Effect of osmolarity on CSF volume during ventriculo-aqueductal and ventriculo-cisternal perfusions in cats

Maraković, Jurica; Orešković, Darko; Radoš, Milan; Vukić, Miroslav; Jurjević, Ivana; Chudy, Darko; Klarica, Marijan

Source / Izvornik: **Neuroscience Letters, 2010, 484, 93 - 97**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1016/j.neulet.2010.07.058

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:957489

Maraković J., Orešković D., Radoš M., Vukić M., Jurjević I., Chudy D., Klarica M. (2010) ***Effect of osmolarity on CSF volume during ventriculo-aqueductal and ventriculo-cisternal perfusions in cats.*** **Neuroscience Letters, 484 (2). pp. 93-7. ISSN 0304-3940**

http://www.elsevier.com/locate/issn/03043940

http://www.sciencedirect.com/science/journal/03043940

http://dx.doi.org/10.1016/j.neulet.2010.07.058

Effect of osmolarity on CSF volume during ventriculo-aqueductal and ventriculo-cisternal perfusions in cats

Jurica Maraković[1], Darko Orešković[2*], Milan Radoš[3], Miroslav Vukić[4], Ivana Jurjević[3], Darko Chudy[1], Marijan Klarica[3]

[1] Department of Neurosurgery, Dubrava University Hospital, Avenija G. Šuška 6, 10 000 Zagreb, Croatia

[2] Laboratory of Neurochemistry and Molecular Neurobiology, Department of Molecular Genetics, Ruđer Bošković Institute, Bijenička c. 54, 10 000 Zagreb, Croatia

[3] University of Zagreb School of Medicine and Croatian Institute for Brain Research, Šalata 11, 10 000 Zagreb, Croatia

[4] University of Zagreb School of Medicine, Department of Neurosurgery, Kišpatićeva 12, 10 000 Zagreb, Croatia

Pages number = 18

Figures number = 4

Corresponding author:

[*]*D. Orešković*

Laboratory of Neurochemistry and Molecular Neurobiology, Department of Molecular Genetics, Ruđer Bošković Institute, Bijenička c. 54, 10 000 Zagreb, Croatia

Fax: 385 1 456 1 177

Tel: 385 1 468 0 218

E-mail address: doresk@irb.hr

Keywords: Cat, Cerebrospinal fluid, Cerebrospinal fluid hydrodynamics, Cerebrospinal fluid volume, Ventriculo-aqueductal perfusion, Ventriculo-cisternal perfusion.

Abstract

The effect of cerebrospinal fluid (CSF) osmolarity on the CSF volume has been studied on different CSF/brain tissue contact areas. It has been shown, on anesthetized cats under normal CSF pressure, that the perfusion of CSF system (12.96 µl/min) by hyperosmolar CSF (400 mOsml/l) leads to significantly higher outflow volume (µl/min) during ventriculo-cisternal perfusion (29.36 ± 1.17 and 33.50 ± 2.78) than the ventriculo-aqueductal perfusion (19.58 ± 1.57 and 22.10 ± 2.31) in experimental period of 30 or 60 min. Both of these hyperosmolar perfusions resulted in significantly higher outflow volume than the perfusions by isoosmolar artificial CSF (12.86 ± 0.96 and 13.58 ±1.64). This results suggest that the volume of the CSF depends on both the CSF osmolarity and the size of the contact area between CSF system and surrounding tissue exposed to hyperosmolar CSF. However, all of these facts imply that the control of the CSF volume is not in accordance with the classical hypothesis of cerebrospinal fluid hydrodynamic. According to this hypothesis, the CSF volume should be regulated by active formation of CSF (secretion) inside the brain ventricles and passive CSF absorption outside of the brain. Obtained results correspond to the new hypothesis which claims that the volume of CSF depends on the gradients of hydrostatic and osmotic forces between the blood on one side and extracellular fluid and CSF on the other. The CSF exchange between the entire CSF system and the surrounding tissue should, therefore, be determined by (patho)physiological conditions that predominate within those compartments.

According to the generally accepted hypothesis of the cerebrospinal fluid (CSF) dynamics, CSF is produced within the cerebral ventricular system, and then circulates slowly from the brain ventricles towards the subarachnoid space cortex to be absorbed into the venous sinuses across the arachnoid villi (1, 10). It is believed the CSF is formed mainly by the secretory activity of the choroid plexuses inside the brain ventricles, and that the majority of the remaining CSF is probably produced by the ependyma (2, 6). Since CSF formation is an active process, the CSF formation rate should not be significantly altered by moderate changes in the intracranial pressure (5, 23). It means that the entire physiological volume of the CSF within the CSF system is preserved by the balance between the secretion of the CSF inside the brain ventricles and passive absorption of the CSF from cortical subarachnoid space (outside the ventricles). This classical hypothesis, with minor modifications, represents a common point of reference in scientific papers, review articles and in numerous textbooks, and is proffered as an unquestionable fact. The hypothesis is applied to explain the removal of cerebral metabolites, an increase in intracranial pressure (ICP) and the development of hydrocephalus.

