Relationship between Changes in Cerebral Blood Volume During Hypoxic-ischemic Insult and Early Period after Insult

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Abstract

To achieve better outcomes in hypoxic-ischemic encephalopathy, categorizing the degree of the hypoxia-ischemia (HI) is important for selecting suitable candidates for therapeutic hypothermia and any additional treatment strategies. We previously developed a novel model of asphyxiated piglets with a uniform degree of histopathological brain injuries that survived for 5 days after insult and showed changes in cerebral blood volume (CBV) that reflected the severity of the brain injuries. However, little is known about the relationship between changes in CBV during and after insult. In this study, an HI event was induced by low inspired oxygen in 23 anesthetized newborn piglets, including three sham controls. CBV was measured using near-infrared time-resolved spectroscopy (TRS). Data were collected before, during, and 6 h after insult. The change in CBV was calculated as the difference between the peak CBV value during insult and the value at the end of insult. The decrease in CBV during insult was found to correlate with the increase in CBV within 6 h after insult. Heart rate exhibited a similar tendency to CBV but blood pressure did not. The CBV increment immediately after resuscitation provides a relatively precise prediction of the severity of HI insult.

Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is a notable cause of neonatal death and developmental disabilities (1). In meta-analyses, nearly 50% of neonates treated with therapeutic hypothermia (TH) still have major disabilities or die due to multi-organ injuries (2). To achieve better outcomes, categorizing the degree of the hypoxia-ischemia (HI) is important for selecting suitable candidates for TH and any additional treatment strategies (3–5). Many studies suggest that TH provides maximum neuroprotection when initiated within 6 h of birth. Therefore, it is important to recognize the changes in cerebral hemodynamics in neonates with HIE as early as possible after HI insult.

Understanding changes in cerebral hemodynamics and cerebral oxygenation status in neonatal HIE is beneficial for the prognosis of the HIE, monitoring of the ongoing therapy, and evaluating the novel therapies. In recent years, gaining insights into oxygenation of the brain by monitoring with near-infrared spectroscopy (NIRS) is considered useful in the management of the newborns who require respiratory support, cardiovascular support, transfusion, newborns exposed to surgery and HIE neonates (6, 7).

In neonatal HIE, HI insult affects cerebral hemodynamics and oxygenation status due to impairment in cerebral autoregulation. Impaired cerebral autoregulation result in adverse neurological outcomes (8, 9). Assessment of vital parameters such as heart rate (HR), mean arterial blood pressure (MABP) and systemic oxygen saturation (SaO_2) may not always reflect the extent of brain injury (10, 11). Thus, for the complete clinical picture, assessment of neonatal cerebral oxygenation and perfusion should be performed.

Several types of NIRS system have been proposed. These include: 1) continuous wave spectroscopy, by which only changes in the concentration of Hb can be estimated from an initial measurement; 2) full

spectral spectroscopy, by which the NIR full spectrum of the NIR range can be measured; 3) spatially resolved spectroscopy (SRS), by which the slope of the light attenuation versus distance is determined at a point distant from the source using a continuous wave; 4) phase-modulated spectroscopy, by which amplitude signals for phase, intensity, and depth of modulation after passage can be measured; and 5) time-resolved spectroscopy (TRS), by which the transit time of each photon through the tissue of interest can be measured. SRS are used mainly in clinical situations for infants to measure cerebral Hb oxygen saturation (ScO2), but it is difficult to determine cerebral oxyHb and deoxyHb concentrations. This is because the SRS cannot assess the optical pathlength; therefore, they cannot measure absolute cerebral blood volume (CBV), but only ScO2. Alternatively, TRS is consists of a picosecond light pulser (a pulse duration of about 100 ps) as a pulsed light source, and a time-correlated single-photon-counting technique for time-resolved measurement. This method provides quantitative measuremen of the oxyHb and deoxyHb concentrations, and absolute values of the CBV and ScO2 without using a tracer in clinical setting (12–16)

