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Frequency Dependent Transmission Characteristics between Arterial Blood Pressure and Intracranial Pressure in Rats

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Abstract— **The pulsatile energy transmission between arterial blood pressure (BP) and intracranial pressure (ICP) is affected by cerebrospinal fluid (CSF) and brain tissue. Studies in dogs have shown that the transfer function (TF) between BP and ICP shows damping of pulsatile energy around heart rate frequency (1-3Hz) with notch filter characteristics, and the amount of damping is sensitive to cerebral compliance. This investigation aimed to assess whether this notch filter characteristic is an intrinsic property of the brain enclosed in a rigid skull and therefore applies across species with a large difference in body size. This was done by determining the TF between BP and ICP in rats with corresponding significantly smaller body size and higher heart rate (5-7 Hz) compared to dogs. Arterial BP and ICP waveforms were recorded in 8 anaesthetized (urethane) adult male Sprague-Dawley rats with solid state micro-sensor transducer catheters. The TF was computed as the ratio of ICP and arterial BP waveform amplitudes for the first 4 harmonics. Arterial BP and ICP signals were normalized for pulse amplitude such that attenuation or amplification is detected for any TF values significantly different to unity. Mean cardiac frequency was 5.72 Hz (range 4.6 – 7.11 Hz). Of the 4 harmonics only the heart rate frequency band showed a statistically significant attenuation of 17%, while the higher harmonics showed a progressive amplification. Findings show that the rat brain acts as a selective frequency pulsation absorber of energy centered at heart rate frequency. This similarity with larger animals indicates a possible allometric mechanism underlying this phenomenon, with notch filter characteristic frequency scaled to body size. This study suggests that the TF between arterial BP and ICP is an intrinsic property of the brain tissue and CSF enclosed in a rigid compartment and can be used to assess changes in cerebral compliance due to abnormal CSF pressure and flow as occur in hydrocephalus.**

I. Introduction

Systems analysis of the cranial cavity, enclosed in a rigid skull containing brain tissue and cerebrospinal fluid (CSF), is performed with arterial blood pressure (BP) and intracranial pressure (ICP) as input and output signals, respectively [1-5] . Transmission characteristics of pulsatile components between arterial BP and ICP are quantified as pressure transfer function (TF) frequency spectra describing the cranial system. The use of a TF model showed high correlation between ICP estimated from arterial BP and the invasively measured ICP in the range 0.85 to 0.96 [1]. This implies that the ICP waveform is mainly affected by the arterial BP waveform rather than other factors such as venous pressure.

Pressure TF spectra have consistently shown the presence of attenuation occurring around the cardiac frequency of experimental animals such as dogs and cats [1, 3-8] compared to higher frequency components on basal conditions. This selective TF spectra attenuation at cardiac frequency was reduced when cerebral compliance (i.e. compensatory CSF volume capacitance) was reduced by infusion of additional CSF volume into the cranium [5, 7, 9]. Reduced damping due to decreased cerebral compliance suggests a potential use of this phenomenon for clinical applications such as quantitative assessment of hydrocephalus [7], if it can be established that this is an intrinsic property of the brain at basal conditions.

To assess whether this selective attenuation (i.e. notch filter) characteristic is an intrinsic property of the brain contained in an enclosed rigid structure across species, this investigation aimed to determine TF in rats, with corresponding significantly smaller body size and higher heart rates (5-7 Hz) compared to previous studies in larger animals with lower heart rates.

II. Methods

A. Surgical preparation

Eight adult (11-26 weeks) male Sprague-Dawley rats weighing 400-650g (Perth Animal Resource Centre) were used for the experiments. The animal research protocol used in this study was approved by Macquarie University's animal ethics committee. Surgical procedures were performed under general anesthesia with intra-peritoneal injection of urethane (1.3g/kg) and spontaneous ventilation. The left femoral vein was cannulated using PE-50 tubing for intravenous access. Intravenous aliquots of 0.3 ml of 10% urethane were administered to ensure maintenance of depth of anesthesia. Body temperature was monitored using a rectal temperature probe and maintained at 37 ±0.5°C using a heating mat.