Opposite to the classical hypothesis, we have shown (22) that at a physiological intracranial pressure in isolated brain ventricles the CSF production and absorption are in balance. Furthermore, when labeled water is infused into the lateral ventricle, it is not distributed to the cisterna magna, but rather absorbed into periventricular capillaries, all of which indicates that the CSF volume (water) is significantly absorbed inside the ventricles (3, 4). Moreover, when the aqueduct of Sylvius had been cannulated, no CSF outflow was observed from the isolated ventricle at a normal CSF pressure, suggesting that no net formation of CSF occurred in the ventricles (20, 21). Also, in isolated brain ventricles no increase in ICP during 190 min was obtained, nor were the ventricles dilatated, which obviously confirmed an absence of active CSF formation (14). Based on our experimental work, we have recently postulated new hypothesis of the CSF hydrodynamic (3, 4, 18) which suggests that CSF is not solely formed inside the brain

ventricles and absorbed outside them in cortical subarachnoid space but equally appears and disappears in the whole CSF system. This means that the volume of CSF depends on the fluid exchange within the brain and medulla spinalis depending on the hydrostatic gradients and osmotic forces present between the blood (capillaries) on one side and the interstitial fluid of brain parenchyma and the CSF on the other. Therefore, total CSF volume within the CSF system should depend on unceasing (permanent) exchange of the CSF with the interstitial fluid (ISF) of the surrounding tissue along the entire cerebrospinal system.

If our hypothesis is correct, the exchange between the CSF and the ISF should depend on fluid osmolarity, as was previously reported (8, 26), as well as on the size of the contact area between the CSF system and surrounding brain tissue. In other words, increase in the CSF osmolarity should result in water retreat from capillaries in the surrounding tissue into ISF (as a consequence of arrival of osmotically active substances from CSF to adjacent ISF), where greater contact area implies greater increase of CSF/ISF volume.

This was tested on anesthetized cats by perfusion of the CSF space with smaller (lateral and the third ventricles; ventriculo-aqueductal perfusion; Fig. 1a) and larger contact area (lateral, the third and the fourth ventricles and cisterna magna; ventriculo-cisternal perfusion; Fig. 1b), one time using isoosmolar, and another time using hyperosmolar artificial CSF (aCSF). That way both types of perfusion were performed at normal ICP and at the same perfusion rates (12.96 μl/min). The volumes of collected samples were compared to each other. If higher osmolarity is to result in substantial accumulation of CSF at a larger CSF area, volume of the collected perfusate should be significantly greater at ventriculo-cistenal perfusion i.e. it would support our hypothesis.

The experiments were performed on adult cats, unselected for age and sex, ranging in weight from 1.6 to 3.8 kg. All experimental procedures were performed in accordance with the European Directive 86/609/EEC on the protection of animals used for experimental and other

scientific purposes, and the Law on Animal Rights and Protection of the Republic of Croatia, with the approval of the institutional Ethical Committee. The animals were anesthetized with an intraperitoneal injection of chloralose (α-chloralose, Fluka; 100 mg/kg). After the femoral artery had been cannulated, blood pressure was recorded via a "T"-connector and samples of blood were taken for the analysis of blood gases. As the cats continued breathing spontaneously under anesthesia no significant changes either in blood pressure or gases were observed.

Two types of experiments were performed: the ventriculo-aqueductal (Fig. 1a) and ventriculo-cisternal (Fig. 1b) perfusion, with both isoosmolar and hyperosmolar aCSF. In each case the cats were positioned in stereotaxy (Cat model, D. Kopf, Tujunga, California, USA) with heads elevated, the external auditory meatus being 15 cm above the stereotaxic table (sphinx position). A 22–gauge needles were placed by a micromanipulator into both lateral ventricles at coordinates 4.5 mm anterior and 9 mm lateral from the zero point of the stereotaxic atlas, and 8–10 mm vertically from the dural surface, until free communication with the CSF was obtained. One needle was connected via a polyethylene tubing to a perfusion pump (Palmer pump) and the perfusion solution was infused at the rate of 12.96 µl/min, whereas the other one was used to measure the CSF pressure (Fig. 1a and 1b) by a Statham strain gauge connected to the polygraph (7D, Grass, Quincy, Massachusetts, USA).

For ventriculo-aqueductal perfusion (Fig. 1a), the aqueduct of Sylvius was approached via transcerebellar route and cannulated so that the external end of the plastic cannula was positioned extracranially. The skull was hermetically closed thereafter. Methodology has been described in detail in our previous publications (14, 18, 21). For ventriculo-cisternal perfusion (Fig. 1b), cisterna magna was also cannulated by a direct puncture with a stainless steel cannula (22 gauge) which was fixed in position by a holder and connected with the plastic tubing filled with aCSF (19). Thirty-min samples of perfusate were collected in both types of perfusion from external end of cannulas adjusted to physiological level of the CSF pressure. After surgical

treatment the CSF pressure was adjusted to physiological value by adjusting the outflow tubing above (6 – 8 cm H_2O) the external meatus (Fig. 1). The level of the external auditory meatus was taken as a zero pressure point. The perfusion was allowed to proceed for 30 min prior to collecting the first sample in order to stabilize the perfusion outflow rate. The samples of perfusate were collected every 30 minutes in duration of one hour in which perfusate consisted of isoosmolar or hyperosmolar aCSF (400 mOsml/l). The aCSF had of the following composition: 8.10 NaCl; 0.25 KCl; 0.14 CaCl; 0.11 $MgCl_2$; 1.76 $NaHCO_3$; 0.07 NaH_2PO_4; 0.13 urea; 0.61 glucose; grams per liter distilled water. Hyperosmolar sucrose solution was prepared by diluting 21.43 g sucrose (Saharoza, Kemika, Croatia) per liter of aCSF.

