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ORIGINAL ARTICLE

Intracranial pressure and mean arterial pressure monitoring in freely moving rats via telemetry; pilot study

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Abstract

OBJECTIVES: Accurate values of the intracranial pressure (ICP) and mean arterial pressure (MAP) are the prerequisite for calculating cerebral perfusion pressure (CPP). Increased ICP values decrease CPP. The origin of ICP increase in the clinical cases after brain ischemia and diffuse brain injury is the cellular brain edema (CE). Short-term monitoring of ICP and MAP is possible only in the unconscious patients, in experiments with rats it used to be possible only in general anesthesia. Long-term monitoring of ICP or MAP in the clinical practice is not possible. We therefore introduce an experimental model with telemetric monitoring.

METHODS: ICP (subdurally) and MAP (intracarotically) were monitored in freely moving rats for 72 hours by DSI™ (Data Sciences International) telemetry system. The control group consisted of 8 rats, the experimental group had 8 animals with CE-induced by water intoxication.

RESULTS: The mean MAP, ICP and CPP values were significantly higher in the experimental group. Average values of MAP were 19.9 mmHg (18%), ICP 5.3 mmHg (55%), CPP 14.5 mmHg (15% higher).

CONCLUSION: The results of the pilot study verified possibilities of long-term telemetric monitoring of the mean arterial and intracranial pressures for the determination of current cerebral perfusion pressure in freely moving rats under physiological conditions and with increased intracranial pressure due to the induced cerebral edema. Detailed analysis of the course of the curves in the experimental group revealed episodes of short-term CPP reduction below the optimum value of 70 mmHg. Interpretation of these episodes requires simultaneous monitoring of rat behavior.

Abbreviations:

ICP	- intracranial pressure	ACC	- carotis communis artery
MAP	- mean arterial pressure	CMAP	- mean arterial pressure in the control group
CPP	- cerebral perfusion pressure	CICP	- intracranial pressure in the control group
CBF	- cerebral blood flow	CCPP	- cerebral perfusion pressure in the control group
CE	- cellular brain edema	CEMAP	- mean arterial pressure in the experimental group
C	- control		
CNS	- central nervous system	CEICP	- intracranial pressure in the experimental group
SEM	- standard error of mean		

CECPP	- cerebral perfusion pressure in the experimental group
i.e.	- id est/that is
g	- gram
ml	- millilitre
mm	- millimetre
Fig.	- figure
mmHg	- millimetre of Mercury

INTRODUCTION

Accurate values of the intracranial pressure (ICP) and of the mean arterial pressure (MAP) are needed to calculate actual brain perfusion pressure (CPP). In pathological conditions that bring increase of ICP but do not result in intracranial hypertension, long-term monitoring is useful for understanding the relationship between MAP and ICP. In clinical settings, both pressures can be monitored for a short time only in unconscious patients, long-term monitoring is not possible. In experimental conditions, using cable-based systems, short-term monitoring is possible during the general anesthesia (Crutchfield *et al.* 1990; Zwienenberg *et al.* 1999; Kozler *et al.* 2017a).

For long-term monitoring of both pressures, the principle of telemetry, which has only recently been introduced in the freely moving laboratory animals, can be used (Hiploylee and Colbourne 2014; Guild *et al.* 2015).

In this pilot study, MAP and ICP were telemetrically monitored in freely moving intact animals and in rats with induced cellular edema (CE) by water intoxication for 72 hours. Our previous work showed that the experimental model of cerebral edema brought about an increase in ICP to 10-14 mmHg while 0-10 mmHg range represents normal ICP level (Kozler *et al.* 2017a). The aim of the present study was to verify the possibility of long-term telemetric CPP monitoring in the same experimental model.

MATERIAL AND METHODS

All experiments were approved by the Ethical Committee of the First Faculty of Medicine (Charles University in Prague) and were in agreement with the Guidelines of the Animal Protection Law of the Czech Republic and Guidelines for the treatment of laboratory animals EU Guidelines 86/609 / EEC. For experiments, male rats of the Wistar strain weighing 400-410 g of our own breed were used

A total of 16 experimental animals was divided into two groups of 8 animals. Control intact animals formed group C. Animals with cellular brain edema induced by water intoxication were in the group CE.

Water intoxication was achieved by fractionized hyperhydration combined with administration of an antidiuretic drug desmopressin. This method is routinely used to induce experimental cellular brain edema and is described in details elsewhere (Silver *et al.* 1999; Vajda *et al.* 2000; Manley *et al.* 2000; Kozler & Pokorny 2003; Kozler *et al.* 2017a; Kozler *et al.* 2017b; Kozler *et al.* 2017c; Kozler *et al.* 2018; Maresova *et al.* 2018).