B. Aortic and Intracranial micro transducer placement

Solid state micro-sensor transducer catheters (Scisense, Ontario Canada) were used for simultaneous intra-aortic and intra-cranial pressure recording. A high sampling frequency of 2 kHz was used to allow accurate waveform analysis.

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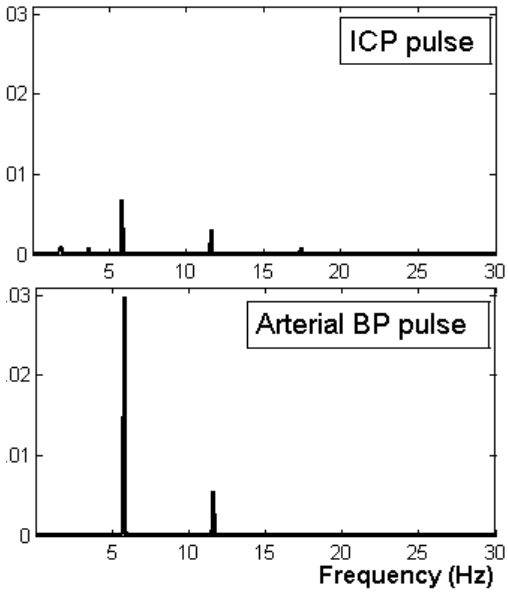

Figure 1. Power spectrum which is generated from 20 second recording from one of the rats. Arterial BP and ICP pulses were normalised for its pulse pressure for compratison.

Calibration of the catheters using a mercury manometer was performed prior to each catheter placement.

The abdominal aortic pressure waveform recording was obtained using 1.9F (Scisense) micro-sensor catheter fed via the left femoral artery to a depth of 6-7 cm to allow recording of the aortic pressure pulse.

Animals were then positioned in a Kopf rodent stereotactic frame for intracranial pressure sensor placement. A midline sagittal scalp incision was made to expose the bregma and lambda. The stereotaxic coordinates for intra-parenchymal intracranial pressure monitoring described by Zwieneenberg *et al* [10] were used.

A left parietal 0.7 mm diameter burr hole was made using an Archimedes micro hand drill at 6 mm posterior to the bregma and 2.5 mm lateral to the midline. Care was used to avoid plunging of the drill bit. The dura was sharply incised using the bevel of a 23 gauge needle. A 1.6F micro-sensor catheter was placed into the brain parenchyma at a depth of 3 mm below the inner table of the parietal bone.

Data from the simultaneous aortic and intracranial pressure waveforms were processed by a data acquisition system (Spike 2 software with Power 1401 mkII system interface, Cambridge Electronic Design). Data were exported to Matlab software for analysis. At the completion of the experiment the rat was euthanized using a lethal dose of pentobarbital (i.v. 80mg/kg).

C. Data analysis

20 seconds of arterial BP and ICP data at basal condition were collected from each animal for the analysis. Arterial BP and ICP signals were normalized for pulse amplitude such that attenuation or amplification was detected for any TF values significantly different to unity.

Amplitude of TF spectra were computed using Matlab software for the first four harmonics from each animal. As in other studies [20] it was found that the first 2 and 3 harmonics contained most the energy (97%, 98%) in the ICP and arterial BP signals respectively. Statistical analysis was conducted using Student's t-test.

TABLE I. SUMMARY OF TF SPECTRA AMPLITUDE

	H1	H2	H3	H4
Mean Frequency (Hz)	5.72 ± 0.82	11.42 ± 1.63	17.03 ± 2.44	22.87 ± 3.29
Frequency Range (Hz)	4.6 - 7.11	9.2 -14.22	13.8 - 21.33	18.4 - 28.44
TF spectra amplitude	0.83 ± 0.07*	1.05 ± 0.19	1.73 ± 0.49*	2.10 ± 1.10*

* denotes a statistically significant difference to unity ($p<0.05$).

III. RESULTS

Mean cardiac frequency of eight rats was 5.72 ± 0.82 (SD) Hz (range 4.6 to 7.11 Hz). Power spectrum from arterial BP and ICP of one of the rats is shown in Fig 1.

