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Non-invasive Cerebrospinal Fluid Pressure Estimation using Multi-Layer Perceptron Neural Networks

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***Abstract*— Cerebrospinal fluid pressure (CSFp) provides vital information in various neurological abnormalities including hydrocephalus, intracranial hypertension and brain tumors. Currently, CSFp is measured invasively through implanted catheters within the brain (ventricles and parenchyma) which is associated with a risk of infection and morbidity. In humans, the cerebrospinal fluid communicates indirectly with the ocular circulation across the lamina cribrosa via the optic nerve subarachnoid space. It has been shown that a relationship between retinal venous pulsation, intraocular pressure (IOP) and CSFp exists with the amplitude of retinal venous pulsation being associated with the trans-laminar pressure gradient (i.e. IOP-CSFp). In this study we use this characteristic to develop a non-invasive approach to estimate CSFp. 15 subjects were included in this study. Dynamic retinal venous diameter changes and IOP were measured and fitted into our model. Artificial neural networks (ANN) were applied to construct a relationship between retinal venous pulsation amplitude, IOP (input) and CSFp (output) and develop an algorithm to estimate CSFp based on these parameters. Results show a mean square error of 2.4 mmHg and 1.27 mmHg for train and test data respectively. There was no significant difference between experimental and ANN estimated CSFp values (p>0.01).This study suggests measurement of retinal venous pulsatility in conjunction with IOP may provide a novel approach to estimate CSFp non-invasively.**

I. Introduction

The retinal venous pulse came to the interest of researchers in late 19th century [1]. Harder and Jonas [2] observed the presence of these spontaneous pulsations in 90% of 384 subjects tested. They recommend that that they could be a good indicator of cerebrospinal fluid pressure (CSFp) and suggested that patients reporting to a clinic with a lack of pulsation had a 90% chance of an abnormality..

The first theory explaining the nature of these pulsations was suggested by Balliart and Elliot [3], [4]. They suggested that for a given cardiac cycle, intraocular pressure (IOP) exceeds the pressure inside the central retinal vein (i.e. retinal venous pressure (RVP)) during ventricular systole hence forcing the vein to collapse. During diastole, RVP exceeds IOP resulting in re-expansion of the vein. Based on this theory two further issues were raised. Firstly, RVP could be higher or lower than IOP and secondly the fact that pressure fluctuations in either one of these parameters does not necessarily transmit to another.

Recent findings [5–7] have all measured RVP and IOP at several levels of IOP and shown that RVP consistently exceeds IOP.

A more recent explanation for the nature of spontaneous retinal venous pulsatility (SRVP) is provided by Levine [8]. He suggests that during an increase in CSFp, CSF pulsations and the mean CSFp rise [9] and approach the intraocular pulse pressure resulting in a zero intravascular pressure gradient over the prelaminar and retrolaminar optic nerve, leading to cessation of the retinal venous pulsation. These findings have been confirmed by other studies [10–13].

Based on this characteristic, we have developed [14–16] a new approach to quantify and estimate CSFp values. Our proposed method is based upon the fact that the degree of SRVP is associated with the trans-laminar pressure gradient; the pressure difference between IOP and CSFp. An increase in trans-laminar pressure gradient will raise SRVP amplitude while a drop in the mount of this pressure difference will lead to lower SRVP amplitude.

The objective of this study is to provide a model to map IOP and SRVP amplitude values onto estimated CSFp values. For this purpose, an artificial neural network (ANN) with a multi layer perceptron structure was used. The error between estimated output and actual output is minimized, hence firm relationships between input and output variables are constructed.

II. Material and Methods

A. CSFp estimation

The Dynamic Vessel Analyzer (DVA,Imedos, Germany) was used to record SRVP amplitude. IOP was measured using Goldman tonometry and SRVP recorded for 20 sec. A single drop of aproclonidine 0.5% (Alcon) was administered to lower IOP measured at 15,30,45 min intervals. 15 min intervals were chosen based on the fact that aproclonidine 0.5% will lower IOP gradually. This was followed by a 20 sec recording of SRVP.

