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Effects of cervical sympathetic nerve stimulation on the cerebral microcirculation: possible clinical implications

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Abstract. The action of bilateral cervical sympathetic nerve (CSN) stimulation on mean cerebral blood flow (CBF) and on its rhythmical fluctuations was studied in normotensive rabbits by using laser-Doppler flowmetry (LDF). A reduction in mean CBF, mediated by α-adrenoceptors, was the predominant effect; it was more often present and larger in size in the vascular beds supplied by the carotid than in those supplied by the vertebro-basilar system. This suggests that the sympathetic action facilitates a redistribution of blood flow to the brain stem. The effect induced by CSN stimulation on CBF spontaneous oscillations was a consistent decrease in amplitude and an increase in frequency, irrespective of the changes produced on the mean level of CBF. The possible implications of the sympathetic action on the state of the blood-brain barrier (BBB) are discussed. Experimental and clinical data dealing with the influence of sympathetic activation on the cerebrovascular system have been compared. As a result the possibility of analysing the spontaneous oscillations of CBF for clinical purposes is suggested.

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INTRODUCTION

The role of the sympathetic system in the regulation of the cerebral circulation has not yet been fully clarified. Studies have been performed by activating the sympathetic supply to the brain in normotensive and hypertensive experimental animals. Under normotensive conditions variable results, such as modest vasoconstriction, diphasic or no effects, have been reported by different authors (Busija and Heistad 1984 and ref. in Sato and Sato 1992) in response to sympathetic activation. Under hypertensive conditions cervical sympathetic nerve (CSN) stimulation produced marked constrictor effects on cerebral vessels (Bill and Linder 1976, Heistad et al. 1978, Tamaki and Heistad 1986). It is generally accepted that the sympathetically-induced vasoconstriction extends the upper limit of cerebral blood flow (CBF) autoregulation so that the flow is kept constant in spite of increases in systemic arterial blood pressure (Owman 1986). A protective function against blood-brain barrier (BBB) disruption has been attributed to this action (Heistad and Marcus 1979, Heistad 1984, Faraci et al. 1987).

The purpose of the present investigation is to study the effect of CSN stimulation on microvascular CBF and on its spontaneous oscillations in various brain areas of normotensive rabbits, under various experimental conditions. In particular, we characterized the morphology of these oscillations and investigated whether or not CSN stimulation induces changes to which a protective function can be attributed. It may be in fact speculated that the amplitude of the CBF waves could be a factor which contributes to modify the state of the barrier. In particular, for a given mean CBF value, the presence of alternate rhythmic dilatation and constriction of the vessels might increase the risk of BBB disruption, under conditions in which it is more vulnerable, such as high blood pressure and factors increasing the barrier permeability. We analysed in particular the low-frequency spontaneous oscillations (LFSOs) which may produce large changes in vessel diameter, as observed in the pial vessels of rats and rabbits using intravital microscopy through a cranial window (Auer and Gallhofer 1981, Hundley et al. 1988, Fujii et al. 1990).

The present study was performed on two cerebral territories, i.e. parietal lobe (PL) and ponto-mesencephalic (PM) areas, chosen as representative of the vascular beds supplied by the carotid and vertebro-basilar systems, respectively. The two territories exhibit different extent of sympathetic innervation, the former being richer than the latter (Peerless and Ysargil 1971, Edvinsson and Owman 1977). Laser-Doppler flowmetry (LDF) was used, which provides continuous, real-time monitoring of microcirculation. The data collected through LDF from superficial and intraparenchimal cerebral areas have been shown by other studies (ref. in Sato et al. 1994) to correlate well with those obtained by using other methods.

The data obtained in the present investigation were compared with some clinical data collected using transcranial sonography (TCD). An analogy was found suggesting the possibility to combine TCD with spectral analysis for clinical purposes.

Some of the results presented here have been published in abstract form (Passatore et al. 1994, Passatore et al 1995).