As summarized in Table 1, TF spectra amplitude at the first harmonic (H1) was only significantly lower than unity ($p=0.0002$) whereas, the second (H2) was not significantly different to unity ($p=0.47$). This significant attenuation at cardiac frequency compared to unity is shown in Fig 2. Pressure TF spectra amplitude at the higher harmonics was significantly greater than the unity (third harmonic, $p=0.004$; fourth harmonic, $p=0.025$) with greater variation.

Pressure TF spectra between arterial BP and ICP from rats showed a similar non-linear pattern to findings in previous studies in dogs [8] (Fig. 3). Compared to the first harmonic, the higher harmonics show similar progressive amplification. No significant difference ($p=0.83$) was found for values of each harmonic between dogs and rats, even though there was a marked difference in cardiac frequency (H1), 3.11Hz and 5.72Hz, respectively. Pressure TF spectra values were normalized based on amplitude of the first harmonic.

IV. DISCUSSION

Studies, characterizing the intracranial system in terms of a transfer function (TF) between arterial blood pressure (BP) (input) and ICP (output) [1, 4, 5, 7-9] have shown the presence of attenuation of TF spectra amplitude at the first harmonic in basal conditions.

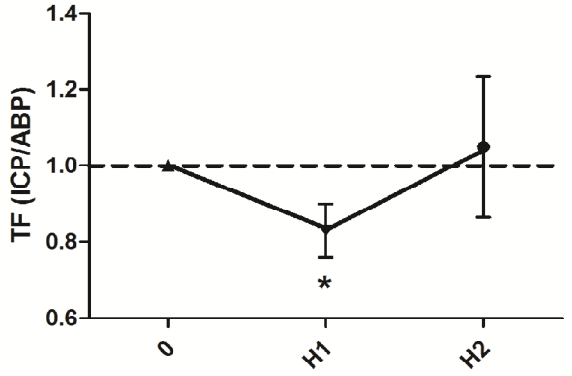

Figure 2. Pressure TF spectra between arterial BP and ICP from 8 rats showed significanlty reduced amplitude at the cardiac frequency (i.e. first harmonic, H1) as reported in previous study with dogs [9, 15,18]. The data are normalised for pulse amplitude with similar mean values. The TF pattern exhibits a notch filter characteristic for pulse amplitude.

More recently, the intracranial system has been considered as an arterial pulsation absorber [5, 6] and termed "a notch filter", with a notch frequency close to the cardiac frequency. Most of the energy of the pressure pulse such as arterial BP and ICP is in the first three and two harmonics respectively. Therefore, the term "notch filter" for selective attenuation around the cardiac frequency is applicable.

Results of this study are in accordance with previous observations of selective attenuation around the cardiac frequency. This phenomenon has been confirmed in pressure TF spectra between arterial BP and ICP in rats, which have a smaller body size and higher high heart rates than dogs, where such studies have previously been conducted.

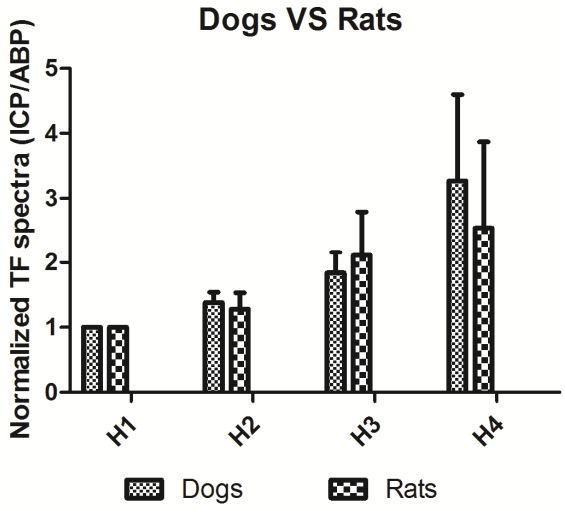

Figure 3. Pressure TF spectra between arterial BP and ICP in rats showed similar non-linear trend in amplification compared to the first harmonic as found in dogs [8]. TF spectra amplitude were normalized based on amplitude at the first harmonic for comparison. No statistical difference (p=0.83) was found. Dog data is from Portnoy et al [8, figures, 3,8-13 during control status].