Peaks and troughs were determined from SRVP recordings at each cardiac cycle. SRVP pulse amplitude was obtained by subtracting the trough from detected peaks at each cardiac cycle. These measurements were designated as the SRVP pulse (SRVPp). SRVPp at each cardiac cycle (cc) is defined as:

$$SRVPp = (Peak\ SRVP) - (Trough\ SRVP) \quad (1)$$

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SRVPp was plotted against IOP levels as 15 min intervals. Assuming a constant central retinal venous pressure and according to our proposed method and other studies [8], [10], [14], SRVPp is associated with the pressure difference between IOP and CSFp which could be expressed as:

$$SRVPp \propto (IOP - CSFp)$$
$$then\ SRVPp = a(IOP - CSFp) \quad (2)$$

Where a is a constant. According to Equation (2), when SRVPp cease to be present (i.e. SRVPp=0), then:

$$a(IOP - CSFp) = 0,$$
$$therefore\ CSFp = IOP \quad (3)$$

Relationship between IOP and SRVPp at 15 minute intervals is shown in Figure 1. In order to model the phenomena described in Equation (3), linear regression has been applied to these plots to estimate the intercept point of the regression line with the x-axis (i.e. IOP) to determine SRVPp=0. More detailed description of CSFp estimation is provided in our previous studies[14–16]. Furthermore, these estimations have been validated against different approaches.

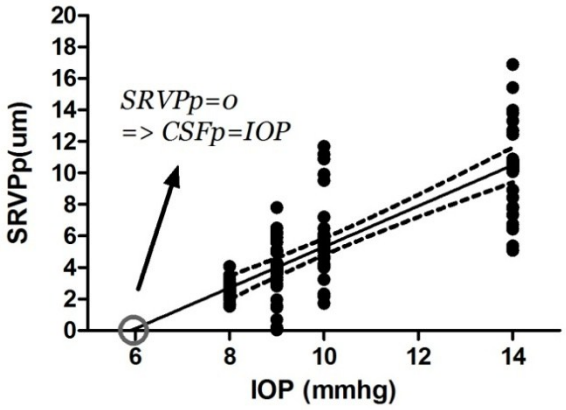

Figure 1. Relationship between SRVPp and IOP at 15 minute intervals for a single subject. Each dot represents SRVPp at a single cardiac cycle for a period of 20 seconds. Solid line is the linear regression applied to the data in order to extract its intercept with x-axis (i.e. IOP). Dashed lines show 95% confidence level.

B. Artificial Neural Netwok

As described in the previous section, CSFp estimation includes extracting a relationship between IOP and SRVPp at 15 minute intervals in order to apply linear regression and estimate CSFp. However, this experiment takes 1 to 1.5 hours and may be uncomfortable for some subjects, specifically in a clinical environment when prompt access to different physiological parameters is vital. Therefore to shorten the experimental time and expedite CSFp estimations we developed a new model based on Artificial Neural Network (ANN). ANN's are capable of extracting a pattern between their inputs and their outputs. Based on these learnt patterns, they are able to estimate the desired output for any given input.

The network is established based on the data acquired from 15 subjects. ANN's are viewed as a general framework for representing non-linear mappings between multi-dimensional spaces where the form of mapping is governed by a set of adjustable parameters. With supervised learning, the training data set consists of both the input to the ANN and an associated target output. In this study, the input is the IOP and baseline mean SRVPp recorded from each individual at any given cardiac cycle. The target output is the estimated CSFp extracted from the linear regression.

The Multi-Layer Perceptron (MLP) regression ANN architecture was selected for this study. Every connection between inputs and neurons is weighted by an adjustable weight parameter. In addition, each neuron also has an associated, adjustable bias weight parameter. The network consists of a single hidden layer with 10 neurons. Ten was the number of neurons above which MSE (Eq.5) was constant within preset limits. In summary the network has a 2-10-1 structure.

