ARTICLE

Immediate response of retinal vessels to isometric muscle contraction

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Abstract

Isometric muscle contraction results in a rise in systemic blood pressure (BP) and constriction of retinal arterioles. The responses in the anaesthetised cat have been studied to provide further insight into the results of human studies. Constriction (median 3.43% of control values) and dilatation (median 4.17% of control values) were observed; the onset of constriction was delayed by 4 s compared with dilatation. There was spatial and temporal variation in the observed calibre changes, and inter-experimental variation in the calibre change/BP ratio. It is concluded that the response of retinal arterioles of measurable size is not unified, and that the two modes of response differ in mechanism.

Key words Retinal vessels, Blood circulation, Blood pressure, Sympathetic nervous system, Isometric contraction

Isometric muscle contraction provokes a reflex sympathetic stimulation with resultant rise in systemic blood pressure (BP);[1] the phenomenon has been used in its clinical form, the handgrip test, to detect autonomic neuropathy, particularly in diabetes.[2] The rise in systemic BP during this test provokes a constriction of the retinal arterioles in the human subject,[3] which is disproportionately reduced in the presence of a degree of diabetic autonomic neuropathy that only slightly reduces the systemic BP response.[4]

It is well known that the retinal circulation exhibits autoregulation,[5] and that the retinal arteriolar calibre responds to altered perfusion pressure.[6] The mechanism of the response to raised BP due to isometric muscle contraction may have several components:[7] myogenic, constriction in response to increased transmural pressure; neurogenic, a response to sympathetic stimulation; and metabolic, due to the altered balance of local metabolites following increased perfusion.

The evidence for sympathetic innervation of the retina is conflicting. The traditional view was that the arterial innervation stopped at the lamina cribrosa,[8] but a number of papers have supported the presence of non-myelinated nerve fibres related to retinal arterioles;[9–11] also the presence of alpha-adrenergic binding sites has been demonstrated,[12] but their relevance to retinal vascular control is uncertain.

The failure of autoregulation in diabetic retinopathy that has been reported[13,14] makes it important to build on the human observations of the response to the handgrip test, and gain further insight into the mechanism of the retinal arteriolar response. In human experimental subjects only intermittent measurements of BP, coupled with groups of retinal photographs were possible,[3] limiting the extent of analysis of the retinal arteriolar response. A suitable animal model was sought for more detailed investigation. Coote *et al.*,[15] studying the nature of the BP response to isometric muscle contraction, stimulated the lower lumbar anterior spinal nerve roots of the cat, producing tetanic contraction of the leg muscles. This physiological preparation was adapted to the investigation now reported.

Materials and method

Acute, non-survival experiments were performed on adult female cats (sex chosen for husbandry reasons) weighing 2.5–4.45 kg. Experiments were carried out in accordance with the Animals (Scientific Procedures) Act 1986, under Project Licence PPL 60/00914. After sedation with Vetalar (veterinary ketamine) 0.3–0.5 ml intramuscularly, anaesthesia was induced with Saffan (alphoxalone and alphadolone, Glaxo) and maintained by continuous intravenous infusion, appropriately adjusted from time to time. Tracheostomy was performed. Atropine 40–60 μg was given intramuscularly. Blood pressure was monitored by a femoral line, using a transducer and continuous chart recording (Devices M4 recorder). Rectal temperature was monitored and maintained close to 39 °C by table heating. A brachial arterial line was used to draw samples for pH and blood gas analysis from time to time.

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The superior cervical sympathetic ganglion on one side was identified, and confirmed by observation of contraction of the nictitating membrane in response to electrical stimulation of the ganglion afferent root. The ganglion and its connections were then completely excised.

The animal was turned prone and the lower lumbar spinal cord unroofed, the spine being secured in a frame. A force transducer was attached to the severed Achilles tendon of the immobilised leg on the side to be stimulated; the transducer output was plotted on the chart recorder. The motor roots of L6, L7 and S1 were isolated, divided close to the cord, and placed on separate bipolar electrodes, connected to a battery driven, opto-isolated stimulator, set to deliver pulses of 0.1 ms duration at 50 Hz, with a voltage of 0.9–9.0 V.

