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Intracranial baroreflex yielding an early Cushing response in human

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Summary

The Cushing response is a pre-terminal sympatho-adrenal systemic response to very high ICP. Animal studies have demonstrated that a moderate rise of ICP yields a reversible pressure-mediated systemic response. Infusion studies are routine procedures to investigate, by infusing CSF space with saline, the cerebrospinal fluid (CSF) biophysics in patients suspected of hydrocephalus. Our study aims at assessing systemic and cerebral haemodynamic changes during moderate rise of ICP in human.

Infusion studies were performed in 34 patients. This is a routine test perform in patients presenting with symptoms of NPH during their pre-shunting assessment. Arterial blood pressure (ABP) and cerebral blood flow velocity (FV) were non-invasively monitored with photoplethysmography and transcranial Doppler.

The rise in ICP (8.2 ± 5.1 mmHg to 25 ± 8.3 mmHg) was followed by a significant rise in ABP (106.6 ± 29.7 mmHg to 115.2 ± 30.1 mmHg), drop in CPP (98.3 ± 29 mmHg to 90.2 ± 30.7 mmHg) and decrease in FV (55.6 ± 17 cm/s to 51.1 ± 16.3 cm/s). Increasing ICP did not alter heart rate (70.4 ± 10.4/min to 70.3 ± 9.1/min) but augmented the heart rate variance (0.046 ± 0.058 to 0.067 ± 0.075/min).

In a population suspected of hydrocephalus, our study demonstrated that a moderate rise of ICP yields a reversible pressure-mediated systemic response, demonstrating an early Cushing response in human and a putative intracranial baroreflex.

Keywords: Infusion studies; Cushing response; transcranial Doppler; cerebral haemodynamics; systemic haemodynamics; baroreflex; intracranial.

Introduction

The Cushing response is a well-known pathophysiological phenomenon: rising intracranial pressure (ICP) to high values produces an increase in arterial blood pressure (ABP) [1]. The Cushing response has been demonstrated to be a sympatho-adrenal systemic response to brainstem ischemia [5, 8, 9]. However, few animal studies [4, 6, 7] found that a moderate rise of ICP could also influence ABP, via a putative pressure-mediated response. If the Cushing response is known in clinical practice, the pressure-mediated response to moderate rise of ICP has never been described in human.

Infusion studies are clinical routine procedures to investigate the circulation of cerebrospinal fluid (CSF) in patients suspect of hydrocephalus. ICP is moderately augmented by mean of an infusion in the ventricular or sub arachnoid space with mock CSF; subsequently the biophysical properties of the CSF circulation are computed [2]. Our work aims at using infusion studies to assess the cerebral and systemic haemodynamics changes during moderated rise of ICP in human.

Material and method

34 patients suspected of normal pressure hydrocephalus (cognitive impairment, gait disturbance and/or urinary incontinence, enlarged ventricles on CT) were included in this study. There were 15 females and 19 males (mean age: 54 years; range 28–76 years). A computerized CSF infusion test with constant–rate infusion [2] was undergone *via* a surgically pre-inserted Ommaya Reservoir connected to the ventricular catheter. The patients stayed supine in a comfortable tilting armchair. The ventricular pressure was measured at baseline for ten minutes, and termed "baseline" ICP. Then the ventricular space was infused with normal saline solution (0.9%) at room temperature (20 °C) with a rate of 1.5 ml min^{-1}. Subsequently ICP rose until a steady-state plateau has been achieved, termed "plateau" ICP (*cf.* Fig. 1). This "plateau" ICP corresponds to the pressure equilibrium at which all the mock CSF infused is reabsorbed.

During the infusion study, arterial blood pressure (ABP) and cerebral blood flow velocity (FV) were continuously and non-invasively measured using photoplethysmography and transcranial Doppler (TCD). The signals of CSF pressure (*i.e.* ICP), ABP and FV were amplified, converted and stored on a computer running our in-house software [2].

Off line, we calculated: ABP mean, systolic, diastolic and pulse amplitude (respectively ABPm, ABPs, ABPd and ABPa), cerebral

