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RESPONSES OF BONE AND JOINT BLOOD VESSELS IN CATS AND RABBITS TO ELECTRICAL STIMULATION OF NERVES SUPPLYING THE KNEE

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SUMMARY

1. Experiments were performed to assess the extent to which knee joint blood flow in cats and rabbits is affected by electrical stimulation of the nerve supply to the knee.

2. Absolute changes in blood flow were measured using the radiolabelled microsphere ($\sim 15\ \mu m$) technique whilst relative changes in blood flow were assessed using laser Doppler flowmetry.

3. Despite deep general anaesthesia, sympathetic nerve fibres innervating cat knee joint blood vessels showed marked 'tone'.

4. Blood flow to the joint capsule (synovium and overlying fibrous and areolar tissues) was substantially reduced (by $\sim 90\%$ in the cat and $\sim 45\%$ in the rabbit) during electrical stimulation of the articular nerve supply.

5. The percentage change in the laser Doppler flowmeter signal did not differ significantly from the percentage change in blood flow measured by microsphere technique.

6. Blood vessels in the cancellous bone of the distal femur (condyles) and proximal tibia (plateau) appear to be innervated by vasoconstrictor fibres which reach their effectors via the articular nerves. However, the cortical bone and red marrow of the diaphysis of the femur do not receive such innervation.

7. The potency of the vasoconstrictor influences acting on joint blood vessels could be of relevance in the pathogenesis of inflammatory joint diseases.

INTRODUCTION

The knee is a synovial joint where the distal end of the femur articulates with the proximal end of the tibia. The joint cavity is lined by a thin layer of tissue known as the synovium and beyond this are various overlying tissues whose composition (skeletal muscle, fat, fibrous tissue) vary depending on the region of the joint (Knight & Levick, 1983). This lack of homogeneity of structure coupled with the extensive anastomoses of the arterial blood supply to the knee (Liew & Dick, 1981) has made measurement of joint blood flow difficult. Venous outflow from the dog knee has been measured using an electromagnetic flowmeter (Cobbold & Lewis, 1956), but this

technique required ligation of non-articular blood vessels which may have altered the pre-existing pattern of blood flow to the joint. Measurement of the clearance rate from the joint cavity of a rapidly diffusing radioactive solute has been used to estimate synovial blood flow in man (Dick, St. Onge, Gillespie, Downie, Nuke, Gordon, Whaley, Boyle & Buchanan, 1970). However, as discussed in a recent review (Levick, 1987), care is needed in interpreting this method because of the non-homogeneous nature of the joint, in addition to requiring data for the area and thickness of the synovium and cartilage. The radiolabelled microsphere technique has been used to estimate blood flow in the dog knee joint (Bunger, Hjermind & Bulow, 1983). This technique provides quantitative data about regional blood flow, but the measurements are discontinuous although several can be obtained in one animal by using different radioactive labels.

Laser Doppler flowmetry (LDF) is a technique which has in recent years been used to investigate regional blood flow in a variety of organs and tissues such as skin (Holloway & Watkins, 1977), brain (Busija, Heistad & Marcus, 1981; Haberl, Heizer, Marmarou & Ellis, 1989*a*; Haberl, Heizer & Ellis, 1989*b*), kidney (Stern, Bowen, Parma, Osgood, Bowman & Stein, 1979), bone (Notzli, Swiontkowski, Thaxter, Carpenter & Wyat, 1989) and intestinal mucosa, (Ahn, Lindhagen & Nillson, 1985). LDF is based on the principle that coherent light scattered by moving erythrocytes experiences a frequency (Doppler) shift that is proportional to the velocity of erythrocytes flowing through the volume of tissue illuminated by the laser radiation (Nillson, Tenland & Oberg, 1980). Although this technique provides a continuous and non-invasive signal related to blood flow, it cannot measure absolute flow but can be usefully employed to assess relative changes in blood flow. LDF has been used to assess blood flow changes in the human knee joint in response to alterations in intra-articular pressure (Geborek, Forslind & Wollheim, 1989), but no studies have been performed to evaluate its use in animal joints and establish its reliability in assessing articular blood flow by comparison with other established techniques (e.g. the microsphere technique). One of the aims of this study was to use both LDF and the microsphere technique to assess the extent of efferent innervation of blood vessels in both the synovium and periarticular structures. A preliminary account of this research has appeared previously (Angerson, Ferrell & Khoshbaten, 1990).