After preliminary tests had established the appropriate level of electrical stimulus, a series of experimental runs was made. Ten control photographic frames of the retina were exposed; then the motor roots were stimulated for 30 s whilst 18 further frames were exposed; finally 18 further frames were exposed after the stimulus had been withdrawn. These periods are described as the control, stimulus and post-stimulus phases respectively. After each run an interval of several minutes was allowed to elapse until the chart record showed that the BP had stabilised, and as nearly as possible resumed its previous value. The polarity of the stimulating electrodes was reversed after each run. The stimulus voltage was increased from time to time to maintain a satisfactory response. During each run the chart recorder provided traces of the BP response, and the muscle tension developed; markers showed the stimulus duration and individual framing times. So far as possible pairs of runs were performed, alternating between the two eyes.

Earlier both pupils had been dilated with cyclopentolate and atropine eye drops, the globes immobilised with rings stitched to the corneal periphery, and the corneas protected by afocal contact lenses. The head was secured in a frame, its orientation being adjustable in the horizontal and vertical axes; adjustable stops allowed return to the desired setting for each eye. The retina was photographed using a Zeiss (Oberkochen) fundus camera, with a Nikon, 250 frame, motor drive back, framing at intervals of 1.6 s. The selected field in each eye, which was maintained throughout the experiment, was chosen to provide the best opportunity for measurement of arterioles lying on the tapetum, the only part of the fundus with sufficient contrast for vessel measurement; the optic disc was always included. Red-free photographs were taken on Ilford FP4 film; the processing and calibre measurements were made as described by Hill and Crabtree[16] with slight modifications, using a Quantimet 800 image analyser. The selection of sites for measurement was guided primarily by their suitability for image analyser measurement, with the overall consideration of achieving a broad distribution spatially and in terms of vessel size. The resulting measurements were entered on worksheets in the Minitab 8.2 accelerated, statistical program; their further analysis is described below.

In five animals, after the completion of the experimental runs, cannulation of the lateral long posterior ciliary arteries (LPCA) on the surface of the globe was undertaken using the technique of Macri,[17] and the BP recorded simultaneously with the femoral BP.

At the conclusion of the experiments the animals were sacrificed by injection of Euthatal.

Analytical techniques

Blood pressure measurements

Diastolic BP measurements only were taken from the chart recordings, as preliminary analysis showed a close proportional correspondence between diastolic and mean BP measurements. The term BP used in this paper refers to the diastolic blood pressure, unless otherwise indicated.

For each run the control mean BP was calculated, and then the stimulus and post-stimulus measurements expressed as percentage changes of the control mean. The BP responses were defined by continuous deviations from the control mean, bounded during the stimulus phase by the first and last positive deviations, and in post-stimulus phase by the first and last negative deviations. The mean values of the BP % changes during the periods of consistent response were taken as the best parameter of magnitude.

Calibre measurements

The data during the stimulus and post-stimulus phases formed a stochastically distributed time series in which consecutive measurements were not statistically independent; in the control period, however, it was assumed that changes in the vessel calibres did not show a significant trend, so that the readings were treated as statistically independent. To meet this situation a customised method of analysis was adopted, which is outlined in the data processing flow chart (Fig. 1).

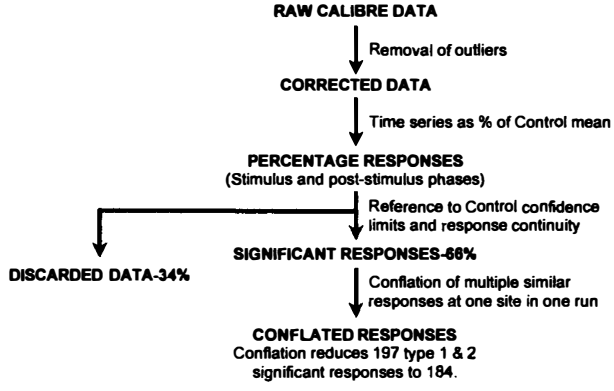

Fig. 1. *Flow chart summarising the processing of calibre data from the image analyser output to the figures reported in the Results section. A detailed explanation, under the same headings, is given in the Analytical Techniques section.*

Preliminary data processing: corrected data

The series of measurements from each site in each run were examined individually; outliers (values whose departure from the smoothed data line obtained by the Minitab 'RSmooth 4253H.twice' procedure[18] exceeded the 2% limits of the control data distribution) were replaced by interpolation. The resultant values were termed corrected data, on which subsequent analysis was based.

