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A Simulation Model for Interaction between Cyclic Variation of Brain Tissue Temperature and Intracranial Pressure

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Abstract: ***The brain responds with high sensitivity in case of cerebral damage. Brain temperature (BT), cerebral blood flow (CBF), cerebral blood volume (CBV) and intracranial pressure (ICP) are essential parameters for brain revival in case of cerebral damage. For this reason, the coordinated learning of BT, CBF and ICP is required for improving the remedial impacts. Thus, in this exploration, a simulation model has been developed for association between brain tissue temperature (BTT), CBF, CBV and ICP to improve the apprehensions of the ICP. It includes the cardiac output, partial pressures of oxygen and carbon dioxide in cerebral artery and vein, temperature variations of brain tissue, cerebral metabolic process and pressure-volume relationship for cranial cavity. The model simulates the interaction between arterial blood pressure, BTT, produced amount of CO_2 from brain tissue, changes in CBV and changes in ICP. The results show that the ICP and CBV will increase with an increase in brain tissue temperature. This model elaborates the physiology of BTT and ICP with less complexity.***

Keywords **: Simulation modeling, intracranial pressure, brain tissue temperature, MATLAB, hyperthermia, cerebral blood volume**

I. INTRODUCTION

The concept of ICP, first proposed by Monro-Kellie [1] states that the sum of intracranial volume of the brain, blood, cerebrospinal fluid and other components is constant. An increase in one component must be compensated by an equal decrease in another component or else increase in ICP. The changes in intracranial pressure may have a severe impact on different neurosurgical issue, for example, hydrocephalus [2], intracranial hemorrhage [3] and cerebrum damage [4]. An uncontrolled increase in ICP is a cause of mortality; hence an appropriate method for treatment of high ICP cannot be ignored. Invasive [5] and non-invasive [6-10] a variety of techniques have been proposed for assessment of ICP. The invasive techniques are required for neurosurgical interventions, with its attendant risk whereas non-invasive techniques are excessively complex to handle of genuine clinical conditions.

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The intricacy between physiological parameters and nearness of nonlinearities make all non-invasive techniques inadequate to handle the clinical outcomes. Despite its significant clinical results, there is no such simulation model yet to explore how ICP is changed with changes in BTT. The ordinary range of ICP is not absolute, it changes with age. In general the value of ICP is under 5-13 mmHg. The range is 3-7 mmHg for youngsters and 1.5-6 mmHg for newborn children [11].

In this research work, we developed a simple simulation model for assessment of ICP with periodic cyclic variation in BTT. With the help of this model we will be able to reproduce the ICP response pattern with changes in BTT for clinical purposes. The hyperthermia and hypothermia; two conditions are taken for simulation to show the variations in the temperature of BT. Model illustrates that how much cerebral metabolic rate of oxygen is changed with changes in BTT and its output product of i.e. carbon-dioxide will change the quantity of deoxygenated blood in veins. Model also depicts that how much cerebral blood volume and intracranial pressure are changed with change in BTT. This model develops a direct relation between BTT and ICP.

The aim of this work is to provide approximate help to improve the comprehension of ICP. The simplifications of this introduced simulation model are presented in description of simulation model. Its limitations are clearly mentioned to maintain a strategic distance from the ill-advised utilization of the model.

II. SIMULATION MODEL DESCRIPTION

To study the ICP pattern with changes in brain tissue temperature, a MATLAB based less complex simulation model has been designed as shown in Fig. 1. Some assumptions have been presented in other scientific models [11-12] for simplification which we are using in our simulation model. The two principle suppositions are talked below.

- The demonstration of simulation model does not separate the proximal and distal regions of the blood vessel; it considers just a single segment of blood vessel arterial-arteriolar, continuing from extensive intracranial supply routes towards cerebral capillaries.
- Weight toward the endpoint of an extensive cerebral vein is expected as ICP. This supposition is approved since the venous cerebro-vascular bed respond as a Starling resistor [13].