METHODS

Surgical preparation and experimental set up

The experiments were performed on 22 rabbits (weight 2.7-3.0 kg). Six animals were anaesthetized with urethane alone (1.2 g/kg), 16 of them with a cocktail of urethane, ketamine (Ketalar, Parke-Davis) and xylazine (Rompun, Bayer) at doses of 400, 5 and 1.5 mg/kg i.v., respectively, then the last two drugs were continuously infused through a cannulated femoral vein (15-17 mg/kg/h and 4-5 mg/kg/h, respectively). Two rabbits belonging to the latter group were administered pancuronium bromide (Pavulon, Organon Teknika, 0.2 mg/kg i.v., repeated doses) and artificially ventilated through the cannulated trachea so that the end-tidal CO_2 was kept at control values.

General surgery included preparation of the CSN on both sides and fixation of its peripheral stump into a small cylinder containing the stimulating electrodes, cannulation of femoral veins for anaesthetic and drug administration, cannulation of a femoral artery for arterial blood pressure measurement. After having fixed the rabbit head in a stereotaxic frame a portion of parietal and occipital bones of about 1 cm^2 each was drilled out, overlying dura mater removed and the exposed brain areas protected with warm mineral oil.

CBF was recorded by a LDF (PeriFlux PF2B, Perimed, Stockholm, Sweden) whose needle-probe (model PF302) was positioned using a micromanipulator. The flow was estimated from a brain tissue volume of approximately 2-7 mm^3, the sampled vessels include arterioles, capillaries and venules with diameters ranging from 5 to 100-500 μm (Bolognese et al. 1993). The probe was placed at a distance of 1 mm from the cortical surface of the PL for cortical CBF recordings or it was inserted in various zones of the PL and of PM structures, at various depths into the parenchyma. After the probe was lowered into the intended area, it was moved a 50 μm step backwards, before starting each recording session, in order to avoid tissue compression. Great care was taken to evaluate in each recorded area whether the functionality was preserved after probe insertion. The presence of cardiac pulsatility and of respiratory modulation in the flow record, together with its stability over time, were considered good indications. After flowmeter needle-probe was inserted, 15 min equilibration time were allowed before starting the trials. *Post-mortem* histological evaluation gave also indication on possible damage produced by the probe as well as precise information concerning localiaztion of its tip.

Unilateral sympathetic stimulations, ipsi- and contralateral to the recorded site, were tested on several occasions, particularly when bilateral stimulation had produced large effects. In 2 rabbits all these trials were repeated after having blocked neuromuscular junctions with pancuronium bromide.

Efficacy of sympathetic stimulation was assessed by observing the extent and the speed of pupillary dilatation and by monitoring the muscle-cutaneous vasoconstriction through an inductive proximity sensor (Model B18/5 OC, Selet Sensor, Torino Italy), (Roatta et al. 1995). The above mentioned evaluations gave information on the functionality of the fast- and slow-conducting components of the CSN, respectively (Passatore and Pettorossi 1976). The experiments were interrupted when these responses became smaller and sluggish.

The following parameters were routinely monitored: heart rate (ECG signal fed into a rate-meter), systemic arterial blood pressure (Elema-Shönander EMT 34), CO_2% and O_2% concentrations (Engström Eliza Duo CO_2/O_2 Analyser, the sampling probe being connected to a needle inserted into the tracheal tube), electromyogram from jaw muscles to detect possible arousal reactions. Body temperature was maintained at 38°C through a heating blanket regulated by feedback from a rectal thermistor probe.

In eight rabbits the adrenoceptor antagonist phentolamine (Regitin, Ciba; 2.0-2.5 mg/kg) and the ß-adrenoceptor antagonist propranolol (Inderal, ICI-Pharma; 1-2 mg/kg) were intravenously administered.

All signals were recorded on a polygraph and stored on magnetic tape for analysis. Statistical analysis of CBF data, related to different CSN stimulation rates and to different tested areas, was performed by using the two-sample Student's *t*-test.

The animals were sacrificed at the end of the experiments by i.v. injection of a lethal dose of urethane, then the brain was removed, fixed in paraformaldeid (4%), longitudinally sectioned and stained according with the Nissl method.

Analysis of recordings

The CBF signals recorded on magnetic tape were off-line acquired on a PC through a digital acquisition board (PC: 486 33 MHz, acquisition board: Microstar DAP 6400/6) after anti-aliasing low-pass filtering (corner frequency 2 Hz), over epochs lasting 60 s or 90 s, at a sampling frequency of 100 Hz.