At the end of ventriculo-aqueductal perfusion experiment, trypan blue (1 mg/ml) was administered (0.5 ml) through the needle placed into the lateral brain ventricle to test blockage of the aqueduct of Sylvius with plastic cannula. If color was observed behind the aqueduct in cavity of the fourth ventricle, experiment was discarded. At the end of experiment, an overdose of thiopentone was injected via femoral vein to euthanize the animals.

Statistical analysis for all the results was performed using paired Student's *t*-test.

Pursuant to the above mentioned, we have shown that there is no net CSF formation in isolated brain ventricles under physiological intracranial pressure (ICP) (21). For that reason in ventriculo-aqueductal perfusion of inflow rate (12.96 μl/min) of isoosmolar aCSF is equal to the outflow rate (21). Namely, if CSF is mainly formed inside the brain ventricles and is absorbed into subarachnoid space, it has to circulate at physiological CSF pressure through the aqueduct of Sylvius or, as is the case in this model (Fig. 1a), via plastic cannula positioned in the aqueduct. Direct (visual) observation of the CSF outflow throughout external end of the cannula (at physiological ICP) should, therefore, represent CSF formation (Fig. 1a). The collected volume of CSF divided by the time of collection represents the rate of CSF formation (21). Such experimental result, that infused volume is equal to outflow volume, enables us to test if

hyperosmolar aCSF could change the volume of collected CSF. If hyperosmolar aCSF extracts fluid from ISF of the surrounding tissue, the outflow rate should be higher than the inflow one. Hence, if net CSF formation does not exist, under the same experimental conditions (physiological ICP; 12.96 µl/min), similar result during ventriculo-cisternal perfusion would be expected (perfusion inside ventricles and subarachnoid space), i.e. equal inflow and outflow rate at isoosmolar perfusion and higher outflow than inflow rate at hyperosmolar perfusion (Fig. 1b).

In the first group of experiments at normal ICP, the outflow rate during ventriculo-aqueductal and ventriculo-cisternal perfusion was measured after isoosmolar aCSF infusion (60 min; 12.96 µl/min; Palmer infusion pump, England), and outflow rate was compared to the pump testing rate (Fig. 2). The volume of samples was determined by weighing (Mettler, Toledo AT 20, Switzerland). No difference between the outflow rate in both groups of perfusion methods was observed during the 30 and 60 min periods of infusion, i.e. the volume of aCSF infused was the same to the fluid volume collected by passage of isolated brain ventricles (ventriculo-aqueductal perfusion; lateral and the third ventricles) or by passage of ventricles and subarachnoid CSF space together (ventriculo-cisternal perfusion; lateral, the third and the fourth ventricles and cisterna magna). In other words, after isoosmolar perfusion at normal ICP, the change in CSF volume was not obtained in perfused part of the CSF system. The absence of reduction or enhancement in detected outflow volume also means that there is no net CSF formation or absorption in studied part of the CSF system.

In the second group of experiments at normal ICP pressure, the outflow rate during ventriculo-aqueductal (Fig. 3a) and ventriculo-cisternal (Fig. 3b) perfusion (60 min; 12.96 µl/min; Palmer infusion pump, England) was measured after hyperosmolar (400 mOsml/l) infusion of aCSF. The outflow rates were compared to results in isoosmolar experiments obtained under the same experimental conditions. After 30 and 60 min of hyperosmolar aCSF infusion, a significant increase in the outflow was observed in comparison with the outflow

obtained during isoosmolar aCSF perfusion in ventriculo-aqueductal (Fig. 3a) and ventriculo-cisternal experiments (Fig. 3b). It suggests that osmotic force significantly influences control of the CSF volume inside the brain ventricles as well as in whole CSF system (brain ventricles and subarachnoid space). The increase of CSF osmolarity has resulted in an increase of CSF volume.

In Fig. 4, effects of the same hyperosmolar infusion (12.96 µl/min; 400 mOsml/l) on different contact areas of CSF/brain tissue at normal ICP pressure are shown; on a smaller contact area by ventriculo-aqueductal perfusion, and on a larger contact area by ventriculo-cisternal perfusion. It is obvious that in spite of the same rate of perfusion and the same osmolarity of perfusate, after 30 and 60 min periods of infusion, a significant increase in the outflow was observed in ventriculo-cisternal perfusion. In other words, if larger contact area of the CSF system is exposed to hyperosmolarity, greater effect on entire CSF volume should be expected.

Similarly as in our study, the net movement of water from the blood into brain tissue was demonstrated during development of osmotic brain edema (7, 25). Namely, when the osmolarity of blood is lower than the osmolarity in the brain parenchyma and CSF (e.g., fast reduction of blood osmolarity in patients with hyperglycemia after administration of insulin and hypoosmolar solution), an osmotic arrival of fluid from the blood into brain interstitial tissue and CSF occurs, which results in brain edema and increased CSF pressure. On the other hand, if the blood osmolarity is increased (e.g., i.v. application of mannitol hyperosmolar solution in treating cerebral edema), a decrease of CSF pressure occurs, due to osmotic movement of water from interstitial brain tissue. This clearly indicates that the net movement of water between different CNS compartments depends on the osmotic gradient. Furthermore, it has been shown that in case of brain ischemia, the ischemic area of brain parenchyma shows an accumulation of water due to an increase of tissue osmolarity (for twenty mOsml/l above control values) (9).