METHODS

Experiments were performed on eight adult cats anaesthetized with pentobarbitone (45 mg kg^{-1}, I.P.) and on nine adult New Zealand rabbits anaesthetized with a 2% halothane/O_2/N_2O mixture. The animals were maintained deeply anaesthetized as, judged by the absence of a flexor withdrawal response to noxious stimuli applied to the forelimb. Arterial blood pressure was also monitored. In each animal one hindlimb was left intact to provide a control knee joint whilst the other (experimental) limb was denervated proximally and a 0·9 mm diameter, fibre-optic probe inserted into the synovial cavity via a 18G hypodermic needle. In the cat, the probe was inserted through the antero-lateral aspect of the knee and advanced posteriorly between the femoral condyles until it made contact with the internal surface of the postero-medial capsule. In the rabbit the probe was inserted through the same region but advanced through the infra-patellar region until it made contact with the internal surface of the antero-medial capsule. The term joint 'capsule', although extensively used in the literature, is imprecise when applied to the knee because of the marked regional variations in the tissues overlying the synovium (Knight & Levick, 1983). In the present experiments the antero-medial 'capsule' corresponds to the areolar-fibrous tissue of the rabbit knee

described by Knight & Levick (1983), which consists of synovium over areolar tissue which in turn rests upon aponeurotic fibrous tissue. The postero-medial 'capsule' in the cat knee corresponds to posteromedial tissue which in the rabbit knee consists of a mixture of areolar, fibrous and adipose tissues (Knight & Levick, 1983).

A laser Doppler flowmeter (Moor Instruments MBF3) connected to a fibre-optic probe provided a measure of relative changes in blood flow in tissue adjacent to the tip of the probe. A continuous recording was made before and during electrical stimulation of the cat posterior articular nerve (PAN) or the rabbit saphenous nerve. The stimulus parameters used for both groups of animals were 10 V amplitude, 1 ms width, 30 Hz train of approximately 1 min duration. Independent, quantitative measurements of blood flow were performed by intraventricular injection of radiolabelled microspheres with timed withdrawal of an arterial blood sample. These were performed immediately before and during nerve stimulation, in the latter case when blood flow changes as registered by the LDF were maximal. In four cats and five rabbits a prior measurement of blood flow was also performed, 15 min after denervation of the experimental knee but before insertion of the fibre-optic probe. The microspheres (NEN-TRAC, New England Nuclear), labelled with ^{113}Sn, ^{57}Co, ^{153}Gd or ^{46}Sc were $16{\cdot}5 \pm 0{\cdot}1$ μm in diameter and were suspended in 0·9% saline with 0·01% Tween 80 to prevent clumping. This was checked microscopically prior to injection, and immediately beforehand the vial containing the microspheres was shaken vigorously by a mechanical agitator. The syringe containing the microspheres was also vigorously agitated until immediately before injection. In a few instances the kidneys were removed at the end of the experiment and checked histologically for evidence of clumping, but none was observed.