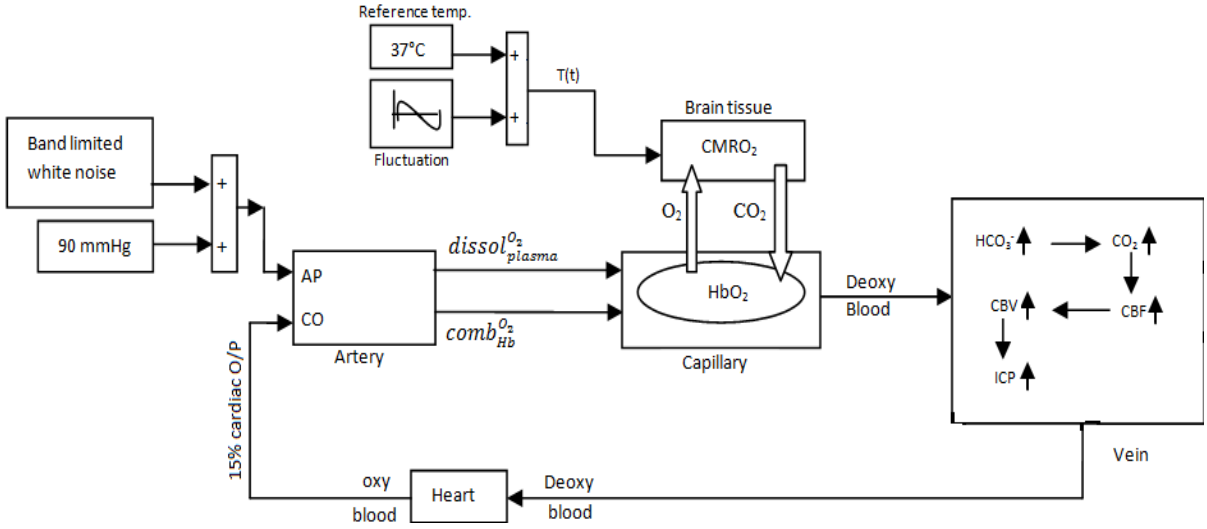


Fig. 1: Simulation model for intracranial pressure

Table I: Abbreviations with their simulation scope

Symbols	Abbreviations	Simulation Range
ABP	Arterial blood pressure	(90±30) mmHg
PaO_2	Partial pressure of O_2 in artery	(75-112) mmHg
$PaO_{2(7.4)}$	Arterial O_2 pressure at 7.4 pH	95 mmHg
CO	Cardiac output	(20-54) ml/min
$PaCO_2$	Partial pressure of CO_2 in artery	(27.6-63) mmHg
$dissol^{O_2}_{plasma}$	O_2 dissolved in arterial plasma	(0.05-0.156) ml
α_{O2}	solubility coefficient of O_2 in plasma	0.00003 ml O_2/1 ml blood/1 mmHg
$comb^{O_2}_{Hb}$	O_2 combined with haemoglobin in artery	(3.85-9.90) ml
β_{O2}	binding coefficient of O_2 with Hb	1.34 ml O_2/1 gram Hb.
A	Magnitude of fluctuation in brain tissue emperature	(37± 3)°C
$[HCO_3^-]$	Increased concentration of bicarbonate ions	(26.28-28.4)
$C^{O_2}_{BT}$	O_2 consumed by brain tissue for cerebral metabolism	(3.565±1.38) ml/100g brain/ min
$P^{CO_2}_{BT}$	Produced CO_2 by brain tissue in cerebral metabolism	(7.073-13.595) ml/100g brain/ min
T_O_2_R_HbO_2	Total O_2 release from HbO_2 due to CO_2 production	(2.24-4.30) ml/100g brain/min
$PvCO_2$	CO_2 pressure in veins	(30-75) mmHg
V_{HbO_2}	Oxygenated blood in veins	(-26.14 to 25.68) ml/min
$V_{deoxy\ blood}$	Deoxygenated blood in veins	(-15 to 30) ml
V_{csf}	Volume of cerebrospinal fluid	(0-0.5) ml/min
dV_{cb}	Changed Cerebral blood volume, in Fig. 2(h) it is represented by CBV	(0.18-0.47) ml
ICP	Intracranial pressure	(12.0-15.9) mmHg

The main aspect of this simulation model is to identify patterns of ICP with changes in brain tissue temperature to improve understanding of ICP. Temperature changes in brain tissue are shown by sine wave and its reference temperature is 37°C. When cerebral blood travels from the arterial segment to the capillary segment, the brain tissue consumes O_2 from the oxygen-rich blood present in the capillary and releases CO_2 as a waste product. O_2 consumption depends on the temperature of the brain tissue. The CO_2 released by the brain tissue is absorbed into the red blood cells of capillary due to pressure gradient. The red blood cells then release bicarbonate ions into the blood plasma, increasing the concentration of bicarbonate ions. More bicarbonate ions increase CO_2 pressure. Increased CO_2 pressure will dilate blood vessels and increase CBF. More CBF means more intravenous CBV and more deoxygenated blood. Deoxygenated blood will increase the weight in the veins.