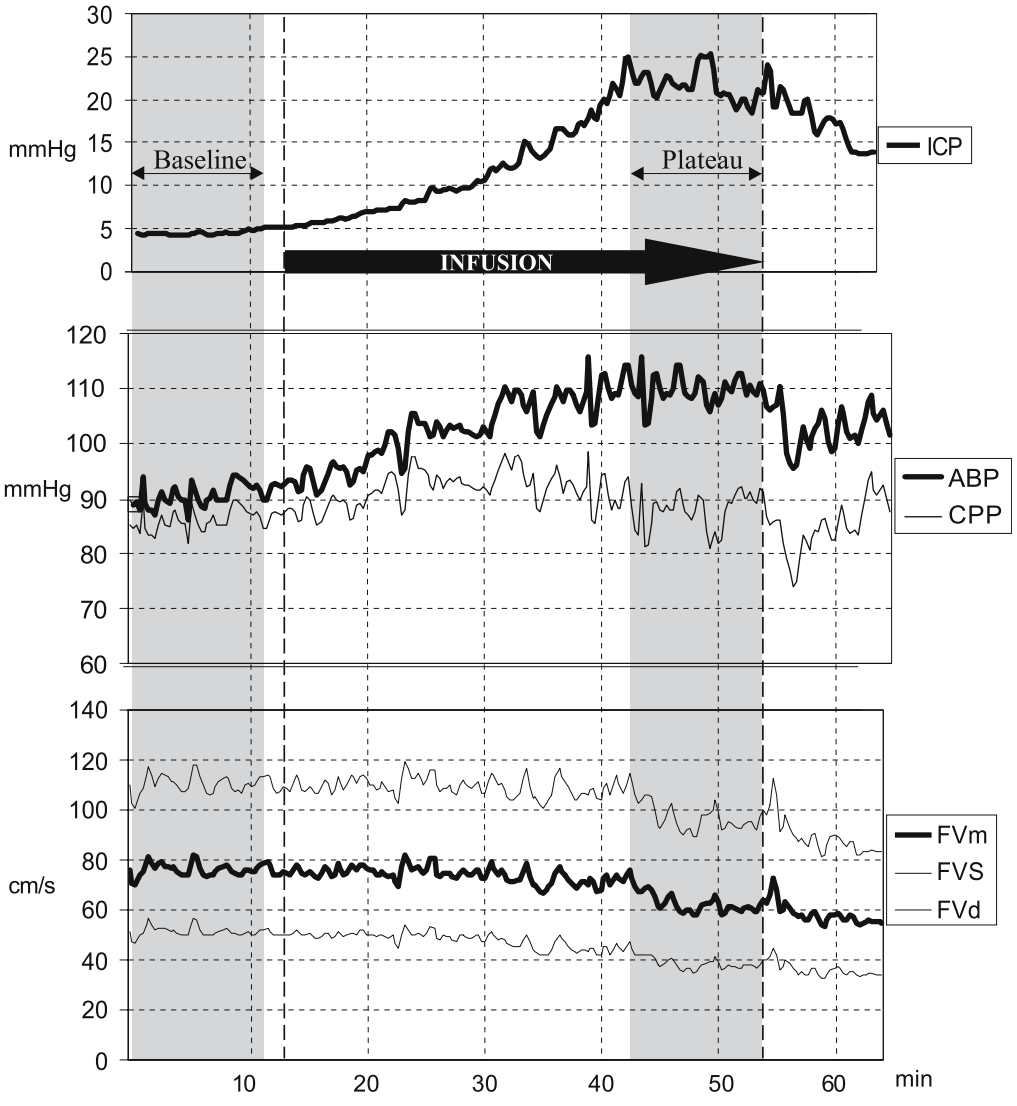

Fig. 1. An example of infusion test: ABPm, ABPs, ABPd and ABPa for ABP mean, systolic, diastolic and pulse amplitude (respectively), ICP and CPP for intracranial pressure and cerebral perfusion pressure; HRm, HRsd and HRcv for heart rate mean, standard deviation and coefficient of variance; FVm, FVs, FVd and PI for flow velocity mean, systolic, diastolic and Gosling pulsatility index

perfusion pressure (CPP = ABPm-ICP), heart rate mean, standard deviation and coefficient of variance (HRm, HRsd and HRcv), FV mean, systolic and diastolic (FVm, FVs and FVd), and the Gosling pulsatility index (PI = (FVs-FVd)/FVm). For every infusion test, we carefully selected ten minutes of recording during the "baseline" period, and ten minutes of ICP steady-state "plateau" (*cf.* Fig.1).

Results

The "baseline" and "plateau" values of the different variables are displayed on Table 1. The arithmetic difference between baseline and plateau, plus the significance level (paired t test) are also shown.

The rise in ICP yielded a significant increase in ABP mean, systolic, diastolic and in ABP pulse amplitude. The concurrent rise in ICP and in ABP had a net negative effect on the CPP, which significantly decreases. There was no change in the mean value of the heart rate, whereas its standard deviation and coefficient of variance significantly increased. The rise in ICP yielded also a significant drop in FV mean, systolic, and diastolic, but an increase in pulsatility index.

Conclusions

The Cushing response should be considered as a four-step process: i) rise in ICP approaching ABP, ii)