If a is the input (i.e. mean SRVPp and IOP) to the MLP and b is the output (i.e. CSFp) of the MLP, a relation mapping the input to the output may be written as follows:

$$b = \sum_{j=1}^{10} W_j f_j + W_o \ ,$$

$$\&\ f_j = \frac{1}{1+exp[-\sum_{i=0}^{2} W_{ij} a_i]} \quad (4)$$

where i (i=1,2) is the number of inputs units, j (j=1...10) is the number of hidden neurons, a_i is the i-th input unit, W_{ij} is the weight parameter between input i and hidden neuron j and W_j is the weight parameter between hidden neuron j and the output neuron. f_j is the activation function of the hidden layer (Figure 2).

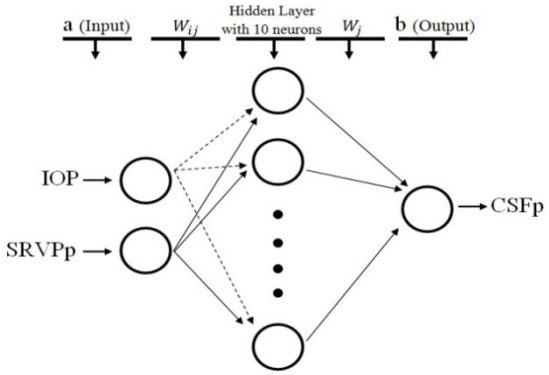

Figure 2. Schematic of ANN used for CSFp estimation based on IOP and mean SRVPp as its inputs

C. ANN Validation

The generalization error between ANN output and target output is quantified using a mean square error (MSE) criterion given by:

$$E_{MSE} = \frac{1}{N}\sum_{n=1}^{N}(t_n - b_n) \quad (5)$$

Where N is the total number of test patterns, t_n is the target output for input pattern n and b_n, is the actual ANN output when presented with pattern n.

III. Results

The average SRVPp ,CSFp and absolute IOP for all 15 subjects are shown in table 1. CSFp using the experimental regression line and ANN has also been shown in this table. An iterative 12 train 3 test algorithm was used to update the ANN performance and minimize the error. Based on this algorithm 12 random subjects were chosen to train and another 3 subjects were applied to the trained network to evaluate its performance (80% train, 20% test). The learning rate was 0.001 and the ANN was updated 1000 epochs to achieve a stable MSE.

TABLE1. AVERAGE SRVPP, EXPERIMENTAL AND ESTIMATED CSFP AND ABSOLUTE BASELINE IOP FOR ALL 15 SUBJECTS TESTED

Subject No.	*Mean SRVPp (μm)*	*IOP (mmHg)*	*CSFp-Experimetal (mmHg)*	*CSFp-ANN (mmHg)*
1	6.3	16	9.5	8.0
2	14.2	12	5.6	5.7
3	21.2	19	12.9	13.0
4	5.6	12	10.9	7.1
5	14.3	15	7.8	7.2
6	4.4	12	3.9	5.0
7	6.4	16	2.8	4.1
8	5.8	13	2.6	5.0
9	4.1	10	3.0	5.1
10	20.1	14	4.8	7.0
11	9.2	18	12.3	11.5
12	10.2	15	6.6	6.3
13	9.8	14	7.0	5.8
14	6.1	15	6.8	5.5
15	9.0	17	6.9	8.4

The best mean square error achieved for the training data was 1.2 mmHg. This value was 2.4 mmHg for the test data. The train/test data were rotated iteratively until all 15 data sets were subjected to the ANN train and test pattern. ANN weights were updated accordingly until minimum MSE was achieved. Student t-test was applied between the two CSFp groups. Results show a non significant difference between experimental and ANN estimated CSFp ($p>0.01$). The average CSFp for experimental and ANN was 6.8 ±3.3 mmHg and 6.9 ±2.4 mmHg respectively.