For each measurement, 1 ml of suspension, containing $1{\cdot}5\text{–}2 \times 10^6$ microspheres, was injected over a period of 15 s into the left ventricle via a cannula inserted into the right carotid artery. A reference sample was withdrawn from the left carotid artery for a period of 60 s, starting 5 s before the microspheres were injected. The withdrawal rate was 5 ml min^{-1} in experiments with two blood flow measurements, and this was reduced to 3 ml min^{-1} in those with three measurements to minimize cumulative blood loss. Each blood sample was replaced by an equivalent volume of saline to maintain blood volume. As it was necessary to leave the femoral arteries intact on both sides, it was not possible to monitor blood pressure during microsphere injection. However, control experiments in two animals involving three successive injections of a 1 ml suspension of 2×10^6 microspheres without withdrawal of an arterial blood sample but continuous measurement of arterial pressure showed that systolic and diastolic blood pressures during and immediately after injection changed by less than 5 mmHg compared to values occurring immediately prior to injection. In the series of eight cats mean arterial blood pressure before the second microsphere injection was $85{\cdot}9 \pm 8{\cdot}3$ mmHg and immediately after injection was $85{\cdot}1 \pm 8{\cdot}6$ mmHg, and these values did not differ significantly ($P = 0{\cdot}951$; $n = 8$; Mann–Whitney U test). Similarly in the series of nine rabbits the mean arterial blood pressure values immediately before and after injection of the second set of microspheres were $80{\cdot}1 \pm 5{\cdot}3$ mmHg and $81{\cdot}8 \pm 6{\cdot}1$ mmHg respectively and these did not differ significantly ($P = 0{\cdot}656$; $n = 9$).

At the conclusion of the experiment the animals were administered an intraventricular overdose of pentobarbitone (200 mg kg^{-1}) or 3 M-KCl and tissue harvested from the following sites from both knees in both species: popliteus muscle, distal femur (femoral condyles), proximal tibia (tibial plateau), posterior capsule (consisting of both synovium and overlying areolar and fibrous tissue), anterior capsule (comprising of synovium, patellar ligament, infrapatellar fat pad and overlying fibrous tissue) and both kidneys. The latter were sampled as a check on the adequacy of mixing and distribution of microspheres. In some experiments additional samples were taken from cortical bone (shaft of femur 1 cm above condyles), and marrow (removed from the shaft). Tissue samples were weighed and then counted (together with the reference blood sample) in a 2-channel gamma counter (Packard 500C) with energy window settings appropriate for the isotope used. Raw counts were corrected for crossover between channels, which was determined by counting pure samples of the two radionuclides. Blood flow in each tissue sample was calculated as the reference sample withdrawal rate multiplied by the ratio of the tissue counts to reference sample counts.

Data in graphs and histograms are presented as means $\pm$ S.E.M. Analysis has been performed using non-parametric statistics; Friedman two-Way ANOVA and Wilcoxon matched-pairs signed rank test for repeated measures of flow in the experimental knee (before and during nerve stimulation) or comparisons of differences between control and experimental knees before and during nerve stimulation.

RESULTS

Capsular blood flow

In all animals tested, electrical stimulation of the nerves supplying the knee joint resulted in sustained reduction in the flowmeter signal throughout the period of stimulation, which recovered thereafter as shown in Fig. 1.

Stimulation of the cat PAN produced larger reductions in the flowmeter signal compared to control (prestimulation) values than stimulation of the rabbit saphenous nerve. This is clearly seen in Fig. 2 which shows that overall, the percentage reduction in the flowmeter signal as a result of nerve stimulation was greater in the cat (78·6 ± 5·5 %; mean ± S.E.M.; $n = 8$) than in rabbit knees (35·8 ± 3·2 %; $n = 9$) and this is also reflected in the percentage reduction in blood flow as measured with the microspheres. In cats the percentage reduction in blood flow resulting from nerve stimulation was 89·8 ± 4·6 % whereas in rabbits the reduction was 42·1 ± 5·4 %. It can be seen that these data are separated into two clusters and comparison of the mean values (laser signal *versus* blood flow) revealed that these did not differ significantly (Mann-Whitney U test) for either the cat ($P = 0·109$) or the rabbit ($P = 0·353$).