It was observed that water accumulation in the brain parenchyma due to an increase of tissue osmolality also occurs in neurotrauma patients (11, 12). It was shown (11) that necrotic brain tissue sampled from the central area of contusion demonstrated a very high osmolality. The cerebral contusion induced an increase in tissue osmolality and a significant decrease of specific gravity in contused tissue has reflected water accumulation (13).

Our previous studies (15, 17) in dogs have shown that bacterial meningitis caused by *Streptococcus pneumoniae* increased CSF osmolarity and pressure. In addition, it has been demonstrated on experimental animals that the same hyperosmolarity which has been applied in different CNS compartments differently affected the CSF pressure (16). Namely, application into CSF space led to significantly higher increase of CSF pressure than such an application into brain parenchyma (16). Thus, effect of osmolarity on the CSF pressure in a smaller area (distribution of osmotically active substances is limited after application into brain parenchyma) was lower than in the larger area (better distribution of osmotically active substances after application in CSF system). These results correspond to our results (see Fig. 4) where the effect of the same hyperosmolarity on CSF volume is also higher in case of distribution along larger area. Therefore, if osmotically active substances from brain necrotic area reach the CSF, significantly greater change of CSF volume and pressure and severe patient's clinical state should be expected.

In conclusion, results obtained in our perfusion experiments on cats suggest that, at normal ICP, the volume of CSF is not regulated via CSF secretion inside the brain ventricles and CSF absorption outside of them. Namely, it has been clearly shown by isoosmolar perfusion experiments that there is no net CSF formation inside the brain ventricles and no passive CSF absorption in the subarachnoid space (Fig.2). In addition, it has also been shown that the volume of CSF depends on the changes in CSF osmolarity (Fig. 3). Thus, increase in CSF osmolarity leads to an increase of the CSF volume. Impact of osmolarity on the CSF volume will be higher

if the contact CSF/brain tissue area exposed to hyperosmolarity is larger (Fig. 4). To summarize, it seems that CSF volume would not depend on the differences between CSF secretion and absorption rates, but on the osmolarity of CSF.

Finally, these results contradict the classic hypothesis, and therefore support recently proposed new hypothesis on CSF hydrodynamics (4, 14, 18), according to which CSF is being permanently produced and absorbed in the whole CSF system as a consequence of filtration and reabsorption of water through the capillary walls into ISF of the surrounding brain tissue. The CSF exchange between an entire CSF system and the surrounding tissue depends on (patho)physiological processes (trauma, ischemia, etc.) which can cause the changes of fluid osmolarity in different CNS compartments.

References

1. A. Brodlet, M. Stoodley, CSF pathways: a review, Br J Neurosurg. 21 (2007) 510-520.

2. P.D. Brown, S.L. Davies, T. Speake, I.D. Millar, Molecular mechanisms of cerebrospinal fluid production, Neurosci. 129 (2004) 957-970.

3. M. Bulat, Dynamics and statics of the cerebrospinal fluid: the classical and a new hypothesis. In: C.J.J. Avezaat, J.H.M. Ejindhoven, A.I.R. Maas, J.T.J. Tans, (Eds.), Intracranial pressure VIII, Springer-Verlag, Berlin, Heidelberg, New York, 1993, pp.726-730.

4. M. Bulat, V. Lupret, D. Orešković, M. Klarica, Transventricular and transpial absorption of cerebrospinal fluid into cerebral microvessels, Coll Antropol. 31 (suppl 3) (2008) 43-50.

5. R.W.P. Cutler, L. Page, J. Galichich, G.V. Waters, Formation and absorption of cerebrospinal fluid in man, Brain. 91 (1968) 707-720.

6. H. Davson, K. Welch, M.B. Segal, Physiology and pathology of the cerebrospinal fluid, Edinburgh, Churcill Livingstone, 1987, 1113 pp.

7. K.G. Go, The normal and pathological physiology of brain water, Adv Tech Stand Neurosurg. 23 (1997) 47-142.

8. G.M. Hochwald, A. Wald, C. Malhan, The effect of osmotic gradients on cerebrospinal fluid production and its sodium ion content and on brain water content, Trans Am Neurol Assoc. 99 (1974) 219-221.

9. K.A. Hossmann, The pathophysiology of ischemic brain swelling. In: Y. Inaba, I. Klatzo, M. Spatz, (Eds.), Brain edema, Springer-Verlag, Berlin, Heildeberg, New York, Tokyo, 1985, pp. 365-384.

10. C.E. Johanson, J.A.III. Duncan, P.M. Klinge, T. Brinker, E.G. Stopa, G.D. Silveberg, Multiplicity of cerebrospinal fluid functions: new challenges in health and disease, Cerebrospinal Fluid Res. (2008) 5, 10 doi:10.1186/1743-8454-**5**-10

11. Y. Katayama, T. Kawamata, Edema fluid accumulation within necrotic brain tissue as a cause of the mass effect of cerebral contusion in head trauma patients, Acta Neurochir. 86 (2003) 323-327.

