the pressure drop along the mesenteric arterial arcade rose from 16 to 31% is of interest. This strongly suggests that at least under these conditions the arcade arteries have an important regulatory function, as others have suggested (Furness & Marshall, 1974; Davis *et al.* 1986; Segal & Duling, 1986; Hébert & Marshall, 1988; Mulvany & Aalkjær, 1990; Duling, 1991). Such a regulatory function was also suggested by our previous experiments in which only the fractional blood pressure at the base of the mesenteric arcade was measured (Christensen & Mulvany, 1993, 1994). There it was shown, for example, that the increased blood pressure associated with I.V. infusion of noradrenaline was not accompanied by any change in this fractional blood pressure; the result strongly suggested that arcade small arteries were contributing to an increased mesenteric resistance. Similarly, in conscious, freely moving, spontaneously hypertensive rats, the fractional blood pressure is the same as in normotensive rats (Christensen & Mulvany, 1994), again suggesting that the arcade small arteries are contributing to the increased vascular resistance seen in hypertension.

Although the present measurements do not provide direct information about the contribution of the arterioles (arteries having not more than one layer of smooth muscle cells; Bloom & Fawcett, 1968) to the pressure dissipation, clearly this must be less than the 51% pressure drop measured in the intramural circulation. Apart from arterioles, this circulation includes many small arteries, the capillaries, the venules and many small veins. Likewise, the contribution of small arteries to the pressure dissipation will be greater than the measured 31%, since this refers only to the arcade small arteries, and does not include the more distal small arteries. Therefore the present results are compatible with small arteries and arterioles contributing roughly equally to mesenteric resistance, and point to a major role for small arteries in resistance regulation in this vascular bed. However, conclusive evidence regarding the contribution of the small arteries to resistance regulation must await experiments in which not only pressure, but also mesenteric flow, is measured under the conditions of the present experiments; such experiments are in progress (Fenger-Gron, 1994).

In conclusion, we have found that in the mesenteric bed of conscious, freely moving rats the main sites of resistance are in the arcade small arteries (31%) and in the intramural circulation (51%). The data suggest that in this vascular bed, the small arteries may play a regulatory role which is at least as great as that of the arterioles.

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