Percentage responses

The mean value of the control measurements of each site in each run was calculated, and the readings during the stimulus and post-stimulus phases expressed as percentage changes of the control mean.

Significant responses

An arbitrary criterion was developed after careful preliminary investigation. A significant departure from the mean control calibre was determined by reference to the 95% confidence limits of the control values, using the following criteria: a continuous series of readings, all of the same sign, of which two (or if there were more than 20 readings in the sequence, then three) readings lay outside the 95% confidence limits of the control group, and half or more of the intervening values were outside the 1st or 3rd quartile boundaries. The boundaries of a series of readings of significance were set as the first and last values that were outside the quartile limits. For each episode the median percentage calibre change was determined, together with the frame of onset and frame duration of the response.

Conflated responses

In a number of instances several responses, all of the same sign, either constriction or dilatation, were found in one run, at a single site, during the stimulus phase; when up to three episodes were detected they were conflated on an empirical basis, provided the separation between the component episodes did not exceed an arbitrary three frames, and there was no change of sign in the intervening values. All values within the conflated episodes were included when determining the parameters of the combined episode. Conflation was justified on the basis of the stochastic nature of the data, where a chance combination of results might fall below the qualifying level for a continuous response.

Inter-experimental variation

As analysis proceeded, it became apparent that a wide variation existed between experiments in the magnitude of calibre responses compared with the percentage change in BP. To facilitate inter-experimental comparison a separate experimental correction factor was calculated for constriction and dilatation responses in each phase; the resultant figures were used only for the comparison of calibre responses and BP rise. The mean of the median percentage changes of all significant response episodes (before conflation) at a site was divided by the BP percentage change to provide a site index. The site indices were averaged for each run, as a mean weighted by the number of episodes at each site; and from this run index an experimental index was calculated as a mean of all runs, weighted by the number of sites with significant episodes in each run. Finally a grand index was calculated, as a mean weighted by the number of significant runs in each experiment; this index was divided by the experimental index to provide a correction factor for each experiment.

Results

Blood pressure responses

The mean blood pressure rise in response to isometric contraction, elicited by motor root stimulation, varied from run to run and between experiments. In those experimental runs where significant calibre responses were recorded, the distribution of mean BP rises had a median of 8.76% (quartiles (Q.) 6.66/13.65) and range of 0.29–29.63%. There was considerable inter-experimental variation in the relation between mean muscle tension developed during the stimulus phase and the resulting BP rise, though within experiments the BP response tended to increase with increasing muscle tension.

In most instances the BP rise ceased when the motor root stimulus was withdrawn, to be followed by a BP fall below the control mean value in the post-stimulus phase, median value 9.74% (Q. 6.38/13.46). In six instances the BP rise was unduly prolonged to within 5 frames or fewer of the end of the post-stimulus phase; this occurred sporadically and did not affect all runs in any one experiment. There was a direct correlation between the magnitude of the stimulus BP rise and the total BP swing in the post-stimulus phase, the regression equation being: $y = 12.9 + 0.62x$ (y, BP [% rise + % fall]; x, BP % rise: $r = 0.44$, $p = 0.002$).

There was no clear relationship between stimulus voltage and mean muscle tension. A median response of 6.98 kg force (Q. 6.09/8.74; 1 kg = 9.81 newtons) was recorded with the smallest stimulus of 0.9 V; and a median 6.22 kg force (Q. 4.90/7.29) with the largest stimulus of 9.0 V. Runs with larger stimulus voltages were excluded because of irregular responses.

LPCA recordings of 7 eyes in 5 animals were made. The ratios, LPCA to femoral artery, of the mean BP (diastolic + 1/3 pulse pressure) showed mean values of 0.81 ± 0.050 (mean ± standard deviation (SD)) for left eyes ($n = 3$) and 0.71 ± 0.078 (SD) for right eyes ($n = 4$); the difference was not significant. Sympathectomy had no significant effect. The LPCA to femoral BP ratio did not alter significantly between control and stimulus phases, but increased significantly in the post-stimulus phase (0.83 ± 0.084 (SD)) as compared with the stimulus phase (0.78 ± 0.066 (SD)) (paired $t = 4.47$; $0.01 > p > 0.001$), during 8 runs conducted on the same stimulus protocol

as the calibre-determination runs. From 5 sites in 3 animals a phase lead over the simultaneous femoral recording of 2–18° at the diastolic/systolic inflection of the pulse wave was recorded; sympathectomy and laterality did not appear to affect the results.