12. T. Kawamata, Y. Katayama, T. Mori, N. Aoyama, T. Tsubokawa, Mechanisms of the mass effect of cerebral contusion: ICP monitoring and diffusion MRI study, Acta Neurochir. 81 (2002) 281-283.

13. T. Kawamata, T. Mori, S. Sato, Y. Katayama, Tissue hyperosmolality and brain edema in cerebral contusion, Neurosurg Focus 15 (2007) 22(5) E5.

14. M. Klarica, D. Orešković, B. Božić, M. Vukić, V. Butković, M. Bulat, New experimental model of acute aqueductal blockade in cats: Effects on cerebrospinal fluid pressure and the size of brain ventricles, Neurosci. 158 (2009) 1397-1405.

15. M. Klarica, B. Gmajnički, D. Orešković, M. Bulat, Osmotic force of the CSF and intracranial pressure in health and disease. In: C.J.J. Avezaat, J.H.M. Ejindhoven, A.I.R. Maas, J.T.J. Tans, (Eds.), Intracranial pressure VIII, Springer-Verlag, Berlin, Heidelberg, New York, 1993, pp.735-737.

16. M. Klarica, N Mitrović, D. Orešković, N. Kudelić, T. Jukić, R. Varda, M. Bulat, Effect of osmolality increase in brain ventricles, subarachnoid space and brain parenchyma on intracranial pressure, Period Biol. 100 (1998) 217-220.

17. M. Klarica, N Mitrović, D. Orešković, T. Jeren, B. Gmajnički, M. Bulat, Osmolality of cerebrospinal fluid during experimental meningitis and post mortem, Period Biol. 98 (1996) 41-44.

18. D. Orešković, M. Klarica, M. Bulat, The formation of cerebrospinal fluid: nearly a hundred years of interpretations and misinterpretations, Brain Res Rev. in press (2010) DOI. 10.1016/j.brainresrev.2010.04.006

19. D. Orešković, M. Klarica, V. Lupret, M. Vukić, The character of the cerebrospinal fluid production, Neurosci Res Communic. 26 (2000) 69-76.

20. D. Orešković, M. Klarica, M. Vukić, Does the secretion and circulation of the cerebrospinal fluid really exist? Med Hypotheses. 56 (2001) 622-624.

21. D. Orešković, M. Klarica, M. Vukić, The formation and circulation of cerebrospinal fluid inside the cat brain ventricles: a fact or an illusion? Neurosci Lett. 327 (2002) 103-106.

22. D. Orešković, P.S. Whitton, V. Lupret, Effect of intracranial pressure on cerebrospinal fluid formation in isolated brain ventricles, Neurosci. 41 (1991) 773-777.

23. M. Pollay, A. Stevens, P.A. Roberts, Alteration in choroid plexus blood flow and cerebrospinal fluid formation by increased ventricular pressure. In: J.H. Wood (Ed.), Neurobiology of cerebrospinal fluid, Vol. 2, Plenum Press, New York, 1983, pp. 687-695.

24. R.C. Rubin, E.S. Henderson, A.K. Ommaya, M.D. Walker, D.P. Rall, The production of cerebrospinal fluid in man and its modification by acetazolamide, J Neurosurg. 25 (1966) 430-436.

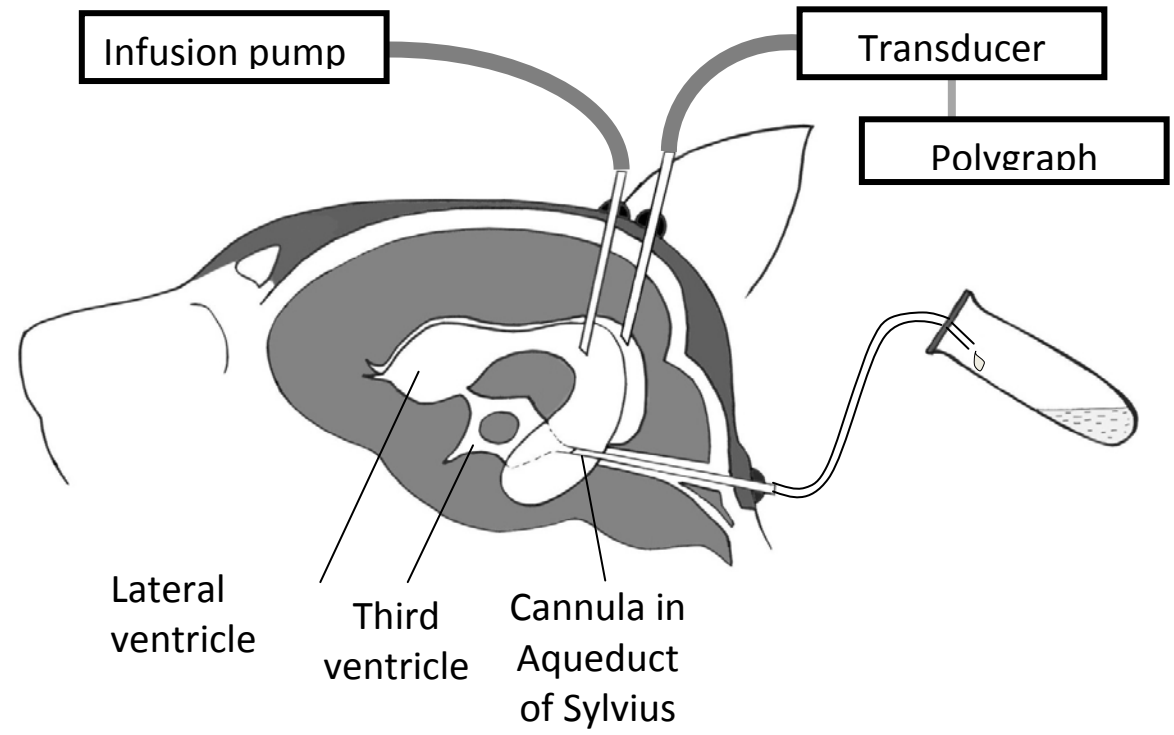
25. J.G. Verbalis, Brain volume regulation in response to changes in osmolality, Neurosci. (2010) doi:10.1016/j.neuroscience.2010.03.042