Measurement of blood flow in the anterior and posterior capsules in both species showed differences in the response to transection and electrical stimulation of the nerve supply to the knee. Blood flow, as measured using microspheres, remained constant in the control (right) knee in both the anterior and posterior regions irrespective of the procedures performed on the experimental (left) knee (Fig. 3*A* and *B*). In the cat, section of PAN prior to insertion of the probe resulted in an increase in flow in the posterior capsule (Fig. 3*A*) but had little effect on the anterior region where the flow differed little from the control knee value (Fig. 3*B*). Subsequent insertion of the fibre-optic probe (via the 18 G hypodermic needle) into the synovial cavity of the experimental knee led to an increase in flow in the anterior region, presumably due to injury hyperaemia, but had little effect on flow in the posterior capsule. This suggests that the presence of the probe in the synovial cavity does not *per se* significantly influence flow, at least over the time course of the experiments. Electrical stimulation of PAN at parameters (10 V amplitude, 1 ms width, 30 Hz) chosen to elicit maximal vasoconstriction produced substantial reduction in blood flow in the posterior region (Fig. 3*A*) and a smaller but significant reduction in flow in the anterior capsule (Fig. 3*B*). In all cases the signal from the flowmeter was monitored continuously and the microspheres injected into the left ventricle only when the flowmeter signal had reached its nadir during electrical stimulation of the articular nerve supply.

In the rabbit, transection of the saphenous nerve above the knee had no effect on blood flow in the posterior region (Fig. 3*C*) and only a small rise in flow occurred in the anterior capsule of the experimental knee (Fig. 3*D*). Insertion of the probe into the experimental knee (through the antero-lateral region) resulted in a large increase in flow which again was probably due to injury hyperaemia (fig. 3*D*). Although flow also rises in the posterior region of the experimental knee, this does not differ significantly from the value in the control knee which also shows a rising trend (Fig. 3*C*). Electrical stimulation of the saphenous nerve to elicit a maximal vasoconstrictor response (as judged by the flowmeter signal) significantly reduced

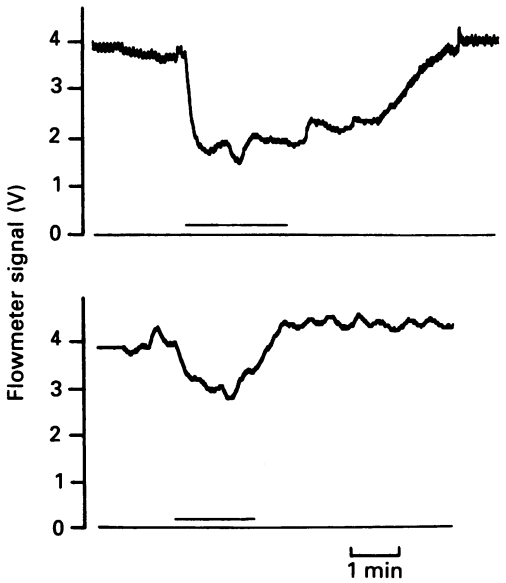

Fig. 1. Flowmeter traces obtained from the cat (upper trace) and rabbit knee (lower trace) in response to electrical stimulation of the posterior articular and saphenous nerves respectively. The bar denotes the period of stimulation (10 V amplitude, 1 ms width and 30 Hz).