Calibre responses

Eleven of 18 experiments showed runs within the 0.9–9.0 V stimulus range. Three types of response were seen: type 1, constriction; type 2, dilatation; and type 3, mixed responses with separate significant constriction and dilatation elements during one run. Sixty-six per cent of all sites measured yielded significant responses. The mean control calibres, over all runs, for the 111 sites with significant responses showed a bimodal distribution (Fig. 2), which peaked at 170 and 240 units (range 108.8–328.8 units). These arbitrary units are equivalent to the calibre measurement in micrometres at the recording film, and represent vessels ranging from the smallest arterioles that could effectively be measured to the largest arterioles near the optic disc – a threefold increase in calibre. The distribution between experiments of significant conflated responses of type 1 (constriction) and type 2 (dilatation) in the stimulus phase is shown in Table 1, where the incidence on the sympathectomised and normal sides is also indicated.

The further analysis concerns only type 1 and type 2 responses after conflation where appropriate; a total of 104 sites yielded 184 responses (Table 1): of these 104 sites 62 yielded significant type 1 or 2 responses in the post-stimulus phase (Table 2). The control mean calibres of these sites showed median values of 212.7 (Q. 168.5/252.7) and 212.5 units (Q. 161.2/252.3) in the stimulus and post-stimulus phases respectively; there was no significant difference between the two distributions.

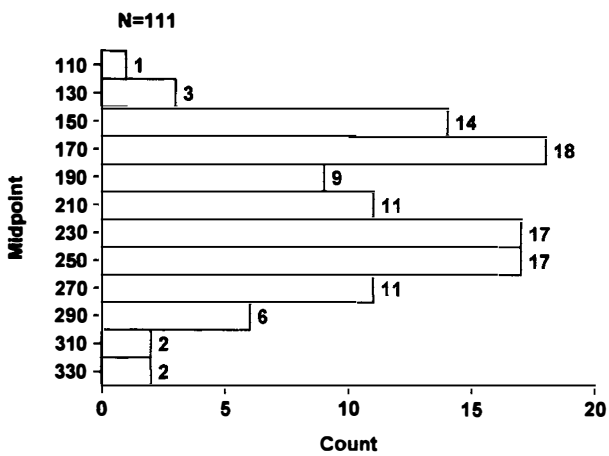

Fig. 2. *Histogram of the mean control calibre distribution of sites showing significant changes during the stimulus phase. The calibre units of the vertical axis are arbitrary (see text).*

Table 1. *Conflated calibre responses: stimulus phase*

	Sympathectomy			Normal		
Expt no.	Runs	Sites	Responses	Runs	Sites	Responses
10	1	3	3	3	3	8
12	3	7	16	–	–	–
13	2	4	7	1	3	3
15	2	6	7	–	–	–
16	2	4	4	2	7	10
17	3	6	15	4	12	27
18	2	4	5	4	5	10
19	1	2	2	2	5	6
20	2	4	5	5	8	21
22	2	4	6	2	8	11
27	–	–	–	3	9	18
Subtotals	20	44	70	26	60	114
Totals				46	104	184

Runs, number of runs with significant calibre changes, in each experiment; Sites, number of sites in each eye with significant calibre changes; Responses, number of conflated responses observed in each eye.
In experiments 12, 15 and 27 one eye only was studied.

Stimulus phase results

Types 1 and 2 responses

Of the 184 responses after conflation, 130 showed constriction (type 1) and 54 dilatation (type 2); the median corrected calibre responses were constriction 3.43% (Q. 2.68/4.90) and dilatation 4.17% (Q. 3.09/5.64), which differed significantly (Mann–Whitney test, confidence interval (CI) 0.01/1.07, $p = 0.048$).