According to our second assumption, more deoxygenated blood will increase the pressure i.e. ICP.

This model is executed with modest number of parameters and every parameter ready to represent a whole physiological in a compact manner. The simplified simulation model is shown in Fig. 1. Table I describes all abbreviations which are used in Fig. 1. The focus of this model is to correlate the intracranial pressure dynamics with brain tissue temperature.

III. CEREBRAL INPUT PARAMETERS

A. Arterial blood pressure (ABP)

ABP is the total pressure exerted by different gases like O_2, CO_2 etc. against the walls in the cerebral arteries. The blood is forced to flow in the cerebral arteries by the left ventricle of the heart. The outflow of blood from the heart is 750 ml/min i.e. 15% of the cardiac output or 50-54 ml/100 gram of brain tissue/min [14-15] called cardiac output (CO). The considered scope of cardiac output (CO) to demonstrate the simulation model is 20-54 ml/100 g/min. Simulation model as shown in Fig.1, consider the normal estimation of strain in

human's arterial blood vessel is around 90 mmHg, and has a vacillation of 20~30 mmHg with the heartbeat. To make the arterial blood pressure waveform, it incorporates the normal estimation value with band constrained background noise reproduction as appeared in Fig. 2(a).

B. Partial pressure of oxygen and carbon dioxide in Cerebral artery (PaO_2, $PaCO_2$)

In simulation, the normal estimation of partial pressure of O_2 is 95 mmHg and its fluctuating scope is 75-112 mmHg. Similarly, the normal estimation of CO_2 is 37 mmHg and their fluctuating scope is 27.6-63.0 mmHg as shown in Fig. 2(e). Fluctuation of O_2 pressure in arterial blood will brings changes in pH value as calculated with the help of Eq. 1 and shown in Fig. 2(b). Due to this partial pressure of O_2, ninety-eight percent of O_2 combines with haemoglobin and form the oxygenated haemoglobin as calculated with the help of Eq. 2 and Eq. 3. And the remaining two percent of O_2 is dissolved in normal blood plasma as determined by Eq. 4.

$$PaO_{2\,(7.4)} = PaO_2 * e^{1.1(pH-7.4)} \quad (1)$$

$$comb_{Hb}^{O_2} = \beta_{O_2}.T_{Hb}.SbO_2 \quad (2)$$

$$(SbO_2) = \frac{\left(\frac{PaO_2}{P_{50}}\right)^n}{1+\left(\frac{PaO_2}{P_{50}}\right)^n} \quad (3)$$

$$dissol_{plasma}^{O_2} = \alpha_{O_2}.CO.PaO_2 \quad (4)$$

Where T_{Hb} is characterized by total amount of Hb present in the blood, SbO_2 is saturated blood, β_{O_2} represents the binding coefficient of O_2 with Hb, $comb_{Hb}^{O_2}$ represents oxygen combined with Hb, P_{50} is characterized by the oxygen pressure in the blood at 50% of saturated haemoglobin [16-19]. The proportion of dissolved O_2 in plasma and combined O_2 with Hb is represented by oxygen dissociation curve (ODC). The ODC rely on the CO_2 content is demonstrated with n in the blood [20-21] and its value is 2.6. The CO_2 content indicates the presence of bicarbonates ions in the blood. Arterial blood moves into cerebral capillary section where cerebral metabolism action is performed. Dissolved O_2 in blood plasma is represented by $dissol_{plasma}^{O_2}$ and α_{O_2} represents the solubility coefficient of O_2 in blood plasma.