We previously developed a novel model of asphyxiated piglets with a uniform degree of histopathological brain injuries that survived for 5 days after insult (17). In all piglets that received HI insult, CBV increased to the peak value before decreasing to a minimum value at the time of resuscitation. These changes in CBV during insult suggested that CBV increased in a compensatory fashion under HI and that cerebral blood flow autoregulation then became impaired, resulting in decreased CBV. In further work, we observed that the decrease in CBV during insult reflected the severity of brain injuries sustained from impaired cerebral autoregulation (17, 18). Hence, we suggested that the degree of HI insult can be estimated by measuring CBV with TRS. Furthermore, when examining CBV changes not only during insult but also after insult in piglets, we found that the increase seen in CBV within 6 h after insult reflected the severity of the histological brain injuries seen at 5 days after the insult (19). Based on these findings in piglets, we then found that the increment in CBV during the first 6 h after birth in human neonates is an indicator of poor neural prognosis thereafter (15).

Even though it has been proved in the piglet that changes in CBV during and after HI insult reflect the severity of brain injuries, little is known about the relationship between the changes in CBV during and after insult. To unravel this relationship, it would be helpful to estimate the cerebral hemodynamic response during HI insult by evaluating the cerebral hemodynamic patterns after it. We hypothesized that piglets with a greater decrease in CBV during HI insult would show a greater increase in CBV within the first 6 h after insult. The objective of this study was thus to evaluate the relationship between the CBV changes during HI insult and within 6 h of the insult in the asphyxiated piglet.

Results

Physiological parameters are shown in Table 1. Piglets in the control group showed no significant differences versus baseline values. All parameters were compared with their respective baseline values. In the HI group, pH and base excess decreased at the time of resuscitation and had returned to baseline at 60 min after insult. Blood glucose increased at the start of resuscitation and returned to baseline 360 min

after insult, whereas lactate had not returned to baseline by 360 min. Compared with the control group, a significant difference was seen in pH, pO_2, BE, blood glucose, lactate, and rectal temperature immediately before resuscitation in HI piglets and pH, BE, and lactate continued in the same manner until 60 min after insult.

Table 1
Values of arterial gas and physiological parameters at baseline, at end of HI insult, and at 60 min, 180 min, and 360 min after insult

	Baseline	End of insult	60 min	180 min	360 min
pH	7.47 (0.07)	6.91 (0.11)	7.32 (0.09)	7.48 (0.07)	7.49 (0.09)
$PaCO_2$ (mmHg)	41.4 (6.2)	31.5 (7.3)	40.0 (11.0) *	41.7 (9.1)	41.1 (11.4)
PaO_2 (mmHg)	103.7 (21.7)	16.2 (5.0)	99.2 (23.2)	90.1 (19.9)	99.9 (23.2) **
Base excess (mmol/L)	5.00 (2.1)	−25.7 (3.5)	−5.5 (2.9)	6.3 (2.4)	6.6 (2.5) *
Blood glucose (mg/dL)	150.1 (39.2)	229.5 (97.3) ***	217.2 (68.2) ***	186.3 (64.7) ***	179.5 (43.6)
Lactate (mg/dL)	21.0 (17.5)	208.3 (29.1) *	109.9 (26.9) **	37.3 (19.8) *	33.2 (13.0)
Hemoglobin (g/dL)	9.5 (1.7)	9.8 (1.8) ***	9.8 (1.6) ***	10.0 (1.7) ***	9.7 (1.8) **
Rectal temperature (°C)	37.9 (0.8)	37.3 (0.7)	37.9 (0.9)	38.1 (0.6)	38.1 (0.6)

Values are shown as means (standard deviation). Abbreviations: HI, hypoxic-ischemic; pH, arterial pH; $PaCO_2$, arterial PCO_2; PaO_2, arterial PO_2.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs baseline by one way-ANOVA.

CBV, MABP, and HR data are shown in Table 2. During insult, CBV increased to a maximum value and then declined. CBV had increased again at 5 min after insult and returned to baseline by 180 min. MABP decreased at the end of insult, had increased at 5 min, and had returned to baseline by 60 min after insult. HR fell during insult, gradually increased from the start of resuscitation, and had stabilized by 60 min after insult.