The power spectra were computed from each acquired epoch through the Fast Fourier Transform (FFT) after DC component removal; neither data windowing nor averaging was performed in order to achieve the maximum frequency resolution (0.017 Hz and 0.011 for epochs lasting 60 s and 90 s, respectively); further smoothing of the spectrum was obtained by zero-padding, extending the epoch length up to 256 s (Marple 1987).

The frequency range in which power spectra are displayed was chosen depending on the component to be observed: 0-0.4 or 0-0.6 Hz for the low frequency spontaneous oscillations, an interval centred approximately around 3 Hz for cardiac oscillations.

RESULTS

Effect of sympathetic stimulation on mean CBF value

In general our figures, obtained by recording CBF through laser-Doppler flowmetry, evidence that the efficacy of the sympathetic stimulation is greater on the vascular beds supplied by the carotid arteries than on those supplied by the vertebro-basilar system. In particular, bilateral CSN stimulation at 30 imp/s was effective in 78% and in 47% of PL and PM areas, respectively, while 10 imp/s stimulation modified the flow in 59% and 31% of these areas, respectively (Fig. 1). Reduction in CBF was largely the most represented effect, the extent of such a reduction being consistently greater in PL than in PM areas (see table in Fig. 1). In the same areas lower frequencies produced effects of proportionally smaller magnitude or were ineffective. Stimulations at 2-3 imp/s were effective on a small number of PL areas only. A modest and transitory increase in flow occasionally preceded the above mentioned reduction. Pure flow enhancements have been seldom observed at all stimulation frequencies, the occurrence of such an effect being percentually greater for lower frequencies. It is note-worthy that the same CSN stimulation often produce either opposite-sign effects or no effect on adjacent areas.

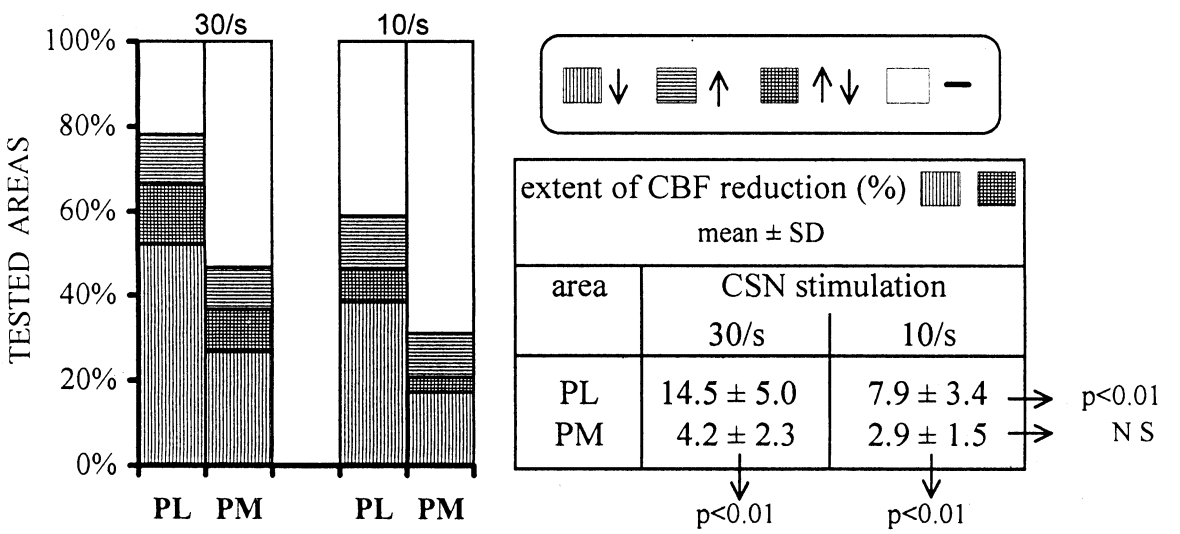

Fig. 1. The histogram reports the percent of occurrence of the 3 types of responses induced by bilateral CSN stimulation at 30 and 10 imp/s on average microvascular CBF in all PL and PM tested areas. In the columns, vertical hatch indicates the CBF increase, horizontal hatch the decrease and cross hatch the areas in which the decrease was preceded by a small and transient increase. Open columns indicate areas unaffected by CSN stimulation. PL tested areas are 96, PM areas 52. In the table is shown the size of the sympathetically-induced flow reduction, expressed as percent change of the mean control value ± SD. One value for each area at each stimulation frequency is computed. *P*-values, obtained by the comparison (one-sided *t*-test) between the effects observed in the 2 territories and at the two stimulation frequencies, are reported below and beside the table, respectively. These data are collected from all experiments, i.e. from the group of rabbits anaesthetized with the cocktail of urethane-ketamine-xylazine and from the group anaesthetized with urethane only. CSN stimulation parameters: 0.5 ms pulse duration, 6-10 V.