C. Cyclic variations of brain tissue temperature

Temperature control of the brain is a profoundly dynamic region of research. The brain's surface temperature is variable, although it is lower than its centre temperature. For these reasons invasive methods has been suggested to measure the brain temperature by inserting the temperature sensor to a depth of at least 1.5 to 2 cm in the brain parenchyma [22]. A number of thermocouple technology based temperature sensors are available for invasive techniques. But non- invasive techniques are safe and highly reliable for the patients. The normal brain temperature is maintained at 37°C [23] and it is considered as a reference point in our simulation model. To demonstrate the hypothermia condition in simulation; the BTT is shifted to down 2-3°C from its reference point 37°C and for hyperthermia [24] it is shifted up 2-3°C from its reference point. This fluctuation is shown by using the sine wave in MATLAB simulator as depicted in Eq. 5. In model we consider the hundred gram of brain tissue to simulate temperature fluctuation and its cyclic variations. BTT is variable but tissue compartment itself is homogeneous in nature taken as an assumption.

$$T(t) = A * \sin(\omega t + \theta) + \varphi \quad (5)$$

T_0 = 37°C, A=37±3°C, ω=1, φ=0, θ=0

Where T(t) represents the temperature at time t, A represents the magnitude of fluctuated temperature in brain tissue, ω represents the frequency of temperature cycle, θ and φ represent the phase and bias condition of temperature cycle. Fig. 2(c) depicted the temperature fluctuations in the brain tissue.

IV. CEREBRAL OUTPUT PARAMETERS

A. Effect on Cerebral Metabolism ($CMRO_2$)

The human brain accounts for only 2 to 3 % of the human body weight, but it consumes 20 to 25 % of the total oxygen consumption of the body. Bran tissue consumes the oxygen and produces carbon dioxide as a waste product. This process is called the cerebral metabolic rate of oxygen ($CMRO_2$). Tissue temperature is an important factor in the consumption of O_2 used by brain tissue. The mathematical relation between BTT and $CMRO_2$ [25-26] is shown in the Eq. 6. At 37°C the $CMRO_2$ is 3.5 ml/100g /min taken as a reference point for simulation. BTT shifted up or down from its reference point will affect the $CMRO_2$ as described in Table II. It shows that the change in 1°C temperature below its reference point has 8.5% falls in $CMRO_2$ with parallel reduction in CO_2 production rate. However, as temperature raises 1°C above 37°C the $CMRO_2$ increases 14.3% dramatically with parallel increase in CO_2 production rate. The $CMRO_2$ assess the double sensitivity in 1°C rise in temperature as compared to 1°C fall in temperature.

Furthermore the CBF will change 1-2 ml/100g/min for each 1 mmHg change in CO_2 pressure [27].

$$CMRO_2 = e^{a+bT} \quad (6)$$

Where a and b are constants and their values are -2.7579 and 0.1089. T represents the brain tissue temperature.

Table II: Change in $CMRO_2$ with change in BTT

BTT (37±3° C)	$CMRO_2$ (ml/100g brain tissue / min)	% Change in $CMRO_2$
34	2.5	28.6 ↓
34.5	2.7	22.8
35	2.8	20 ↓
35.5	3.0	14.3
36	3.2	8.5 ↓
36.5	3.3	5.7
37	3.5	Optimum value
37.5	3.7	5.7
38	4	14.3 ↑
38.5	4.2	20
39	4.5	28.6 ↑
39.5	4.7	34.3
40	4.95	41.4 ↑

B. Effect on partial pressure of carbon dioxide

When arterial oxygenated blood reaches in the capillary section, then brain tissue consumes the oxygen from oxygenated blood and releases the CO_2. And the total amount of CO_2 produced by brain tissue enters in the capillary segment due to its partial pressure gradient [28-30] as described below in two ways:

- The remaining 90 % CO_2 is absorbed into the red blood cells and produces bicarbonate ions and increase its volume in the blood as shown in Fig. 2(d). These bicarbonate ions increase the pressure of CO_2.
- 10 % CO_2 broke down in blood plasma which increment the weight of CO_2 (complies with Henry's law)

We found that the produced amount of CO_2 is 2.7 times more than consumed O_2 in cerebral metabolism as shown in Eq. 7. The Increased pressure of carbon dioxide in the venous due to the increasing concentration of bicarbonate ions has been calculated with the help [31] of Eq. 8 as shown in Fig. 2(f). Where pk is constant and its value is 6.1.

$$P_{BT}^{CO_2} = 2.7 * C_{BT}^{O_2} \quad (7)$$

$$pH = pk + log\left[\frac{HCO3^-}{0.03*PvCO_2}\right] \quad (8)$$

Where $P_{BT}^{CO_2}$ represents produced amount of CO_2 by brain tissue and $C_{BT}^{O_2}$ represents the consumed amount O_2 by brain tissue.