Table 2
Values of CBV, MABP, and HR at maximum value during HI insult, at end of insult, at 5, 60, 180, and 360 min after insult

Parameter	Maximum	End of insult	5	60	180	360
CBV (mL/100 g brain tissue)	7.0 (1.1)	5.8 (1.2)	6.4 (1.1)	5.6 (0.8)	5.1 (0.8)	5.1 (1.0)
MABP (mmHg)	75.2 (8.2)	46.1 (10.6)	86.8 (11.8)	67.6 (8.3)	65.0 (10.5)	62.7 (11.9)
HR (bpm)	198 (37)	140 (29)	193 (32)	250 (28)	254 (28)	223 (33)

Values are shown as means (standard deviation). Abbreviations: CBV, cerebral blood volume; MABP, mean arterial blood pressure; HR, heart rate; bpm, beats per minute.

There was a positive correlation between changes in CBV during insult and changes in CBV at all time points after insult (5, 60, 180, and 360 min; Fig. 2). Similarly, the MABP increment during insult showed a positive correlation with that at 5 min after insult. However, the remaining time points showed no correlation with the MABP increment during insult (Fig. 3). The HR increment during insult and the HR increments at all time points after insult also showed a positive correlation (Fig. 4).

Discussion

In this study, we have revealed the relationships between the decrease in CBV during HI insult and the increase in CBV within 6 h of the insult in HIE piglets. This CBV decrease during insult and increase within 6 h after it was correlated. HR showed a similar tendency to CBV but MABP did not.

During HI insult, CBV increases rapidly in a compensatory fashion, followed by impaired cerebral blood flow autoregulation and vasoparalysis that result in gradually decreased CBV due to decompensation (20, 21). In our previous translational HI piglet studies, greater decreases in CBV from baseline during insult were associated with severe brain damage or death (17).

With respect to the increase in CBV after HI insult, we have two theories to explain why greater decreases in CBV during insult were followed by greater increases in CBV after insult.
The first is severe cerebral vasoparalysis due to impaired cerebral autoregulation. Cerebral hypoperfusion, and thus decreased CBV, which are induced by severe systemic hypotension, would impair cerebral vascular autoregulation during the HI insult. After the initial resuscitation, cerebral blood flow would become passive due to a rise in systemic BP and result in an increase in CBV in the acute period immediately after resuscitation. The second is cerebral venous congestion due to heart failure, although we failed to identify a relationship between the CBV increase and the severity of the cardiac dysfunction from the data obtained in the present study, such as HR and BP. Our previous studies showed that increases in CBV at 1, 3, and 6 h after insult were associated with depressed neurocortical activity at the respective time points (18) and also histopathological brain injury at 5 days after insult (19).

Hence, this sequence of more pronounced cerebral hypoperfusion during insult being followed by greater cerebral hyperfusion after insult reflected impaired cerebral autoregulation and resulted in severe brain injuries.
In clinical practice, HIE neonates are at risk of cerebral blood flow dysregulation. Several studies have shown that impaired cerebral autoregulation (pressure-passive cerebral blood flow) after birth was associated with poor neurological outcomes (22) and increased mortality (23). Therefore, our work additionally suggests that CBV monitoring with TRS within the first 6 h after birth can estimate the degree of hypoperfusion during labor in HIE neonates and, further, can categorize the severity of brain injuries by recognizing the patterns of sequential changes in CBV during and after insult.

Significant cardiovascular dysfunction with redistribution of blood flow occurs in HI. In the initial stages of HI, cardiac output (CO) is well compensated and the distribution of blood to organs is maintained. However, blood is gradually redistributed to vital organs such as the brain and heart (24, 25). Myocardial ischemia results in ventricular dysfunction, which leads to a fall in stroke volume. Despite this reduced stroke volume, CO remains unchanged due to increased HR in the compensation phase. In the decompensation phase, HR also falls. Based on the literature, we speculated that the function of the HR increase after insult is to deliver the necessary oxygen to compensate for the HI. This would explain the association in the present study between the decrease in HR during the insult and the increase in HR after it.