26. A. Wald, G.M. Hochwald, C. Malhan, The effects of ventricular fluid osmolality on bulk flow of nascent fluid into the cerebral ventricles of cats, Exp Brain Res. 25 (1976) 157-167.

Figure legend

Figure 1.

The experimental model scheme of ventriculo-aqueductal (**a**) and ventriculo-cisternal perfusion (**b**) on cat.


Infusion pump
Transducer
Polygraph
Lateral ventricle
Third ventricle
Cannula in Aqueduct of Sylvius

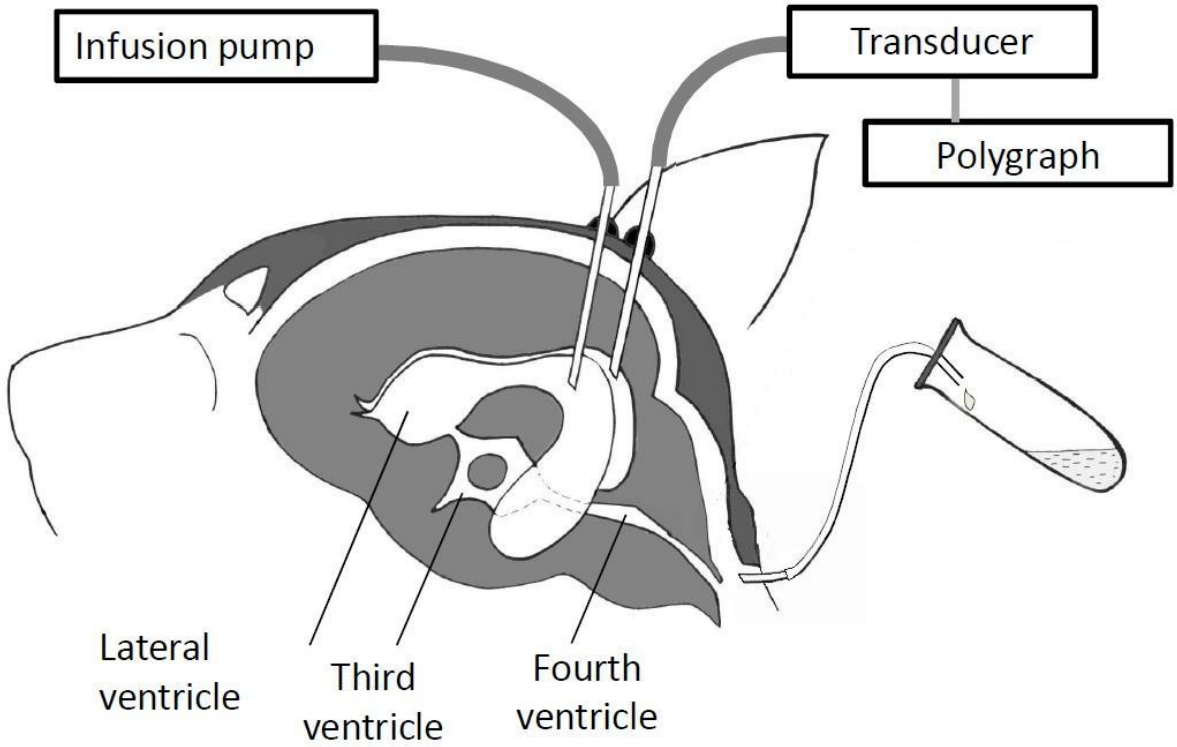

Infusion pump
Transducer
Polygraph
Lateral ventricle
Third ventricle
Fourth ventricle

Figure 2.

The rate of aCSF infusion obtained by pump testing (n=5; □; 12.96 µl/min) during the 30 and 60 min and the outflow rate obtained on cats by aCSF ventriculo-aqueductal (n=6; ▤) and ventriculo-cisternal perfusion (n=6; ⊡) under the same duration (30 and 60 min) and rate of infusion (12.96 µl/min). The results are shown as mean value ± SEM. Differences between the outflow and infused rates are not statistically significant.