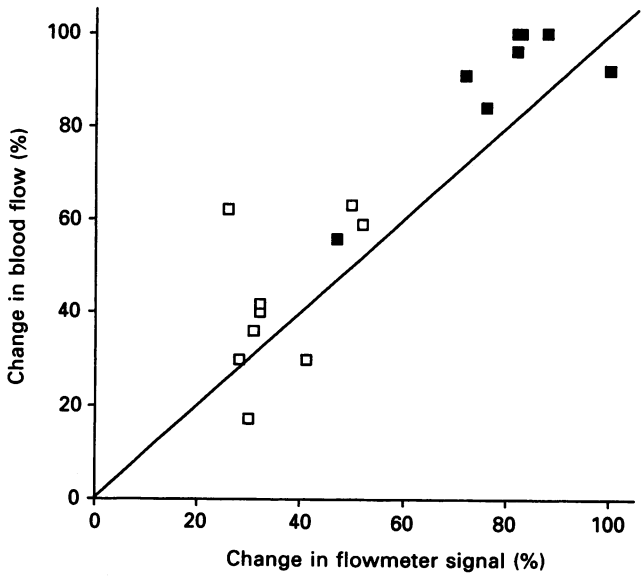

Fig. 2. Comparison of the percentage change in blood flow measured using microspheres with the percentage change in the flowmeter signal before and during joint nerve stimulation for both cat posterior capsule (■) and rabbit anterior capsule (□). Stimulus parameters as in Fig. 1.