MABP changes during HI constitute a complex phenomenon. MABP is influenced by multiple factors, including CO, autonomic function, neuroendocrine response, degree of vasoparalysis, and peripheral resistance (24, 26). In HI neonates, autonomic dysfunction with attenuation of parasympathetic activity and increased sympathetic activity influence the hemodynamic changes (27, 28). During HI, due to the autonomic dysfunction, compensatory tachycardia and increased BP occur initially and are followed by decompensation with a fall in HR and BP. After resuscitation, an initial reduction in myocardial contractility is accompanied by increased ventricular resistance to maintain the redistribution of the blood supply to the brain and heart.

A graphical summary of this study and our previous work with the HI piglet model is shown in Fig. 5. We can categorize three patterns of changes in CBV during and within 6 h after HI insult.

A schematic representation of the patterns of changes in CBV are shown according to severity of insult: (A) in mild HI insults, a slight CBV decrease during the insult and a decrease to baseline after the insult; (B) in moderately severe insults, a CBV decrease during the insult above the baseline and a decrease after the insult that is smaller than that of (A); and (C) in severe insults, a CBV decrease during the insult to below the initial basal level of CBV and an increase after the insult.
The angles of the CBV changes from the basal horizontal line after insult are $\alpha < \beta < \gamma$ (angle values of α and β are negative, whereas that of γ is positive). The categorization of each group was related to the prognosis within 5 days after insult. In pattern (A), the piglets all survived 5 days after the insult with no obvious neural pathological damage. In pattern (B), the piglets survived, but they had neural pathological

damage. In pattern (C), the piglets did not survive after the insult due to severe convulsions or cardiac and respiratory failure. Thus, we can categorize the animals into groups by using the changes in CBV measured by TRS within 6 h after the insult to estimate future prognosis. This categorization could be applied to neonates with asphyxia to predict prognosis and we will plan to investigate this in future work.

The limitations of this study are as follows. In HIE, the important determinants of outcomes are not only the severity of HI during insult, but also the duration and frequency of the insult, sexual dimorphism, and the presence of infection/inflammation (5, 25, 26). We could only assess HI severity in this study.

Conclusion

In this study, greater decreases in CBV during HI insult were associated with greater increases in CBV after insult. By using TRS, evaluating CBV changes within 6 h of HI insult has the potential to categorize the severity of the HI and enable timely and appropriate therapy to be initiated.

Materials And Methods

Ethical approval and animal preparation

The study protocol was approved by the Animal Care and Use Committee of Kagawa University (15070-1) and in accordance with Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines. The study was carried out in compliance with the ARRIVE guidelines. All methods were carried out in accordance with relevant guidelines and regulations. Twenty-three newborn piglets within 24 h of birth (14 males, 9 females; body weight 1560-2200 g) were anesthetized and surgically prepared.

Before the experimental procedures, the piglets were placed under a radiant warmer and their activities and alertness were briefly observed. Anesthesia was induced with 1%–2% isoflurane (Forane® inhalant liquid; Abbott Co., Tokyo, Japan) in air using a facemask. Each piglet was then intubated and mechanically ventilated with an infant ventilator. The umbilical vein and artery were cannulated with a 3- or 4-Fr neonatal umbilical catheter (Atom Indwelling Feeding Tube for Infants; Atom Medical Co., Tokyo, Japan). The umbilical vein catheter was placed 5 cm from the incision for blood pressure (BP) monitoring, and the umbilical artery catheter was placed 15 cm from the incision for blood sampling. After cannulation, the piglets were anesthetized with fentanyl citrate at an initial dose of 10 μg/kg followed by continuous infusion at 5 μg/kg/h and were then paralyzed with pancuronium bromide at an initial dose of 100 μg/kg followed by continuous infusion at 100 μg/kg/h. Maintenance solution (electrolytes plus 2.7% glucose [KN3B]; Otsuka Pharmaceutical Co., Tokyo, Japan) was infused continuously at a rate of 4 mL/kg/h via the umbilical vein (glucose was infused at a rate of 2 mg/kg/min). Arterial blood samples were taken at critical points and when clinically indicated throughout the experiment. Each piglet was then placed in a copper mesh-shielded cage under a radiant warmer to maintain a rectal temperature of 38.0 ± 0.5°C. Inspired gas was prepared by mixing O_2 and N_2 gases to obtain the oxygen concentrations required for the experiment. Ventilation was adjusted to maintain PaO_2