C. Effect on Cerebral blood volume

The blood course is large convoluted in the human brain. When brain tissue releases the CO_2 then this CO_2 combines with the present oxygenated blood and release the O_2 again. In this process the amount of oxygenated blood will decrease in veins as calculated in Eq. 9. Simultaneously, the amount of deoxygenated blood will increase as determined in Eq. 10 and shown in Fig. 2(g). More deoxygenated blood will dilate the blood vessel and increase the cerebral blood flow as well as cerebral blood volume. The changing amount of blood volume in venous have been calculated from Eq. 11. The total change in cerebral volume is the combined effect of change in volume of cerebrospinal fluid (CSF) and change in volume of cerebral blood as shown in Eq. 12 and Fig. 2(h). For model simplification, the volume of CSF is taken as 0-0.5 ml/min. Another important factor is the elasticity of blood vessel Ke, which is taken as 0.2 ml^{-1}.

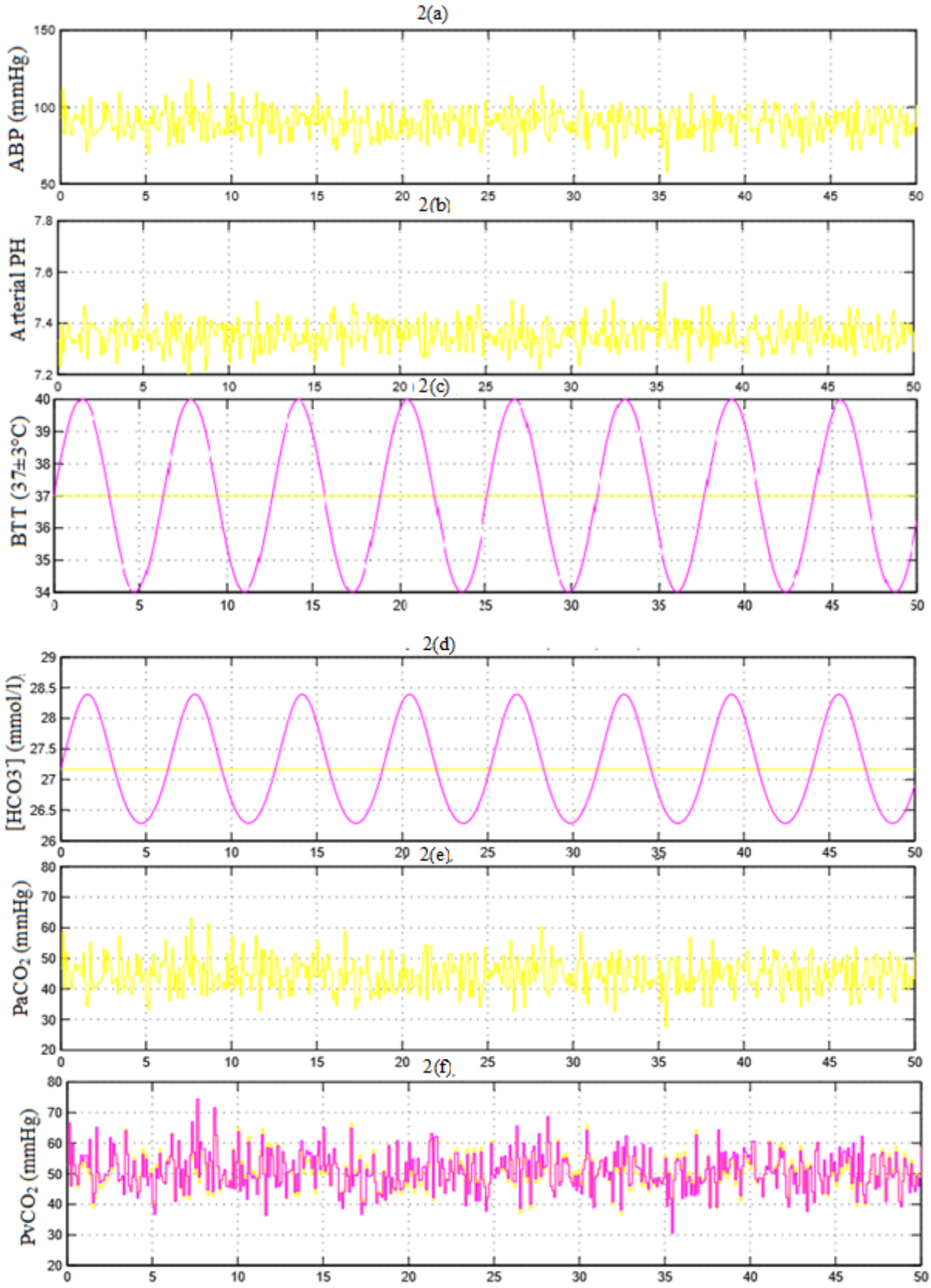
$$V_{HbO_2} = A_{HbO_2} - CMRO_2 - T\_O_2\_R\_HbO_2 \quad (9)$$