The DSI™ telemetry system (Data Sciences International) was used to monitor ICP and MAP. Its implantable components were the transducer and two pressure sensors. The components were implanted in spontaneously breathing rats under inhalation anaesthesia by isoflurane (Florante ®, AbbVie Ltd.).

At first, the surgery necessary for the implantation of the intracranial sensor together with a pocket for transducer were prepared. In the prone position, a midline skin incision was done extending rostrally to the frontal bone and caudal to the cervicothoracic transition. Trasducer was placed in a subcutaneous pocket formed on the back at the level of thoracic spine. The ICP pressure sensor was placed subdurally from the trephine located in the right frontal bone 2 mm in front of bregma; access to the intracranial space, adjustment of the sensor and its fixation are described elsewhere (Kozler *et al.* 2017a). The incisura was closed with a continuous suture. The animal was then turned to the supine position. The microsurgical approach exposed the carotis communis artery (ACC) on the right. From the arteriotomy a pressure sensor for MAP monitoration was introduced into the ACC lumen with the sensor tip located as close as possible to the cranial base (ACC exploration, sensor insertion and fixation are described in detailes in: Kozler and Pokorny 2003, Kozler *et al.* 2015). The wound was closed by continuous suture and inhalation anesthesia was terminated.

ACC was chosen to accommodate the MAP sensor in accordance with the original CPP definition based on MAP measurement at the level of the head (Lassen 1959). In clinical practice, MAP is usually measured from the level of right atrium where the pressure sensor is implanted via the venous pathway (v. subclavia, v. jugularis). With a standard head elevation of 30 degrees in patients with brain edema, due to the height difference between the location of the ICP sensor and the MAP sensor, the CPP value is up to 11 mmHg higher than that with the MAP sensor at the cranial base level (McCann *et al.* 2001; Rosner and Coley 1986). In the existing experimental models of telemetric monitoring of both pressures, abdominal aorta (Guild *et al.* 2015) or femoral artery (Hiploylee & Colbourne 2014) were used to store the pressure MAP sensor.

During the vertical motor activities (rearing, grooming), some discrepancy during the telemetry measurement of the monitored pressures due to the height difference of the sensors is possible. We did not expect that such MAP sensor location could bring significant measurement error in our experimental models. During the rearing, the height difference between the brain and the abdominal aortic area in a rat with an average weight of 400g is about 4 cm. Nevertheless, to minimize possible errors, we chose ACC to accommodate the MAP pressure sensor as the closest arterial region relative to the ICP sensor location.

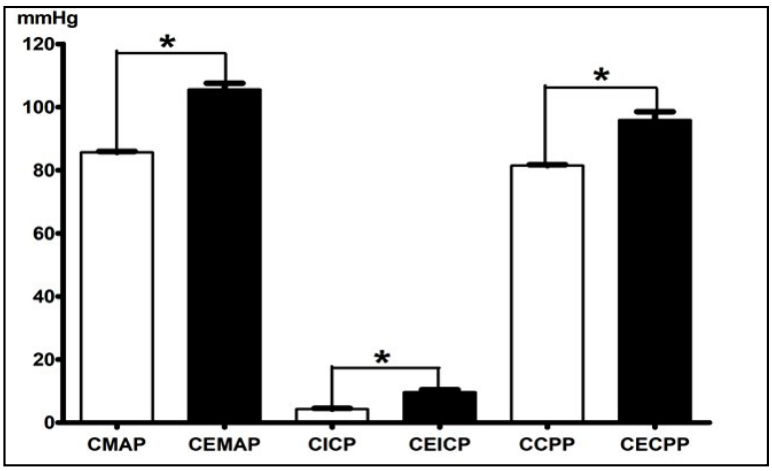

Fig. 1. Values of MAP, ICP and CCP

Legend: CMAP= mean arterial pressure in the control group; CEMAP= mean arterial pressure in the experimental group; CICP= intracranial pressure in the control group; CEICP= intracranial pressure in the experimental group; CCPP= cerebral perfusion pressure in the control group; CECPP= cerebral perfusion pressure in the experimental group.

Columns represent average values of pressures from 8 animals in each group during 72 hours, mean ± SEM, significant differences are given, * $p < 0.5$.

The awakened and freely moving animal was placed in a cage on a receiver that transmitted signals from the transducer to the PC hardware. The recorded and stored data were evaluated by software as the values of the pressure, and in the form of a pressure curve over the entire reference period, i.e. in 72 hours. Detailed information on pressure sensor design, transducer, transmission, registration and data analysis can be obtained at: www.datasci.com/solutions/neuroscience.