With regard to the time course of the sympathetically-induced effect, the latency of the response was 2 to 10 s after stimulus onset, fully developed and reached a maximum after 20-60 s, usually it remained rather stable throughout the stimulation, seldom it slowly and slightly decreased in size. After sympathetic stimulation was discontinued the mean CBF exhibited variable patterns in its return to control; time course ranged between 20 s and 4 min depending on the stimulation parameters. High stimulation frequencies and durations usually required longer time for recovery.

Compared with the bilateral stimulation, unilateral sympathetic stimulation produced considerably smaller changes in ipsilateral PL microcirculation, virtually no effect on the contralateral side and on PM areas.

The sympathetically-induced changes in mean CBF did not show significant differences in the 3 groups of experiments, i.e. performed on rabbits anaesthetized with urethane alone, with urethane-ketamine-xylaxine and with the same anaesthetic cocktail plus the paralysing agent pancuronium bromide.

The effect induced by CSN stimulation on CBF in the same area was compared before and after α- and ß-adrenergic blockade. The sympathetically--induced decrease in CBF was almost completely abolished after α-blockade. The phase of flow increase, when present in control trials, was not significantly affected by α-blockade while it was consistently reduced or abolished by ß-blockade.

Presence of rhythms in basal recordings

The analysis of the morphology of microvascular CBF waves recorded in normotensive rabbits under basal conditions allows the identification of four different rhythmical variations: (1) the I order rhythm which is the one at highest frequency, synchronous with the heart rate, which expresses the pulsating flow in arteriolar and pre-arteriolar segments; it is visible when the time constant of 0.2 s is used while it is considerably attenuated with 1.5 s value; (2) the II order rhythm, synchronous with the respiratory rate, visible with 1.5 s time constant; (3) low frequency spontaneous oscillations (LFSOs) with frequency ranging between 4 and 12/min, attributed to vasomotion, they are visible with 1.5 s and 3.0 s time constant; (4) very low frequency spontaneous oscillations with frequency ranging between 0.3 and 2/min, also attributed to vasomotion.

Most of the work reported here refers to LFSOs classified as such if they met the following requirements: presence of a periodicity with rather regular frequency, peak-to-peak amplitude of the flow oscillations grater than 10% of the mean CBF value. In this group flow records were also included which exhibited "spindle type" oscillation patterns, i.e. grouping of regular waves with the above described characteristics, lasting minimum 30 s, intermingled with phases of smaller amplitude and irregular fluctuations.

LFSOs were not related to changes in systemic arterial blood pressure. They were present in 41% of the tested areas in animals anaesthetized with the cocktail urethane-chetamine-xylazine while they were never observed in those anaesthetized with urethane. Their amplitude ranged up to 40% of the mean control value. The systemic arterial blood pressure was not significantly different in the two groups of rabbits.

Effect of sympathetic stimulation on CBF oscillations

The bilateral CSN stimulation at 30 imp/s was effective on 65% of the areas exhibiting LFSOs. The most common finding was a reduction in amplitude of these waves (92%), mostly associated with an increase in their frequency (66%). The same effect, though less often represented and smaller in size, was obtained with stimulation frequencies as low as 2-3 imp/s. At variance with the effects on mean blood flow, stimulation was effective on a higher percentage of areas in the brain stem than in the parietal lobe. This effect on the waves could be associated or not with changes in the mean CBF value. The sympathetically-induced changes in the