The Bland-Altman test [17] was used to assess the agreement or any consistent bias between the two methods. The difference in mean CSFp between the two groups is plotted against the average of both groups. For data to be distributed normally (Gaussian), the difference in the mean should lie between μ-2σ and μ+2σ (dashed line-Figure 3), in which μ is the average of the difference (also known as the bias) and σ is the standard deviation. For the given data, μ is -0.04 and σ is 1.7. Considering these values the upper and lower limit would be 3.31 and -3.39 respectively. (Figure 3).

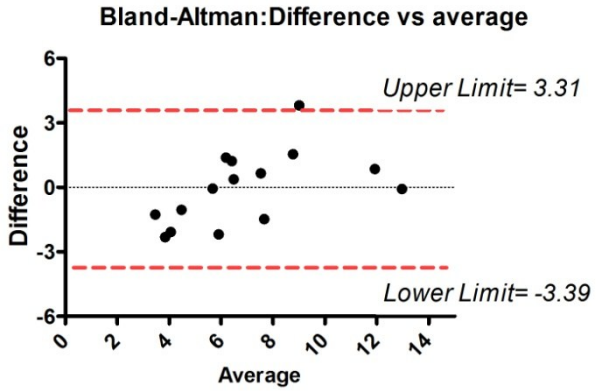

Figure 3. Bland-Altman test applied to depict the performance of the two methods (ANN and experimental) used to estimate CSFp. Y-axis is the difference between estimated CSFp from experimental data and the estimated CSFp using the ANN. X-axis is the average of these two parameters.

IV. Discussion and Conclusion

In this study we have proposed an artificial neural network algorithm firstly to estimate CSFp based on baseline IOP and SRVPp measurements and secondly to minimize the cumbersome experimental procedure needed to estimate CSFp, mainly described in our previous study.

While further invasive experiments are required to validate these estimates, nevertheless we compared our findings with an alternative approach using software developed by Cambridge University known as ICM+. Our results were comparable and non-significantly different to those estimated by ICM+ for the same subject ($p>0.01$) . ICM+ uses arterial blood pressure waveform along with middle cerebral artery flow velocity in order to estimate CSFp.

There may be the possibility of the effect of blood pressure or heart rate on the variability of SRVPp during administration of aproclonidine 0.5% to lower IOP. This has been justified in our previous study [14]. Neither blood pressure nor heart rate has indicated any direct affect on SRVPp as a result of aproclonidine 0.5% administration. Mean retinal venous and arterial caliber did not change either.

Our results support the theory developed by Levine [8], where SRVPp are a result of the trans-laminar pressure gradient (i.e. IOP and CSFp). We have assumed a constant retinal venous pressure which also plays a vital role in the presence of SRVP. This assumption will not affect the overall results provided in this study since we have only

applied this method to normals. However, this has to be taken into account if subjects with neurosurgical or ophthalmic subjects are examined, where RVP may be more elevated or variable.

Ophthalmodynamometry is a reliable technique to assess retinal venous pressure. Firsching [18] studied 22 subjects which had surgical procedures to place intraventricular catheters in their brain to measure CSFp. Ophthalmodynamometry was performed in these subjects in order to record venous outflow pressure (VOP). Their results demonstrate a significant correlation between VOP and CSFp ($p<0.001$). These findings have also been confirmed by other studies [19], [20].

Our study is limited by the small number of subjects. We acknowledge that the subjects chosen for this study were all normal and therefore a broader range of patients with neurosurgical or ophthalmic abnormalities should be recruited to assess the model's applicability. Nevertheless, estimated CSFp in our model falls in the normal range (0-15 mmHg)[21] supporting our proposed method. Further experiments are required to determine this relationship with SRVPp, IOP and CSFp and include in our described model.

In conclusion, measurement of baseline SRVPp in association with baseline IOP and applying the proposed ANN model can provide a prompt initial assessment of CSFp values. All of our experiments are based on devices used in ophthalmology clinics and so this approach could be incorporated in these devices as a software plugin to provide information on CSFp.

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