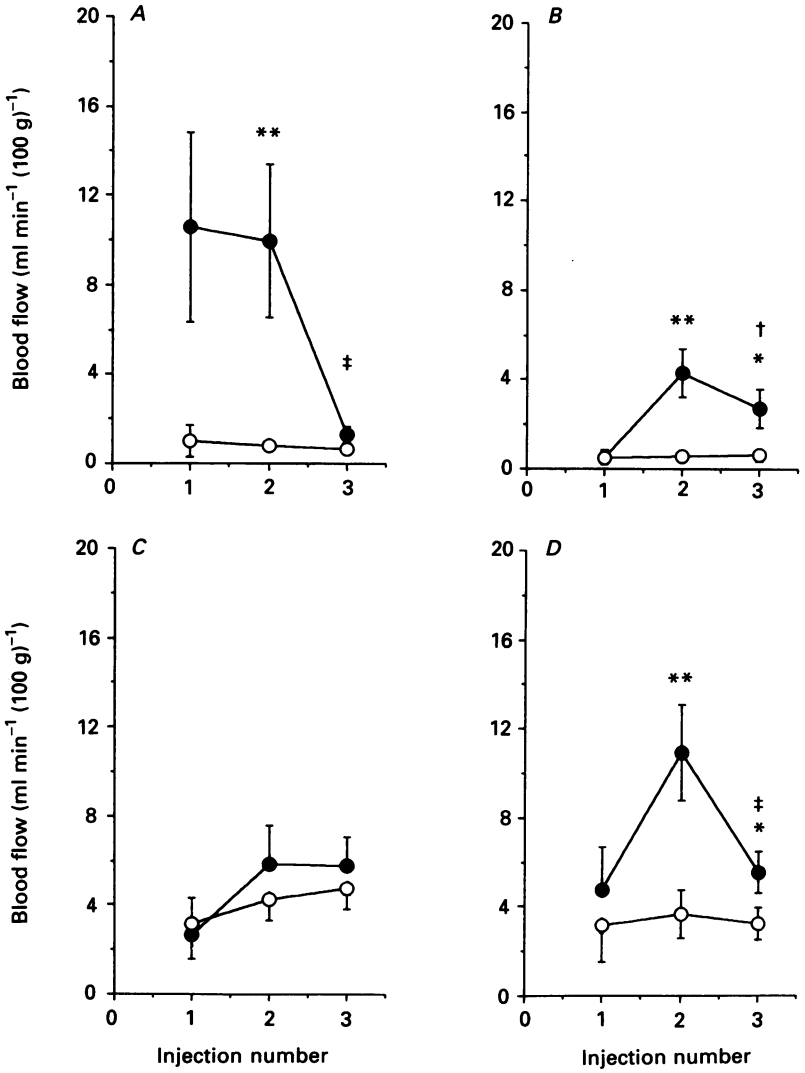

Fig. 3. Measurement of blood flow changes using microspheres for the cat posterior capsule (*A*), cat anterior capsule (*B*), rabbit posterior capsule (*C*) and rabbit anterior capsule (*D*). Injection 1 was given after the PAN of the experimental knee (●) was sectioned. The control knee (○) remained intact throughout. Injection 2 was administered after insertion of the flowmeter probe into the synovial cavity of the experimental knee. Injection 3 occurred during electrical stimulation (parameters as in Fig. 1) of PAN in the cat and the saphenous nerve in the rabbit. * = means of experimental and control knees differ: $P < 0{\cdot}05$. ** = means of experimental and control knees differ: $P < 0{\cdot}01$. † = means of experimental knee differ between injections 2 and 3: $P < 0{\cdot}05$. ‡ = means of experimental knee differ between injections 2 and 3: $P < 0{\cdot}01$. No statistical comparisons between experimental and control knees performed for injection 1 due to low n values ($n = 4$ for cat and $n = 5$ for rabbit).

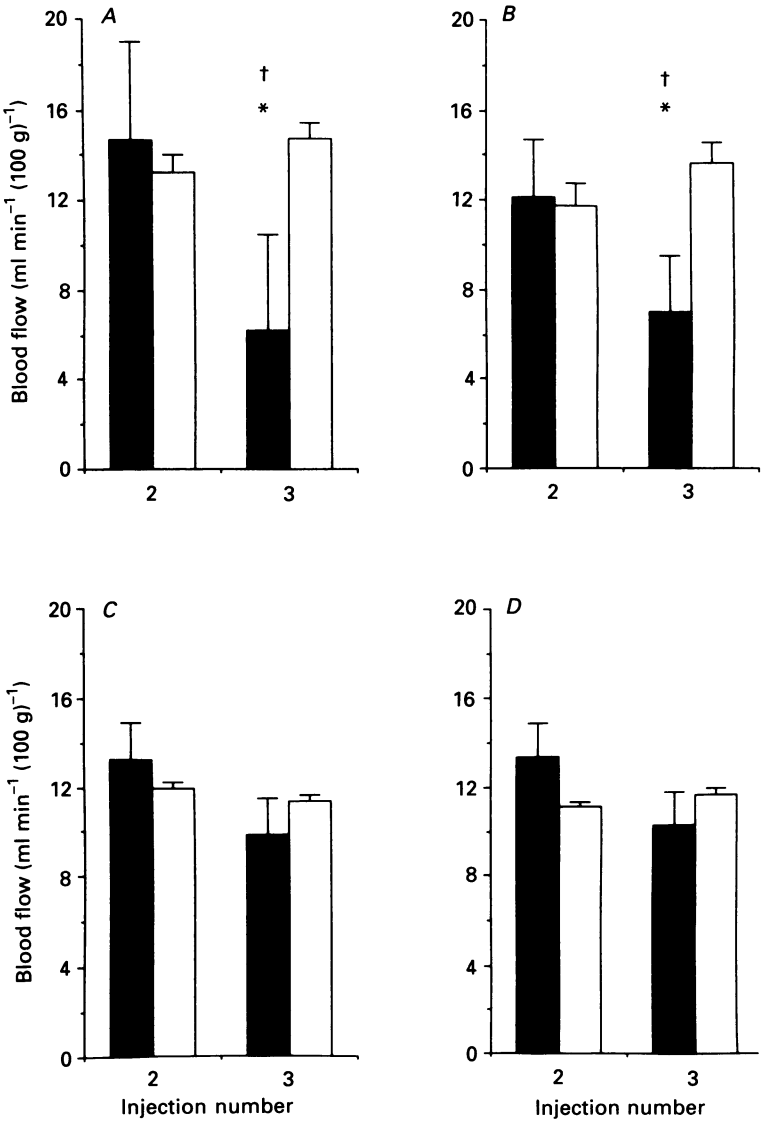

Fig. 4. Measurement of blood flow changes for the cat femoral condyles (*A*), cat tibial plateau (*B*), rabbit femoral condyles (*C*) and rabbit tibial plateau. (*D*). Injection 2 was administered before stimulation of PAN (cat) or the saphenous nerve (rabbit), and injection 3 was given during stimulation of these nerves. Filled histogram represents the experimental knee and the open histogram the control knee. Stimulus parameters as in Fig. 1. * = means of experimental and control knees differ: $P < 0{\cdot}05$. † = means of experimental knee differ between injections 2 and 3: $P < 0{\cdot}05$.