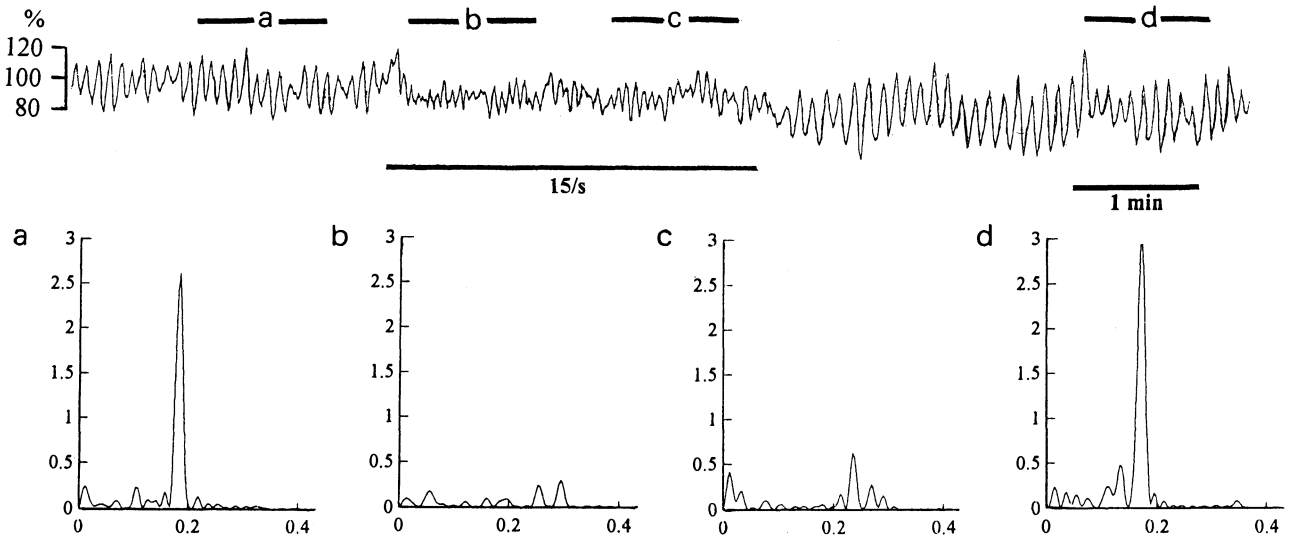

Fig 2. Effect of bilateral CSN stimulation on cerebral blood flow, the low-frequency spontaneous oscillations of which show a regular pattern. Each plot represents the CBF power spectrum computed in the various phases of the trial as indicated by bars on top of the figure. CBF amplitude is expressed as percent variation of the control mean value; power spectra are displayed in arbitrary units in the range of 0-0.4 Hz.

morphology of the CBF waves is shown by spectral analysis (Figs. 2 and 3). When a clean low-frequency rhythm was analysed, as in Fig. 2, a narrow single lobe located at the corresponding frequency was observed; during sympathetic stimulation there was a loss of the dominant rhythm, a shift toward higher frequencies and a broadening of the spectrum which denotes loss of regularity in the oscillation. After the end of the stimulation, a transient phase of increase in amplitude above control values and decrease in frequency preceded the return to control, which required 2 to 6 min. In those areas in