The distributions of control calibres and duration of responses were similar in the two groups; but the distributions of BP percentage rise, though similar in profile, showed a slightly higher median value in the constriction response group (9.13%) compared with the dilatation group (8.01%), which had the larger calibre response. The sympathectomy status had no significant effect on the magnitude of the responses.

As the control mean calibre decreased, there was a significant increase in the size of constriction responses, though with considerable residual variance; for a control

Table 2. *Conflated calibre responses: post-stimulus phase*

Expt no.	Runs	Sites	Responses
10	4	4	6
12	3	6	8
13	2	1	2
15	2	4	6
16	3	8	9
17	7	17	28
18	4	5	5
19	2	2	2
20	3	6	10
22	3	5	6
27	2	4	4
Totals	35	62	86

Runs, number of runs with significant calibre changes in each experiment; Sites, total number of sites with significant calibre changes; Responses, total number of conflated responses observed.
Figures include both eyes, except for experiments 12, 15 and 27, in which one eye only was studied.

calibre of 330 units the predicted response was 2.70%, while for a control calibre of 130 units the predicted response was 4.98%. There was no correlation between the size of dilatation responses and the control mean calibre.

Repeated responses

A single site was observed in repeated runs on 70 occasions, with 2–5 replications. Each response was compared with its predecessor; on 35 occasions there were straight runs of type 1 or type 2 responses, in similar proportions to the general incidence of these responses; in the remaining 35 instances the responses were mixed, of differing types in succeeding replications. During the repeated runs there were 62 instances where the control mean calibre changed significantly between one run and the next (*t*-test significant at the 95% level); in only 19 instances did the response change also, in 17 instances in the same direction as the control calibre change.

Distance from optic disc

There was no evidence that the magnitude of calibre response was related to the distance from the optic disc, which might have been expected were sympathetic neural innervation an important factor.

Response timing

The modal onset for calibre responses in the stimulus phase was frame 11, the first recorded frame after stimulus onset, when 60 responses were recorded (28% of the total). Responses were also recorded as late as frame 30 (when the BP response to stimulus was prolonged); however, the incidence of responses declined rapidly, with a median of 14 frames, 4 frames after the onset, and third quartile of 19 frames. The duration of responses was very variable, but the longer durations tended to span the time elapsing from onset to the end of the BP response.

The time of onset differed between types 1 and 2: in the constriction group (type 1) the median time was frame 15.5, while in the dilatation group (type 2) the response was more rapid, with a median of frame 12, the second frame after the onset of stimulus and approximately 4 s earlier. This frame difference is just significant (Mann–Whitney test, CI 0.00/2.99, $p = 0.049$).

Where sympathectomy was present, there was a longer delay, possibly significant, in the time of onset of constriction responses, the median onset in normal eyes being frame 15 (Q. 12/17.25) while in sympathectomy eyes it was frame 17 (Q. 12.25/22.75) (Mann–Whitney test, CI 0.0/4.0 $p = 0.067$). For dilatation responses the median onset for both normal and sympathectomy eyes was frame 12.

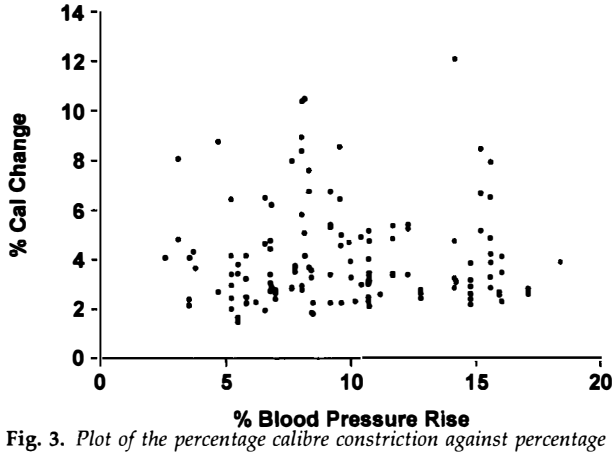

Fig. 3. *Plot of the percentage calibre constriction against percentage blood pressure rise in the stimulus phase, using corrected calibre data. The percentage changes refer to the control mean. No correlation is seen.*

Calibre response and BP rise

The range of site indices (calibre response/BP rise) was 0.25–0.86 for type 1 responses and 0.18–1.00 for type 2 responses. When this inter-experimental variation had been removed (see Analytical Techniques) the adjusted calibre responses, for both types, showed a significant regression on BP rise. The two situations for type 1 are illustrated in Figs. 3 and 4. The regression equations are: type 1, $y = 1.57 + 0.306x$; $r = 0.50$, $p<0.001$; type 2, $y = 1.54 + 0.461x$; $r = 0.51$, $p<0.001$ (y, % calibre change; x, BP percentage rise).