RESULTS

The results of pilot study are presented in Fig.1-4

Presented results have shown differences between values of all three monitored pressures. MAP, ICP and CPP were always significantly higher in the experimental group. ICP was elevated due to increased brain volume caused by the induced edema, as it was observed in our previous ICP monitoring study with a fixed, cable system (Kozler at el. 2017a). Along with the increased ICP, also MAP and CPP values were significantly higher.

Fig. 1 brings results of the real increase in the monitored pressures in the experimental group compared to the control group. MAP was higher in the experimental group on average by 19.9 mmHg (18%) while ICP was higher on average by 5.3 mmHg (55%). The calculated CPP was higher in the experimental group by an average of 14.5 mmHg (15%).

Fig. 2 shows a control group (full lines) of physiological cerebral autoregulation with intact intracranial homeostasis. All three curves are linear and parallel. Fig. 2 illustrates in the experimental group (broken lines) the homeostatic effect of cerebral autoregulation during impaired intracranial volume homeostasis caused by cerebral edema induced by increased brain volume (Lassen 1959, Armstead 2016, Smith 2015). Unlike the control group, in the experimental group the curves were neither linear nor parallel; however, the CECPP curve was constantly above the 70mmHg value.

DISCUSSION

Cerebral autoregulation is a homeostatic process granting constant cerebral blood flow (CBF) necessary for the normal brain function. Self-regulation works when the cerebral perfusion pressure (CPP) is kept within the range of 50 to 150mmHg or the mean arterial pressure (MAP) is maintained between 60 and 160mmHg. In the latter case, intracranial pressure (ICP) is calculated with CPP = MAP-ICP. The optimal CBF is supported either by vasoconstriction of small brain arteries when MAP or CPP increases and by vasodilation in case MAP or CPP decline (Lassen 1959; Smith 2015; Armstead 2016). For the homeostatic effect of brain autoregulation, the preservation of intracranial volume homeostasis is crucial - Monro-Kellie doctrine (Monro 1783; Kellie 1824). Some known pathological states, such as post-traumatic or post-ischemic diffuse brain edema, significantly increase the brain volume that may overcome this homeostatic mechanism and result in the increase of ICP. An increase above 20 mmHg leads to life-threatening intracranial hypertension; elevated ICP values in the range of 11-20 mmHg are usually not life-threatening, but may decrease CPP to such an extent that optimal CBF is no longer provided for normal brain cell function (Gupta 2015).

Relations between increasing volume, the state of compensation and the increasing pressure are described in the form of pressure-volume curve

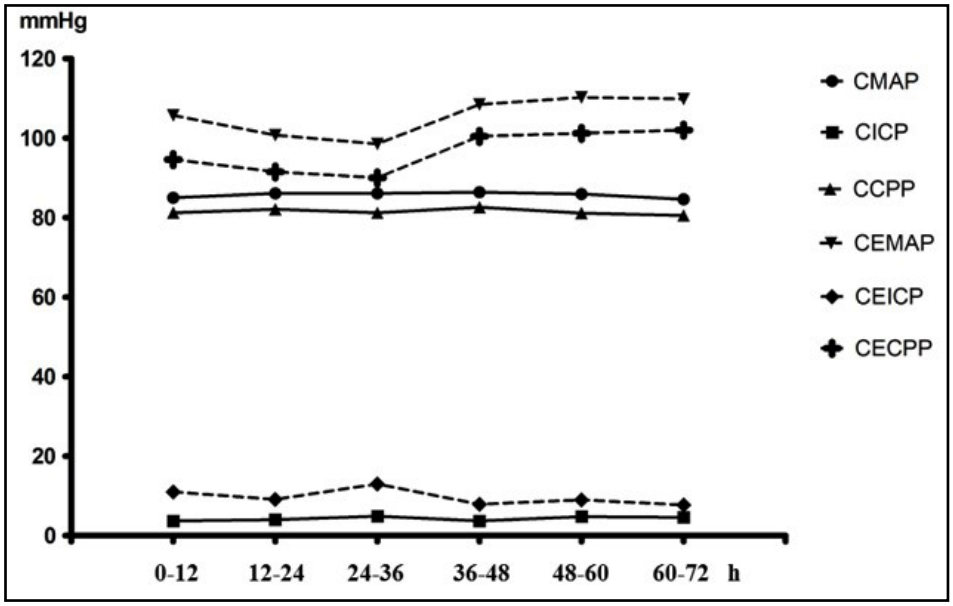

Fig. 2. Fluctuations of MAP, ICP and CCP values during 72 hours period

Legend: CMAP= mean arterial pressure in the control group; CICP= intracranial pressure in the control group; CCPP= cerebral perfusion pressure in the control group; CEMAP= mean arterial pressure in the experimental group; CEICP= intracranial pressure in the experimental group; CECPP= cerebral perfusion pressure in the experimental group.
Full lines - control animals; broken lines - experimental group; individual characters represent average values of pressures during consecutive 12 hour intervals.