Table 1. *Changes in ICP and other haemodynamic parameters*

	Baseline	Plateau	Difference	
ICP (mmHg)	8.2 ± 5.1	25 ± 8.3	16.8 (+204.8%)	<0.0001
ABPm (mmHg)	106.6 ± 29.7	115.2 ± 30.1	8.6 (+8.1%)	<0.0001
ABPs (mmHg)	145.3 ± 36.4	156.7 ± 37.4	11.4 (+7.8%)	<0.0001
ABPd (mmHg)	76.5 ± 31.4	90.5 ± 26.5	14 (+18.3%)	<0.0001
ABPa (mmHg)	35.1 ± 19.3	38.0 ± 22	2.9 (+8.3%)	0.049
CPP (mmHg)	98.3 ± 29	90.2 ± 30.7	−8.2 (−8.3%)	<0.0001
HR (min^{-1})	70.4 ± 10.4	70.3 ± 9.1	−0.08 (−0.1%)	0.903
HRsd	3.11 ± 3.31	4.5 ± 4.5	1.4 (+44.8%)	<0.0001
HRcv	0.046 ± 0.058	0.067 ± 0.075	0.021 (+46%)	0.0005
FVm ($cm\ s^{-1}$)	55.6 ± 17	51.1 ± 16.3	−4.5 (−8.2%)	<0.0001
FVs ($cm\ s^{-1}$)	83.0 ± 22.9	80.7 ± 23.3	−2.3 (−2.8%)	0.011
FVd ($cm\ s^{-1}$)	37.9 ± 12.8	33.4 ± 12.2	−4.5 (−12%)	<0.0001
PI	0.828 ± 0.209	0.946 ± 0.257	0.118 (+14.3%)	<0.0001

oligemia or ischemia of the medulla oblongata, iii) sympathetic and sympatho-adrenal activation, finally iv) systemic effects. In a way, the Cushing response ought to be considered as a pre-lethal phenomenon [3]. Our study demonstrates that, in awake subjects, a moderate rise of ICP produces i) a rise in ABP, ii) a drop in CPP, iii) a reduction in FV and iv) an increase in the heart rate variance.

In the population suspected of hydrocephalus, our data support the notion that a moderate rise of ICP yields a reversible pressure-mediated systemic response, demonstrating an early Cushing response in human.

The early Cushing response raises three issues: the concept of intracranial baroreflex, its influence on cerebral haemodynamics and on autonomic status.

1. The concept of intracranial baroreflex is supported by the notion that intracranial pressure can influence directly *via* a reflex loop systemic haemodynamics. As we demonstrated an intracranial baroreflex, therefore there should be an intracranial baroreceptor to trigger the reflex.
2. ICP bears direct and indirect influences on cerebral haemodynamics. The direct influence on cerebral perfusion is driven by CPP, altered directly by ICP. However, the changes in cerebral haemodynamics during changes in CPP are dampened by the mechanism of autoregulation. ICP has an indirect effect on cerebral haemodynamics, *via* the changes in systemic haemodynamic related to the putative early Cushing response. Therefore, when ICP rises, the secondary increase in ABP lessens the drop in CPP. The intracranial baroreflex could be considered as a protective mechanism to maintain cerebral haemodynamics. However, the significant reduction of flow velocity during the rise in ICP remains to be clarified, as one would expect flow velocity to be maintained.
3. The rise in ICP probably interferes with the sympathetic/parasympathetic balance of the cerebral vasculature, as suggested by the change in heart rate variance. The drop in flow velocity can be related to changes in autonomic status.

The early Cushing response demonstrated in our subgroup of patients, is a new physiological concept and might be of clinical importance.

References

1. Cushing H (1901) Concerning a definite regulatory mechanism of vasomotor centre which controls blood pressure during cerebral compression. Bull Johns Hopkins Hosp 12: 290–292
2. Czosnyka M, Whitehouse H, Smielewski P, Simac S, Pickard JD (1996) Testing of cerebrospinal compensatory reserve in shunted and non-shunted patients: a guide to interpretation based on an observational study. J Neurol Neurosurg Psychiatry 60(5): 549–558
3. Fitch W, McDowall DG, Keaney NP, Pickerodt VWA (1977) Systemic vascular responses to increased intracranial pressure. 2. The "Cushing" response in the presence of intracranial space-occupying lesions: systemic and cerebral haemodynamics studies in the dog and the baboon. J Neurol Neurosurg Psychiatry 40: 843–852
4. Fitch W, McDowall DG, Paterson GM, Hain WR (1977) Systemic vascular responses to increased intracranial pressure. 3. Effects of individual balloon inflations on intracranial pressure and the systemic effects. J Neurol Neurosurg Psychiatry 41: 340–344
5. Johnston IH, Rowan JO, Harper AM, Jennett WB (1972) Raised intracranial pressure and cerebral blood flow. I. Cisterna magna infusion in primates. J Neurol Neurosurg Psychiatry 35(3): 285–296
6. Hayreh SS, Edwards J (1971) Vascular response to acute intracranial hypertension. J Neurol Neurosurg Psychiatry 34: 587–601

7. Nakamura K, Osborn JW Jr, Cowley AW Jr (1987) Pressor response to small elevations of cerebroventricular pressure in conscious rats. Hypertension 10(6): 635–641
8. Rowan JO, Teasdale G (1977) Brain stem blood flow during raised intracranial pressure. Acta Neurol Scand [Suppl] 64: 520–521
9. Van Loon J, Shivalkar B, Plets C, Goffin J, Tjandra-Maga TB, Flameng W (1993) Catecholamine response to a gradual increase of intracranial pressure. J Neurosurg 79(5): 705–709

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