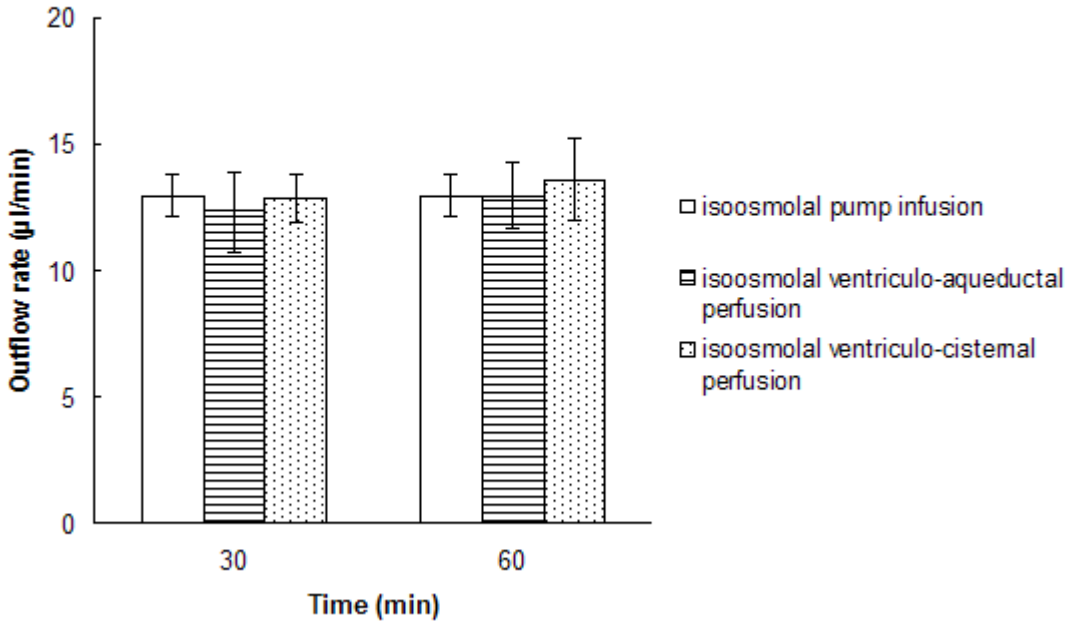
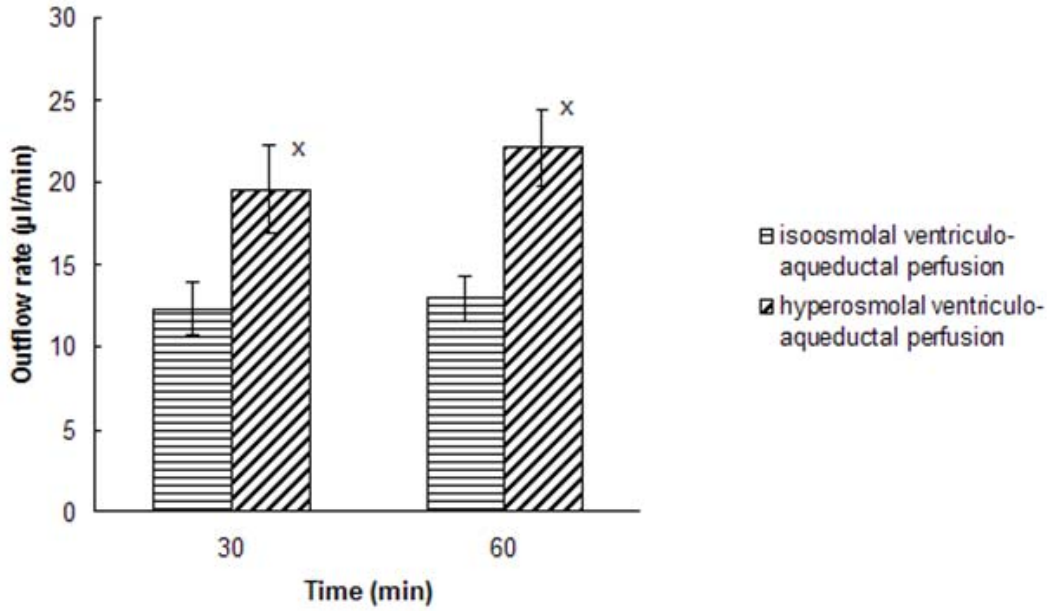


Figure 3.

a) The outflow of perfusate in cats during the 30 and 60 min by ventriculo-aqueductal perfusion (12.96 µl/min) with isoosmolar (n=6; ▤) and with hyperosmolar (n=6; ▨; 400 mOsml/l) aCSF; and **b)** the outflow of perfusate in cats during the 30 and 60 min by ventriculo-cisternal perfusion (12.96 µl/min) with isoosmolar (n=6; ▥) and with hyperosmolar (n=6; ▩; 400 mOsml/l) aCSF. The results are shown as mean values ± SEM. Differences between the outflow rates during isoosmolar and hyperosmolar perfusion of aCSF are statistically significant ($^{x}p<0.05$; $^{xx}p<0.02$).