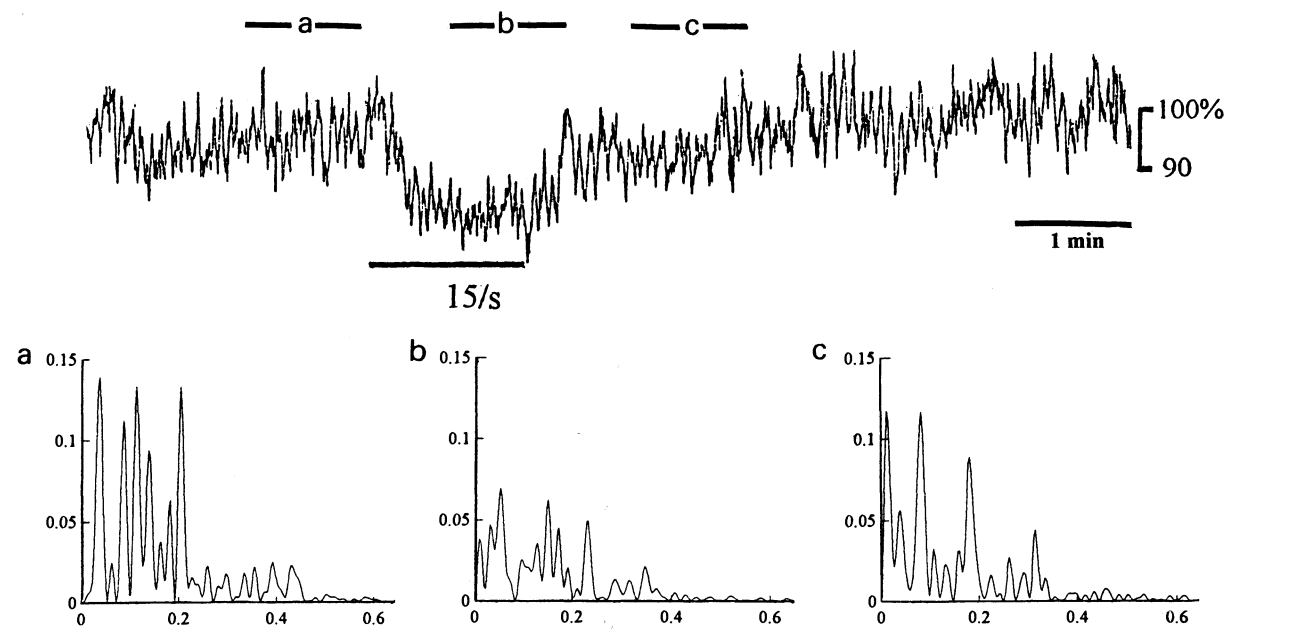

Fig. 3. Effect of bilateral CSN stimulation on cerebral blood flow exhibiting irregular low-frequency oscillations. Indications as in Fig. 5 except for the frequency range of the power spectra, here extended to 0.6 Hz.

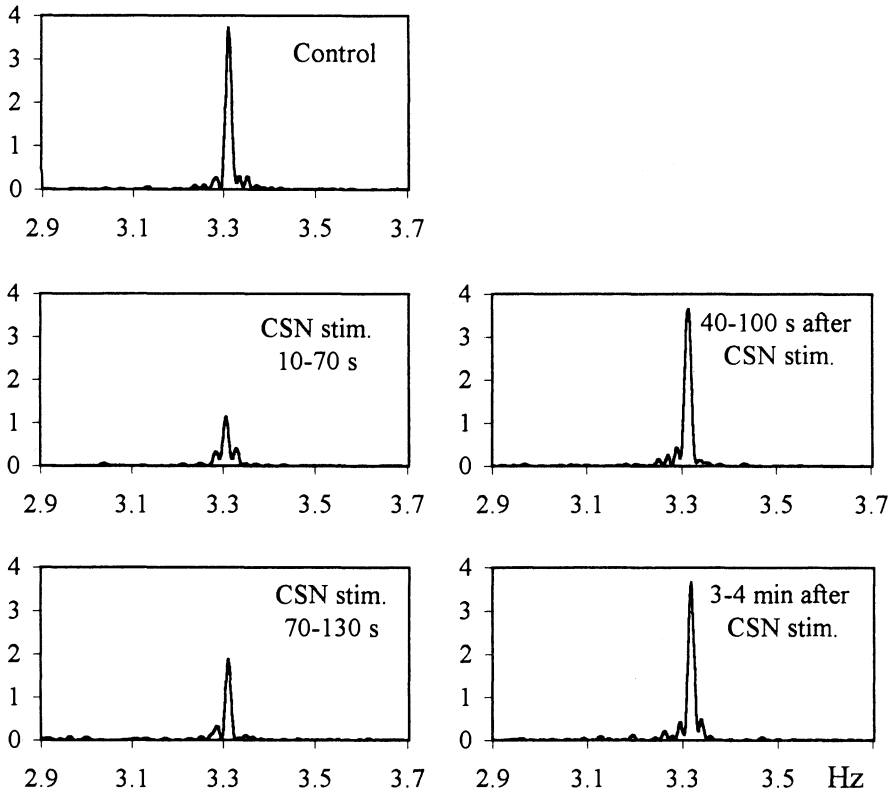

Fig. 4. Power spectra displayed in the range of 2.9-3-7 Hz show the effect of bilateral CSN stimulation on the cardiac oscillations of CBF. The stimulation produces a marked decrease in the amplitude of the cardiac component while its frequency remains stable throughout the trial.

which the spectral analysis evidenced a less regular oscillatory pattern, sympathetic stimulation still induced a reduction in the power of the spectral components (Fig. 3).