blood flow in the anterior capsule of the experimental knee (Fig. 3*D*) but had no effect on flow in the posterior region (Fig. 3*C*).

Bone blood flow

Bone blood flow was found to be affected by some of the procedures but not others. Transection of the nerve supply to the knee did not affect blood flow in either femur or tibia in both species of animals. In cats, femoral and tibial blood flows in the experimental knee were $14 \pm 2{\cdot}3$ and $11{\cdot}2 \pm 2{\cdot}1$ (mean $\pm$ S.E.M. ml min^{-1} $(100\ g)^{-1}$; $n = 4$) respectively and these values did not differ significantly from those in the contralateral (control) knee. In the rabbit, femoral and tibial blood flows in the experimental knee were $13{\cdot}2 \pm 2{\cdot}7$ and $13{\cdot}3 \pm 2{\cdot}7$ (mean $\pm$ S.E.M. ml min^{-1} $(100\ g)^{-1}$; $n = 5$) respectively and these values did not differ significantly from those in the control knee. As expected, insertion of the flowmeter probe into the synovial cavity of the knee did not increase bone blood flow in either instance. In the cat, electrical stimulation of PAN resulted in significant reductions in blood flow to both femur and tibia during the period of stimulation (Fig. 4*A* and *B*) with both areas showing $\sim$ 50% fall in blood flow, the control knees remaining essentially unchanged. In the rabbit although similar trends were observed for both femur and tibia (Fig. 4*C* and *D*), the values obtained just failed to reach significance. However, there was a significant difference in the change in flow on stimulation between the experimental and control knees ($P < 0{\cdot}01$).

In some animals, samples were also taken from the shaft of the femur about 1 cm proximal to the femoral condyles and the marrow and cortical bone were separated. None of the procedures performed on the experimental knee, including electrical stimulation of the nerve supply to the knee, produced significant alterations in blood flow in either species. In the cat, marrow and cortical blood flows were $44 \pm 5{\cdot}8$ and $1{\cdot}6 \pm 0{\cdot}6$ (means $\pm$ S.E.M. ml min^{-1} $(100\ g)^{-1}$; $n = 4$) respectively in the experimental knee and these values did not differ significantly from those in the control knee, nor did they vary in the experimental knee with probe insertion into the joint or during PAN stimulation. In the rabbit, the marrow and cortical flows were $34{\cdot}3 \pm 6{\cdot}4$ and $5{\cdot}5 \pm 1{\cdot}2$ ($n = 5$) respectively and these also differed little from the control knee values and were unaffected by probe insertion or nerve stimulation.

In all experiments samples were taken of the popliteus muscle which is closely applied to the inferior margin of the posterior capsule. However, flow to the muscle in both species was unaffected by any of the different experimental conditions. Mean popliteus muscle blood flow (ml min^{-1} $(100\ g)^{-1}$) in the experimental knees was $3{\cdot}4 \pm 0{\cdot}3$ for cats ($n = 8$) and $5{\cdot}8 \pm 0{\cdot}5$ for rabbits ($n = 9$) and these did not differ significantly from the values obtained in the control knees of both species, nor were they affected by nerve stimulation.