(Langfitt *et al.* 1964). A condition for maintaining normal brain internal functions is ICP<20mmHg and CPP>70mmHg (Kirkman & Smith 2014; Czonsyka & Miller 2014), but for this principle, class I evidence is still missing (The Brain Trauma Foundation 2007).

The results of this pilot study revealed three findings that are consistent with the above-mentioned physiological principles.

The first observation is that cerebral perfusion pressure (CPP) values in the experimental group during each 12 hour period of monitoring were greater than 70mmHg and the mean arterial pressure (MAP) values were significantly higher in the experimental group compared to the control group.

This phenomenon is explained by the role of CPP in blood flow autoregulation. CPP is the pressure that

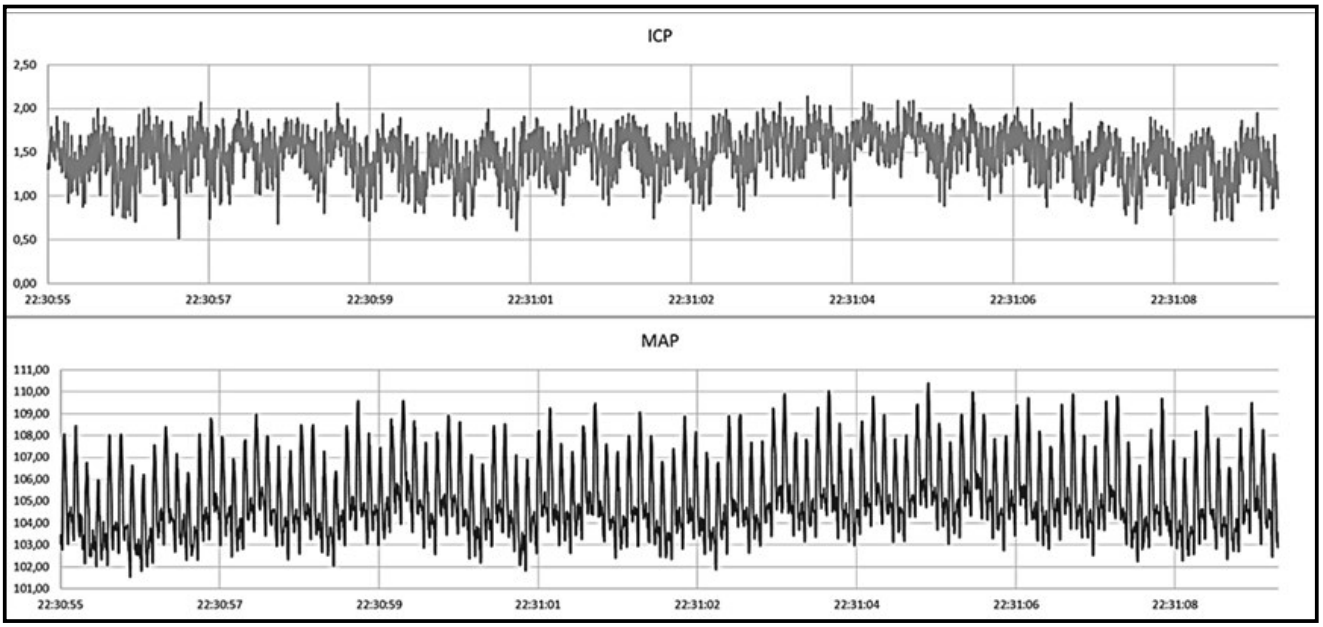

Fig. 3. Examples of ICP an MAP records; control group

Legend: ICP=intracranial pressure, MAP=mean arterial pressure, X axis=pressures in mmHg, Y axis=time of recording in seconds.