Post-stimulus phase results

During the post-stimulus phase analysis was confined to those sites that had already shown significant responses in the stimulus phase. Sixty-two sites gave significant responses in the post-stimulus phase; their distribution between experiments is shown in Table 2, and the interrelation of stimulus and post-stimulus responses in Table 3. The median post-stimulus responses following stimulus constriction were: constriction 3.22%

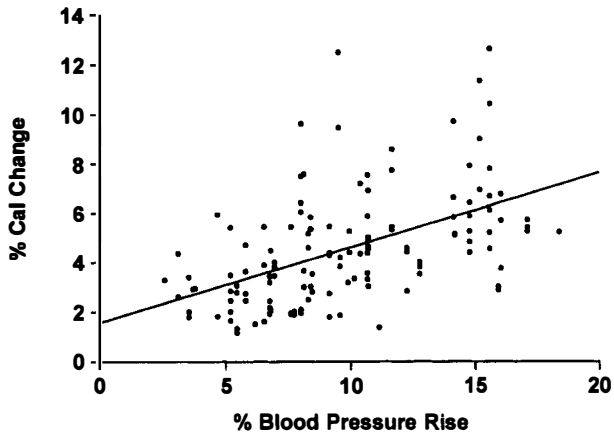

Fig. 4. *Plot of the percentage calibre constriction against percentage blood pressure rise in the stimulus phase, using calibre data adjusted for inter-experimental variation. The percentage changes refer to the control mean. The calculated regression is inserted.*

Table 3. *Relation to calibre responses: post-stimulus to stimulus*

	Post-stimulus response		
Stimulus response	Constriction	Dilatation	Other
Constriction	34	22	3
Dilatation	2	22	3
Subtotals	36	44	6
Total			86

Figures indicate the number of conflated responses of each type – 1 (constriction), 2 (dilatation), 3 (other) – occurring after type 1 or 2 stimulus responses at the same site.

(Q. 2.4/4.76), dilatation 2.89% (Q. 2.45/4.10); and following stimulus dilatation, post-stimulus dilatation 4.60% (Q. 3.27/6.16). The post-stimulus dilatation responses differed significantly, at 2.89% and 4.60% respectively, following stimulus responses of constriction and dilatation (Mann–Whitney test, CI 0.30/2.25, $p = 0.012$). Sympathectomy had no effect on the magnitude of any of the post-stimulus responses. The excess in the number of post-stimulus dilatation responses (22) following stimulus dilatation, over the combined constriction and other responses (5; Table 3, line 2), is significant (chi-square 9.48, $0.01>p>0.001$).

The onset of post-stimulus calibre responses occurred shortly after the BP fall, the median delays being 2.0–2.5 frames in all groups except that of post-stimulus constriction following stimulus constriction, where there was an apparently longer median delay of 8.5 frames. Sympathectomy had no effect on the timing of their onset.

Inspection of the individual time series charts of BP and calibre responses revealed additional information about the three main groups of post-stimulus calibre response. In the 22 cases of dilatation following stimulus constriction, 19 followed closely on the BP inversion from rise to fall, while 3 further cases showed some delay, prolonged in 1. Constriction following stimulus constriction appeared to be a continuous event in 32 cases, allowing for the stochastic nature of the data; as the levels recorded did not immediately reach significance an apparently long delay in onset of the post-stimulus response appeared; in 2 cases there was a return to control levels followed by a late constriction. Two groups of response were found in the 22 cases where dilatation followed stimulus dilatation: 13 showed continued dilatation throughout, though this did not always reach significance; 9 showed a period of return to control levels before post-stimulus dilatation, in all but 2 of these the stimulus phase dilatation was early and short-lived.