In addition to the spectral analysis of LFSOs, an analysis in the frequency range of I order waves has been performed in trials in which these waves exhibited a large amplitude (Fig. 4). During CSN stimulation there was a consistent decrement in the power of the cardiac component, in analogy with what was observed for the low frequency waves. Heart rate was unaffected by CSN stimulation as shown by the persistence of the main lobe at the same frequency value.

DISCUSSION

Sympathetic action on CBF mean value

From our results it appears that the sympathetic stimulation is effective in a larger number of areas in the parietal lobe, which is supplied by carotid arteries, than in the brain stem, which is supplied by the vertebro-basilar system. This observation is consistent with the extent of sympathetic innervation in these two vascular beds as shown by morphological data (Peerless and Yasargil 1971, Edvinsson and Owman 1977). The most common finding of our experiments was a decrease in microvascular flow, which was sometimes preceded by a modest and transient increase. An increase was observed in a small number of areas and seemed percentually more represented in the brain stem and for low frequency stimulations, as reported by Saeki et al. (1990) in cortical areas of the rat. In addition these authors suggest that the coexistence of sympathetically-induced dilator and constrictor effects on cerebral vessels may be responsible for some of the discrepancies emerging from the literature (see ref. in Sato and Sato 1992). In fact, changes in the relative amplitude and time course of these two different effects may produce a diphasic response as well as a pure increase or decrease. From our experiments the coexistence of two opposite effects is also suggested by the following findings: (1) the decrease and the increase in CBF are mediated by the

activation of α- and of ß-adrenergic receptors respectively, as also observed in the rat (Saeki et al. 1990); (2) a larger variability of the responses to sympathetic stimulation was observed in the areas in which diphasic effects were present.

The functional implication of the non-uniform sympathetically-induced effects in various cerebral areas and within the same area is that this system may be able to produce a redistribution of blood flow. In particular, the fact that the sympathetic vasoconstrictor action is exerted preferentially on the rostral portion of the brain could produce a redistribution of flow with improvement of the perfusion to lower structures such as the limbic system and the brain stem. It may be argued that, in emergency conditions associated with sympathetic hyperactivity, such an action could favour the perfusion of areas which are responsible for preserving the vital functions and the homeostasis.

Sympathetic action on CBF spontaneous oscillations

LFSOs, which are attributed to vasomotion (Hudetz 1992), exhibited a frequency ranging between 4 and 12/min in different areas and were not related to changes in the mean level of arterial systemic blood pressure. They were present in 41% of the tested areas in the animals anaesthetized with the cocktail of urethane-chetamine-xylazine and absent in those anaesthetized with urethane alone. This different behaviour cannot be attributed to different levels of systemic arterial blood pressure, often indicated as one of the mayor factors in determining the presence of LFSOs (Auer and Gallhofer 1981, Hudetz 1992). Their amplitude ranged up to 40% of the mean control value. It is possible that both the occurrence and the amplitude of oscillations are underestimated even in the former condition since, in awake rabbits, vasomotion producing large modifications in vessel diameter was observed in all the arterioles, at least in the pial district (Hundley et al. 1988), using intravital microscopy. Frequency of LFSOs was rather stable over time in each area, while contiguous areas in the same cerebral structure could exhibit waves of different size and frequency.

Bilateral sympathetic stimulation has been shown to considerably affect the morphology of CBF low frequency spontaneous oscillations. This effect consisted of a decrease in amplitude and an increase in frequency of such oscillations, irrespective of changes induced on CBF mean value. A tonically inhibitory effect exerted by the autonomic nervous system on vasomotion is also suggested by Hundley et al. (1988) who reported a larger occurrence of vasomotion in autonomically-inhibited than in normally-innervated rabbits.

With regard to the possible mechanism of the sympathetic action on LFSOs, their reduction in amplitude and increase in frequency corresponds to a reduction in the excursion of the capillary wall, which suggests an increased stiffness of the up-stream system, likely due to the constriction of the relevant cerebral arteries and arterioles. This is also suggested by the change in the power in the fast component of the spectrum, i.e. the I order waves, which shows an analogous decrement during CSN stimulation.