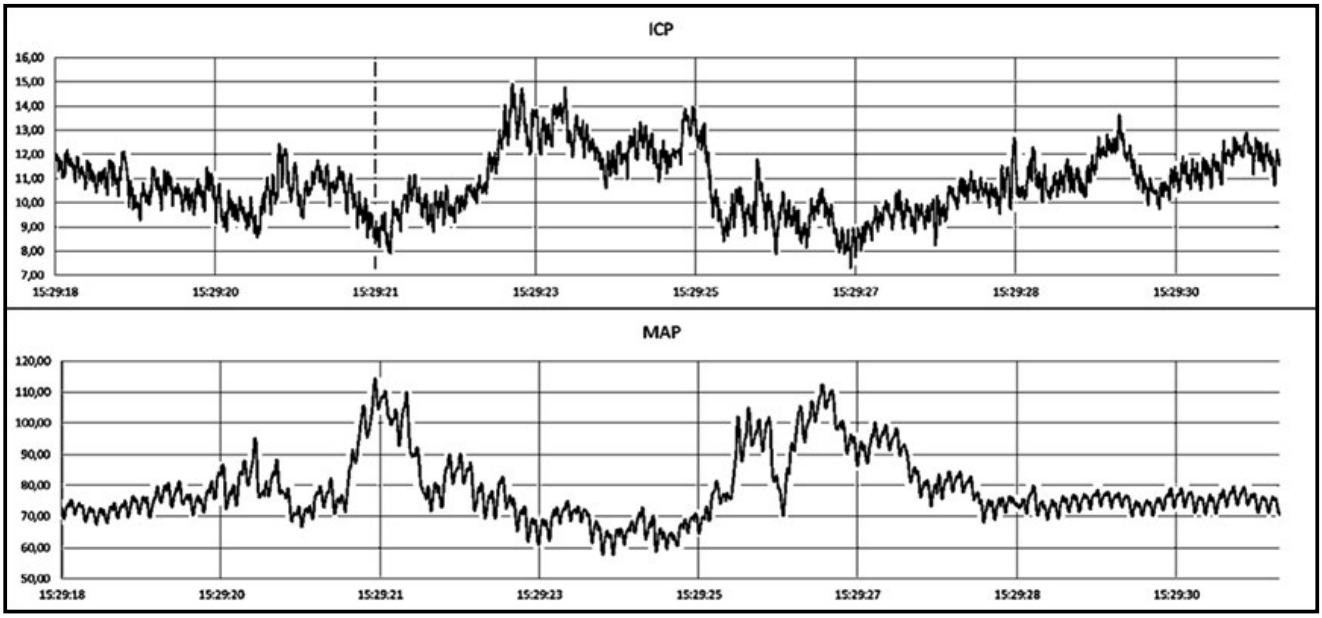

Fig. 4. Examples of ICP an MAP records; experimental group with induced CE
Legend: ICP=intracranial pressure, MAP=mean arterial pressure, X axis=pressures in mmHg, Y axis=time of recording in seconds.

generates the blood flow (CBF) through the brain, and therefore represents the difference between the filling pressure (pressure in the brain arteries) and the outflow pressure (the pressure in the brain veins), which is the same as the ICP. Thus, the CPP not only corresponds to the difference between the filling and the outflow pressure within vascular system, but it also represents the difference between MAP and ICP. If ICP increases as a result of increased brain volume due to edema, MAP must be increased so that CPP is sufficient to provide an adequate difference between filling and outflow pressure in the cerebral vascular bed, thus providing sufficient CBF (Smith 2015).

The second observation is based on records. Fig. 4 documents in the experimental group the generally low amplitude of MAP and ICP curves, compared to the amplitude of the curves in the control group. Example of a record at Fig. 3 illustrates the high amplitude of the MAP and ICP curves in the control group. Finding presented in Fig. 4 can be explained by induced cellular brain edema (Liang *et al.* 2007; Kozler *et al.* 2018).

The third finding represents the episodic records lasting several seconds, documenting the decrease of MAP to 70-80 mmHg and an increase of ICP to 10-12 mmHg (see Fig. 4), which were observed between 24th and 36th hour of continuous recording (see Fig. 2), when the average ICP was the highest and the average MAP was the lowest. During these episodes, CPP fell below the optimum value of 70mmHg. We have not yet been able to explain this finding due to the lack of continuous monitoring of the rat behavior along with pressures monitoring.

CONCLUSIONS

The results of the pilot study verified the possibilities of long-term telemetric monitoring of the mean arterial and intracranial pressures for the determination of current cerebral perfusion pressure in freely moving rats under physiological conditions and with increased intracranial pressure due to the induced cerebral edema. The course of the pressure curves of the experimental group at the low cerebral perfusion pressure periods will require a detailed analysis of the causes and consequences of these episodic pressure changes. Successful interpretation of results is seen in the next experimental model with simultaneous monitoring of pressure curves and rat behavior.

CONFLICT OF INTEREST

There is no conflict od interest.

ACKNOWLEDGMENTS

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