Discussion

An important finding in this study was the variation in the type of arteriolar response to the rise in systemic BP during the stimulus phase. Whilst the stochastic nature of the time series data, and the empirical technique for determining the significance of the calibre variations, may account for some of the findings, the existence of 54 dilatation responses alongside 130 of the anticipated constriction responses offers strong evidence that local factors contribute to the response to altered arteriolar perfusion pressure. The innate rhythm of arteriolar tone[19] may account for the variable nature of the responses at the same site observed repeatedly; but correlation between the change in control calibre and the subsequent calibre response was weak, with only 17 instances out of 62 where a change in control calibre was followed by a matching change in calibre response, i.e. a reduction in the control calibre by a constriction response or vice versa.

Active constriction responses of the retinal arterioles had a median onset time 4 s later than the passive dilatation responses, suggesting that either local metabolic processes, triggered by increased perfusion, or systemic humoral influences[7] were important factors in the constriction response. Dilatation, on the other hand, was the immediate passive response of vessels with low initial tone.

The presence of acute unilateral sympathectomy appeared to have no effect on the magnitude of calibre response in the stimulus phase, though the onset of constriction responses was slightly delayed. By contrast established unilateral sympathetic denervation in human subjects resulted in a reduced response on the affected side during the handgrip test,[20] strongly suggesting a neural component in the retinal arteriolar response to systemic sympathetic activity. These results indicate a species difference in the response between man and the cat, with a reduced role for sympathetic innervation in the latter.

The extent of inter-experimental variation in the ratio between mean BP rise and calibre response was considerable, and accords with the observation of Lanigan *et al.*[3] in man that there was no correlation between BP rise and arteriolar constriction; Lanigan suggested that the two effects might be independent, not causally related. Two hypotheses are possible, one relating to the local response, the other to systemic factors. It is generally agreed[21] that the seat of capillary perfusion pressure control lies in the precapillary arterioles; the arterioles accessible to measurement in this study are larger, and may vary in their responsiveness without affecting the well-established autoregulation of the retinal circulation.[5,22] The predicted constriction response almost doubles from 2.70% to 4.98% on passing from the largest to the smallest calibre of arteriole observed, supporting the view of increasing responsiveness as the precapillary arterioles are approached.

Systemically, Bill *et al.*[23] have demonstrated the protective role of ocular sympathetic vasomotor nerves in acute arterial hypertension; but the simultaneous observation of LPCA and femoral artery pressure showed no significant change in the pressure ratios during BP elevation, indicating that regulation at the level of the proximal arteries was unlikely at the levels of BP elevation encountered in these experiments.

The analysis of the post-stimulus phase results included arbitrary judgements based on the inspection of the stochastically generated time series. This procedure, whilst it can only indicate trends, can be justified since all the data runs examined were known to hold significant site responses in both stimulus and post-stimulus phases. It enabled further understanding of the three major response patterns: dilatation or constriction, following constriction in the stimulus phase, and dilatation following dilatation in the stimulus phase. The first pattern, stimulus constriction followed by post-stimulus dilatation, is the anticipated autoregulatory arteriolar response to a rise followed by a fall in perfusion pressure. Constriction in both phases, the second pattern, was revealed as a continuous event through both phases – a persistence of the initial response. The third pattern, dilatation in the post-stimulus phase following stimulus dilatation, was either continuous or intermittent – a persistence in varying degree of reduced arteriolar tone.

The differences between human retinal vessel responses, measured by similar techniques, and the responses in the cat have already been touched upon when considering the effects of unilateral sympathectomy. The morphology of the microvascular bed in the cat is similar to that in man, though the retinal arterioles are branches of the ciliary arteries, the central retinal artery being vestigial.[24] Functionally, the results of this study were similar to those of the normal human studies already reported;[3] those data were further analysed[25] and demonstrated the variability of responses, in both sign and magnitude, during a single handgrip test, and at the same site in sequential tests.

The important results of this study are, firstly, the clear identification of passive retinal arteriolar responses of dilatation of rapid onset when systemic BP is raised, in contrast to the slower onset of active responses of constriction. Secondly, the retinal circulation can no longer be regarded as responding to changes of perfusion pressure in a unified fashion; rather its component arterioles must be seen as responding individually, and variably in time and location, according to local factors, most probably their own inherent state of muscular tone and the ambient metabolic condition.

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