DISCUSSION

The present results demonstrate a number of features of the innervation of articular blood vessels in cats and rabbits. Transection of PAN in the cat resulted in elevation in blood flow in the posterior capsule suggesting that a significant level of

sympathetic vasoconstrictor tone normally exists, even in the presence of pentobarbitone anaesthesia. In the rabbit anterior capsule nerve section had much less effect, as did electrical stimulation of the saphenous nerve when compared to the pronounced vasoconstriction induced by stimulation of PAN in the cat. This may be related to species differences or more likely, to the different nerves used in the two groups of animals. Preliminary experiments have shown that electrical stimulation of the rabbit PAN using the same stimulus parameters as in the present experiments results in $\sim 80\%$ reduction of the flowmeter signal (unpublished observations). Measurement of regional blood flow to the capsule using radiolabelled microspheres indicated that laser Doppler flowmetry provides a reasonably accurate indication of relative changes in blood flow. It should be borne in mind that the laser Doppler flowmeter provides a highly localized measurement of blood flow, whereas the microsphere measurements refer to the joint capsule sample as a whole. Discrepancies between the two techniques may therefore reflect redistribution of blood flow within the joint capsule associated with nerve stimulation. The correlation between the LDF technique and the microsphere technique was greatest in the cat, probably due in part to the potent vasoconstrictor responses observed in this species. This potency may be due to the density of efferent innervation of the posterior region of the joint. In the cat, PAN is the largest of the articular nerves supplying the knee (Freeman & Wyke, 1967; Langford & Schmidt, 1983) and the same may be true also in the rabbit. It is noticeable that in the rabbit stimulation of the saphenous nerve had no effect on blood flow through the posterior region (Fig. 3*C*) whereas in the cat, stimulation of PAN caused a small reduction in flow in the anterior region (Fig. 3*B*). This may be because PAN innervates, to a variable extent, part of the antero-lateral capsule (Freeman & Wyke, 1967). This being so, the lack of effect of PAN section on blood flow through the anterior region (injection 1 in Fig. 3*B*) is difficult to understand. It may be that high frequency electrical stimulation of PAN is required to elicit a vasoconstrictor response in this region.

Blood flow to the distal end of the femur and proximal portion of the tibia was found to be unaffected by transection of the nerve supply to the knee in both species, indicating a low level of sympathetic 'tone' to the vessels in these structures. Nevertheless, these blood vessels are innervated by vasoconstrictor fibres travelling in the nerves supplying the knee joint as electrical stimulation of these resulted in reduced blood flow in these regions. Again, the effect was smaller, although still significant, in the rabbit. As far as the femur is concerned, this innervation appears to be limited to the condyles as neither the red marrow nor the cortical bone 1 cm rostral was affected by nerve stimulation. An interesting possibility is that in addition to efferent innervation of bone blood vessels, there may also be afferent fibres travelling via articular nerves to innervate the bone. This could explain why in some single unit recordings from knee joint afferents although afferent nerve fibres could be identified, no receptive fields could be found in the joint capsule for both receptors giving rise to myelinated afferents (Ferrell, 1977) and those whose afferents were thinly myelinated or unmyelinated (Schaible & Schmidt, 1986).

The finding that blood flow in the popliteus muscle was unaffected by PAN stimulation indicates that the territory supplied by this nerve is limited to articular structures, even though it has been shown that some muscle afferent fibres can travel

in PAN (Burgess & Clark, 1969; McIntyre, Proske & Tracey, 1978) although the number of these fibres is small (Ferrell, 1977, 1980).

The potency of the vasoconstrictor effects observed in the joint capsule may be of relevance in the pathogenesis of inflammatory joint disease, particularly as it has been observed that experimentally-induced knee joint inflammation in the rabbit results in sensitization of post-junctional α-adrenoceptors (Khoshbaten & Ferrell, 1990). It is possible that enhanced vasoconstriction in the inflammatory state induces a relative hypoxia which acts as a stimulus to the angiogenesis which is known to accompany inflammatory diseases such as rheumatoid arthritis. A better understanding of the factors regulating synovial blood flow may help to explain some of the features of such disease states.

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