a


30
25
20
15
10
5
0
Outflow rate (µl/min)
x
x
30
60
Time (min)
isoosmolal ventriculo-aqueductal perfusion
hyperosmolal ventriculo-aqueductal perfusion

b

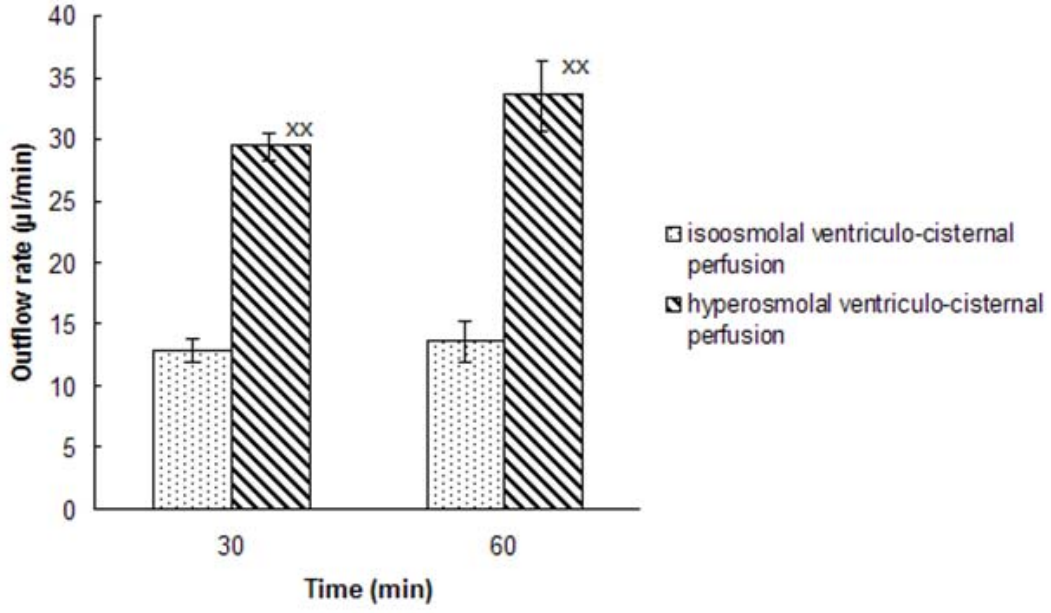
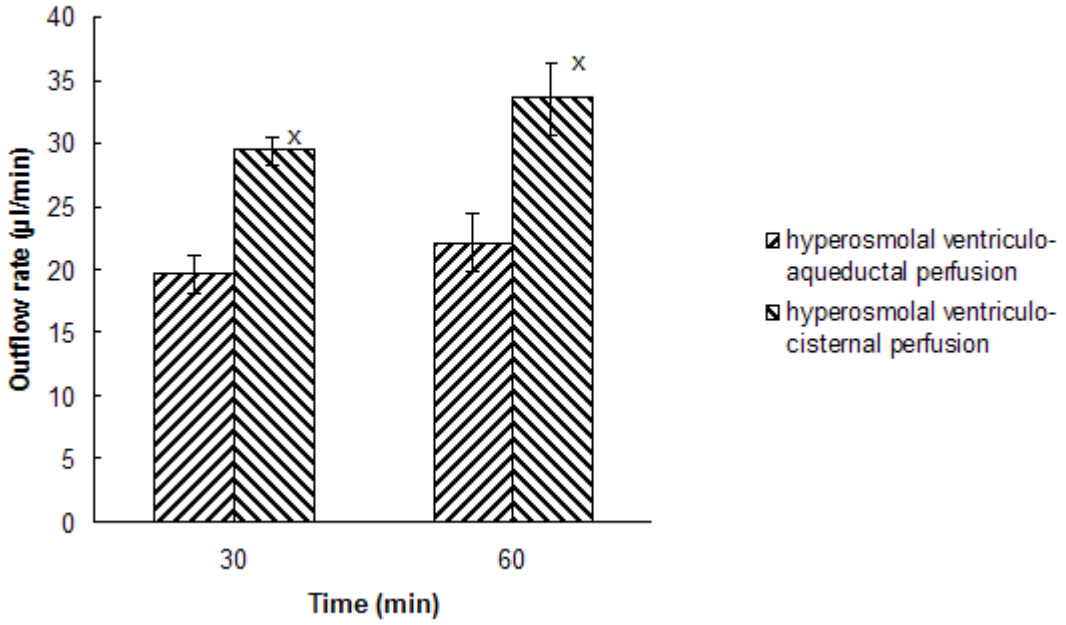

40
35
30
25
20
15
10
5
0
Outflow rate (µl/min)
xx
xx
30
60
Time (min)
isoosmolal ventriculo-cisternal perfusion
hyperosmolal ventriculo-cisternal perfusion

Figure 4.

The outflow of perfusate in cats obtained by ventriculo-aqueductal (n=6;▨) and ventriculo-cisternal perfusion (n=6;▧) with hyperosmolar aCSF (400 mOsml/l) under the same rate (12.96 µl/min) and duration (30 and 60 min). The results are shown as mean values ± SEM. Differences between the outflow rates of ventriculo-aqueductal and ventriculo-cisternal hyperosmolar perfusion of aCSF are statistically significant ($^{x}p<0.05$).



Acknowledgements

We thank Mrs Katarina Karlo for her skilled technical assistance. This work has been supported by the Ministry of Science Education and Sport, Republic of Croatia (Projects: 1. Hydrodynamics of the cerebrospinal fluid. No. 098-1080231-2328 and 2. Pathophysiology of the cerebrospinal fluid and intracranial pressure. No. 108-1080231-0023).