A. Intrinsic property of cranial system

It is generally accepted that ICP pulsations are mostly effected by arterial BP except during severe venous hypertension or loss of autoregulation [11]. Arterial BP is highly pulsatile as is cerebral arterial flow in conductance vessels. It also has a relatively high mean velocity, as measured by transcranial Doppler techniques [12, 13]. This high pulsation of cerebral inflow and pressure into the cranium is effectively dissipated as it travels to the cerebral capillary beds, located only a short distance from the large vessels. Cerebral capillary flow has almost no pulsatile component [14].

Previous studies in large animals such as dogs and cats showed that the cranial system effectively absorbs the arterial pulsations around their cardiac frequency [1, 4, 9]. The current study showed similar results in rats with their higher heart rate and smaller body size. This study suggests that arterial pulsation absorbance by the cranial system may constitute an intrinsic property across species in order to remove highly pulsatile energy from the arterial pulsation. This may be associated with a possible protective mechanism of the cranium for its thin and rigid microvasculature [15] from the strain and stress on the endothelium due to pulsatile energy [16].

B. Clinical application

Increased CSF volume by CSF infusion into the cranial cavity space induces a reduction in cerebral compliance. This has been shown to cause the removal of the notch characteristic of pressure TF spectra between arterial BP and ICP [5]. Appearance and disappearance of this notch filter phenomenon can have potential clinical applications for the diagnosis of hydrocephalus [7]. Previous studies [9] also showed an increase of TF amplitude when cerebral compliance was reduced by intraventricular infusion or an epidural balloon inflation. This was described as non-linear to linear pattern change due to cerebral autoregulation [4]. Therefore, CSF infusion studies in rats to confirm the disappearance of this notch filter (i.e. current non-linear pattern changes to a linear pattern) is of interest for future studies.

Studies suggest improved clinical assessment by the use of the ICP waveform. ICP pulse pressure, measured from the invasive ICP waveform showed improved outcome when used as treatment management target in a critical care environment [17] compared to the traditional approach of maintaining mean cerebral perfusion pressure (i.e. arterial BP-ICP) less than 70mmHg. Peripheral (brachial or radial) and also central aortic BP pulse pressure waveforms (closer to the brain than peripheral pulse pressure), can be readily measured non-invasively by means of applanation tonometry [18]. Therefore, ICP waveform can be derived from the arterial BP by using this pressure TF spectra characteristic between arterial BP and ICP [19].

C. Phase of pressure TF spectra

Due to the spatial difference in the position of the catheters for measurement of ICP and BP, the phase of pressure TF spectra was not considered in this study to confirm the notch filter characteristic. Piper *et al* [2] measured the coefficient of variation of amplitude and phase in transfer function between arterial BP and ICP from head-injury patients. The first harmonic has a coefficient of variation of less than 20%, whilst the higher harmonics showed a larger variation between repeated measurements. Further investigations should be aimed at assessment of the relative contribution of phase on the pressure TF spectra.

D. Heart rate and pressure TF spectra

The results showed that a notch filter around the cardiac cycle may be an intrinsic property of the cranial system. It is of further interest to see whether the TF spectra are consistently reproducible in the same animal across a range of heart rate frequencies. Further studies using the drug zatebradine or cardiac pacing would allow the assessment of the TF spectra across a range of heart rate frequencies [21].

V. Conclusion

This study showed significant attenuation at the cardiac frequency of the TF spectrum between arterial BP and ICP in rats. Results were in accordance with other studies with larger animals with slower heart rates such as dogs. This study also showed a non-linear pattern of the TF spectrum between arterial BP and ICP in rats as found in dogs or cats. The study suggests that arterial selective frequency attenuation by the cranium may be an intrinsic property of the brain tissue and CSF enclosed in a rigid compartment.

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