$$V_{deoxy\ blood} = A_{HbO_2} - V_{HbO_2} \quad (10)$$

$$dV_{cb} = \frac{A_{HbO_2} - V_{HbO_2}}{A_{HbO_2}} \quad (11)$$

$$\Delta V = V_{csf} + dV_{cb} \quad (12)$$

Where V_{HbO_2} represents the oxygenated blood in venous, A_{HbO_2} is the oxygenated blood in artery, $T\_O_2\_R\_HbO_2$ represents total O_2 release from oxygenated blood due to CO_2 production, $V_{deoxy\ blood}$ represents deoxygenated blood in venous, dV_{cb} represents the changed amount of cerebral blood, ΔV represents total change in cerebral volume and V_{csf} represents the volume of CSF.


2(a)
ABP (mmHg)
2(b)
Arterial PH
2(c)
BTT (37±3°C)
2(d)
[HCO3] (mmol/l)
2(e)
PaCO2 (mmHg)
2(f)
PvCO2 (mmHg)

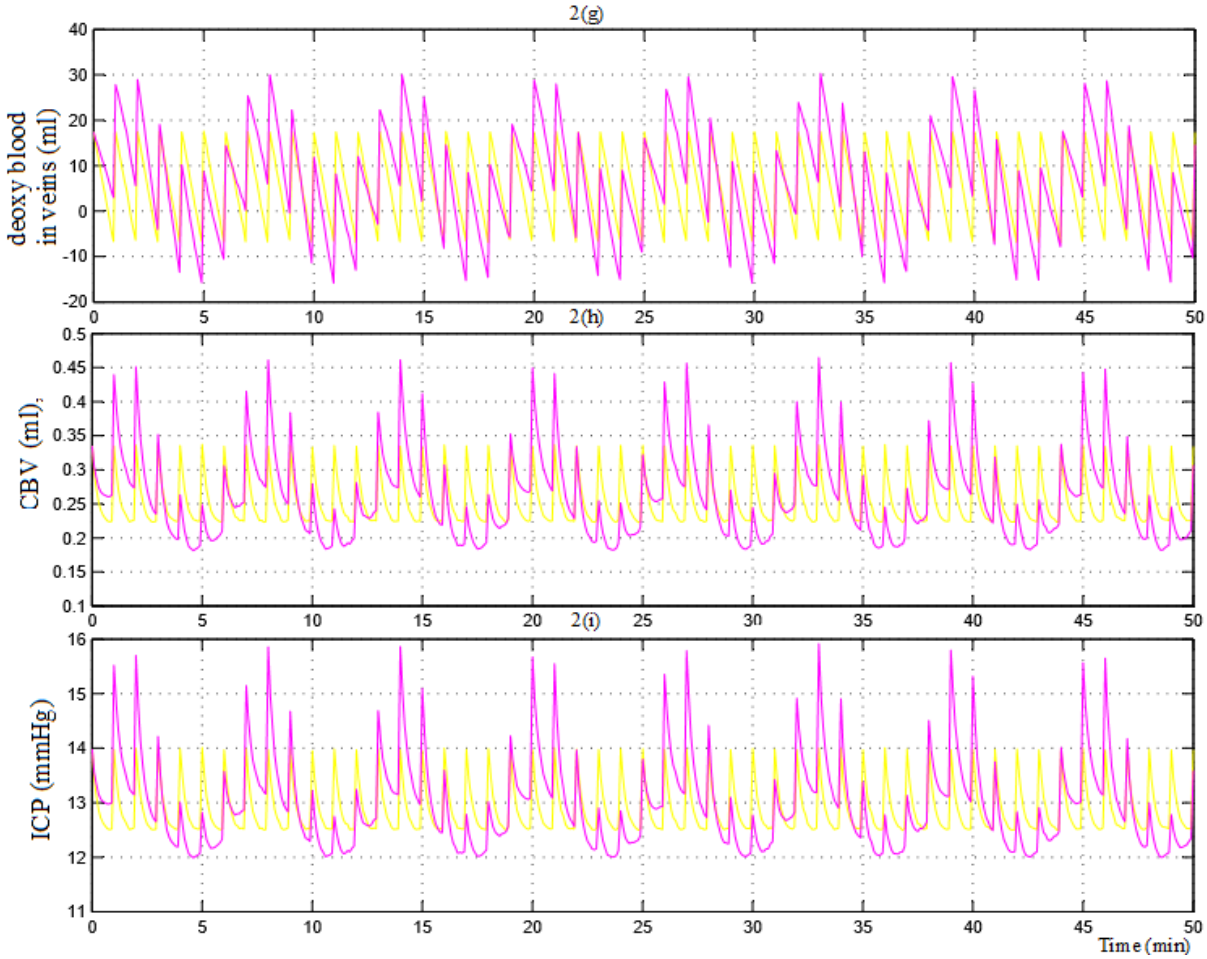