From the above findings it may be suggested that sympathetic system could influence the cerebral circulation by affecting not only the mean level of cerebral perfusion but also the amplitude of the rhythmical oscillations of the flow which are reported to modify local microvascular perfusion by improving capillary blood flow and capillary-tissue fluid exchange (Fagrell et al. 1980, Burrows et al. 1981, Schmid-Schönbein et al. 1981, Intaglietta and Gross 1982, Hudetz et al. 1987). In addition large excursions of the capillary wall have been reported to stimulate the endothelial release of nitric oxide (NO) (Pohl et al. 1986, Rubanyi et al. 1986) which exerts a dilator activity on the vessels (Diéguez et al. 1993, Pearson and Vanhoutte 1993). Then it may be argued that sympathetic system activation, by decreasing vessel pulsatility, should also prevent or reduce NO release, thus potentiating the direct constrictor effect on the brain vessels.

The large oscillations of the vessel wall may represent a factor of risk in some conditions, as, e.g.,

when in acute and chronic hypertension cerebral vessels undergo passive distension with a high susceptibility to "break-through" of autoregulation and to disruption of BBB (Mayan et al. 1986, Baumbach 1988, Tuor 1992). An increase in permeability of the barrier may be also induced by brain injury (Pardridge 1985), by pharmacological treatment (Sakaki et al. 1990) etc. Under such circumstances the additional presence of large vessel-pulsatility might increase the risk of BBB disruption, which might be prevented or limited by the sympathetically-induced decrease in the amplitude of pulsatility.

An evaluation of the integrity of the BBB was performed in cats by Bill and Linder (1976) by using as indicator the leakage of Evans Blue and unilateral sympathetic stimulation. They showed that the breakdown of the barrier during elevation of systemic arterial blood pressure is absent or less marked on the sympathetically-stimulated side than on control side. Furthermore Sakrab and Johanson (1989) report a higher resistance of the BBB to blood pressure increase in conscious than in anaesthetized rats. Their data may be interpreted as being the result of a protective influence of the sympathetic system on the barrier; anaesthetics could in fact impair the protection since they considerably reduce the activity in several sections of the sympathetic system (Greisheimer 1965, Passatore and Pettorossi 1976, Grassi and Passatore 1990).

It is interesting to see whether or not the above role of the sympathetic innervation has clinical implications. Stressful conditions (reproduced by standardized methods such as hand grip, cold pressor test, tilting) which in some patients cause coronary vasoconstriction (Glass 1997) are not reported to exert a similar effect on the cerebral circulation. Moreover in vivo it is quite difficult to explore the sympathetically-mediated responses in the cerebral circulation. In our clinical section, however, some results were obtained by applying a 5-min lasting cold pressor test and by monitoring bilaterally the blood flow velocity induced in the middle cerebral artery (MCA) by means of transcranial Doppler sonography (TCD) (Micieli et al. 1994). The test performed on healthy humans induces significant decrease of mean velocity in the MCA of both sides. The FFT analysis of these velocity signals shows the presence of LFSOs. The cold pressor test induces modifications of these oscillations consisting of an increase in their frequency and a contemporary decrease in their amplitude. The involvement of the "central" sympathetic pathways in causing the observed haemodynamic change was demonstrated by the fact that pre-treatment with clonidine, an alpha-2 agonist which is known to inhibit the central noradrenergic firing, induced a marked reduction of the response to the 5-min cold pressor test (Micieli et al. 1994).

There is a strong analogy between the above data collected on humans and those obtained in animal experiments of this investigation, during direct stimulation of the CSN. The existence of such an analogy has suggested to couple spectral analysis to Doppler sonography in order to evaluate sympathetic dysfunction in cerebral circulation. Preliminary data collected on patients exhibiting neurological central degenerations, like the so-called Multiple System Atrophy associated with autonomic failure, show an almost complete absence of response to the cold pressor test. In addition a wide spectrum of responses has been recorded in diabetic patients with or without reduced sympathetic control of the cardiovascular function (Micieli et al. 1995). The same technique has evidenced a correlation between the LFSO amplitude and the presence of carotid artery obstruction (Diehl et al. 1991). These preliminary data encourage the use of the above methodology for clinical purposes as it represents a non invasive technique which might provide information on the progress of the disease.

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