Fig. 2: 2(a) represents the arterial blood pressure, 2 (b) shows how much pH changes at different blood pressure, 2(c) shows the cyclic variation of brain tissue temperature, changes in concentration of bicarbonate ions due to variations in brain tissue temperature is shown in 2(d), 2(e) represents the CO_2 pressure in cerebral artery, 2(f) shows the changes in CO_2 pressure in venous, 2(g) shows the changed amount of deoxygenated blood in the venous due to change in the brain tissue temperature, 2(i) represents the changes in ICP due to changes in CBV

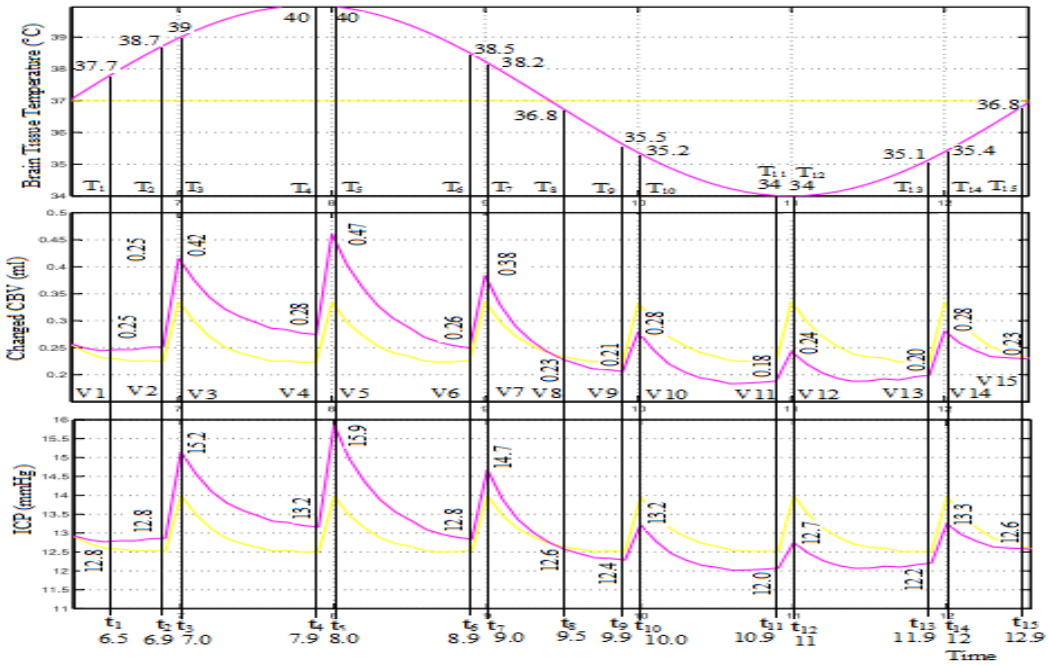


Fig. 3: 3(a) represents the temperature variations of brain tissue for a single cycle, changes in cerebral blood volume (CBV) with brain tissue temperature are shown in 3(b), a change in ICP due to a change in CBV is shown in 3(c).

Table 3: Interpretation of ICP and CBV pattern with changes in BTT for single a cycle

S.No	Cycle	Time interval (min) Δti = t(i+1)-t(i)	Change in Temperature (°C) ΔTi = T(i+1)-T(i)	Change in CBV (ml) ΔVi =V(i+1)-V(i)	Change in ICP (mmHg) ΔICPi = ICP(i+1) - ICP(i)	Interpretation of result	
1	+ive half cycle	0.4	1	0	0	NC in CBV, NC in ICP	IC
2		0.1	0.3	0.17	2.4	CBV ↑ , ICP ↑	HD
3		0.9	1	-0.14	-2	CBV ↓, ICP ↓	HD
4		0.1	0	0.19	2.7	CBV ↑, ICP ↑	HS
5		0.9	-1.5	-0.21	-3.1	CBV ↓, ICP ↓	HD
6		0.1	-0.3	0.12	1.9	CBV ↑, ICP ↑	HS
7		0.5	-1.4	-0.15	-2.1	CBV ↓, ICP ↓	HD
8	-ive half cycle	0.4	-1.3	-0.02	-0.2	CBV ↓, ICP ↓	HD
9		0.1	-0.3	0.07	0.8	CBV ↑, ICP ↑	HS
10		0.9	-1.2	-0.1	-1.2	CBV ↓, ICP ↓	HD
11		0.1	0	0.06	0.7	CBV ↑, ICP ↑	HS
12		0.9	1.1	-0.04	-0.5	CBV ↓, ICP ↓	HD
13		0.1	0.3	0.08	1.1	CBV ↑, ICP ↑	HS
14		0.9	1.4	-0.05	-0.7	CBV ↓, ICP ↓	HD

IC-Initial compliance, HS-Heart systole, HD-Heart diastole, NC- No change, ↓-Decrease the value, ↑-Increase the value

D. Effect on Intracranial pressure (ICP)

The intracranial pressure is a serious component that affected by any changes in CBV. Generally, the normal range of ICP is 5-13 mmHg. The skull is a rigid box and components inside the skull consists of brain (80%, 1400ml), blood (10%, 150ml) and cerebrospinal fluid (CSF 10%, 150ml) [32]. If any change in the volume of one of these three components then there must be settlement by decrease in the volume of remaining components otherwise ICP will increase. The ICP at time t rely on three main elements [33]: entirety of progress in volume of CSF and blood, flexibility of vein and introductory estimation of ICP (0) as portrayed in Eq. 13 and as shown in Fig. 2(i). The ICP (0) is taken as 10 mmHg in demonstration.

$$ICP(t) = ICP(0).e^{\Delta V.Ke} \quad (13)$$

V. RESULT AND DISCUSSION

The results of simulation model demonstrate that the ICP will increase/decrease with increase/decrease in the BTT. To study the pattern of ICP with parallel variations in the temperature of brain tissue, we created another Fig. 3 for a cycle. In Fig. 3 positive and negative cycle is divided into seven segments. And demonstration of each segment is given in Table 3. Table 3 demonstrates the time interval, change in temperature, change in cerebral blood volume and change in ICP between two consecutive segments of each temperature cycle. From this we interpret the results that when there is no change in cerebral blood volume then ICP will remain constant. But if BTT and CBV will increase/decrease then ICP will also increase/decrease.

In Table 3 demonstration: The heart takes about 0.9 minutes for diastole and 0.1 minute for systole. There is no change in CBV and ICP in the 1st segment of the positive cycle. The result suggests that when the heart diastoles, both CBV and ICP will decrease with an increase in the temperature of the brain tissue, as shown in segment 3rd, 5th, 7th of positive cycle and in section 12th, 14th of negative cycle. When there is no change in temperature in the segment 4th and 11th, both CBV and ICP are still increasing because the heart is in its systole state. The CBV and ICP both will increase/decrease with increase/decrease of tissue temperature in diastole state as saw in 2nd, 8th and 10th segments. In 6th and 9th segment CBV and ICP both are increasing with decrease in temperature due to systole state of heart. The overall picture found that with increase in BTT will increase the $CMRO_2$, CBV and ICP. Similarly with decrease in BTT will decrease the $CMRO_2$, CBV, and ICP.

But this model has its own limitations also. Model is unable to simulation the concept of auto regulation. In future we will emphasise to overcome this limitation.

VI. CONCLUSION

Clinically, the brain temperature is an important factor to manage. The aim to develop this model is to improve the comprehension of BTT and ICP. The major verdict of this simulation study is that the rise in brain tissue temperature is associated with rise of $CMRO_2$, CBV, CO_2 pressure and ICP. But the results may vary with individuals and these findings are for novel knowledge.

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