and $PaCO_2$ within their normal ranges. Arterial BPs were measured and recorded via the umbilical arterial catheter.

Time-resolved near-infrared spectroscopy and analysis

A portable three-wavelength TRS system (TRS-10; Hamamatsu Photonics K.K., Hamamatsu, Japan) was applied using probes attached to the head of each piglet. The light emitter and detector optodes were positioned on the parietal region with a 30-mm interoptode distance. In the TRS system, a time-correlated single-photon counting technique is used for detection. The concentrations of oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) were calculated from the absorption coefficients of oxyHb and deoxyHb, under the assumption that background absorption was due only to 85% (by volume) water. The total cerebral hemoglobin concentration (totalHb), cerebral hemoglobin oxygen saturation (ScO_2), and CBV were calculated as described previously (12, 13).

Hypoxic-ischemic insult protocol

The protocol is described in detail in our previous studies (3, 10-12). Briefly, after anesthesia induction, the piglets were stabilized. The HI insult was induced by decreasing the fraction of inspired oxygen (FiO_2) to 4%. Low-amplitude aEEG (LAEEG < 5 μV) was achieved by additional reductions of FiO_2 to no less than 2%. FiO_2 was adjusted during the insult to maintain LAEEG at < 5 μV, heart rate (HR) at > 130 beats/min, and mean arterial BP (MABP) at > 70% of baseline. The insult was terminated by resuscitation with 100% FiO_2 for 10 min. Control animals (n = 3) received 21% FiO_2 for the duration of the experiment. CBV, vital parameters, and aEEG were measured continuously for 360 min after insult.

Data analysis

The MABP, HR, and CBV values were analyzed from before insult to 360 min (6 h) after it. CBV changes during insult were defined as follows: Changes in CBV during insult = (maximum CBV value during insult) – (CBV value at the start of resuscitation).

CBV was measured continuously for 6 h after resuscitation. Changes in CBV values at 5, 60, 180, and 360 min after insult were calculated as follows: Changes in CBV at each time point = (CBV values at each time point) – (CBV value at the start of resuscitation).

In addition, the following relationships were analyzed (Fig. 1): (1) relationship between changes in CBV during insult and changes in CBV at each time point after insult; (2) relationship between the MABP increment at maximum CBV during insult and MABP increment at each time point after insult; and (3) relationship between the HR increment at maximum CBV during insult and HR increment at each time point after insult.

Statistical analysis

GraphPad Prism 5J (GraphPad Software, La Jolla, CA) was used for all statistical analyses. Significant correlations were assessed by Spearman's p rank test for the relationship between changes in CBV, HR, and MABP during and after insult. Physiological variables of the HI group were compared with those of the control group using the Mann–Whitney *U* test and, in each group, these variables were compared with those of pre-baseline data using Dunnett's multiple comparison test. Statistical significance for all tests was set at $p < 0.05$. All values are presented as means ± SD.

Declarations

Author contributions (Decide the co-authors and Check the initials please)

T.M., S.N., and T.K. designed the study and drafted the article. Y.H., Y.N., M.A, and K.K. performed the animal experiments. A.M., T.W., and Y.H. performed the data analysis. T.M., S.N., Y.K., and T.K. critically revised the manuscript and contributed to the final approval of the version to be published.

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Disclosure

The authors declare no conflicts of interest.

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Figures

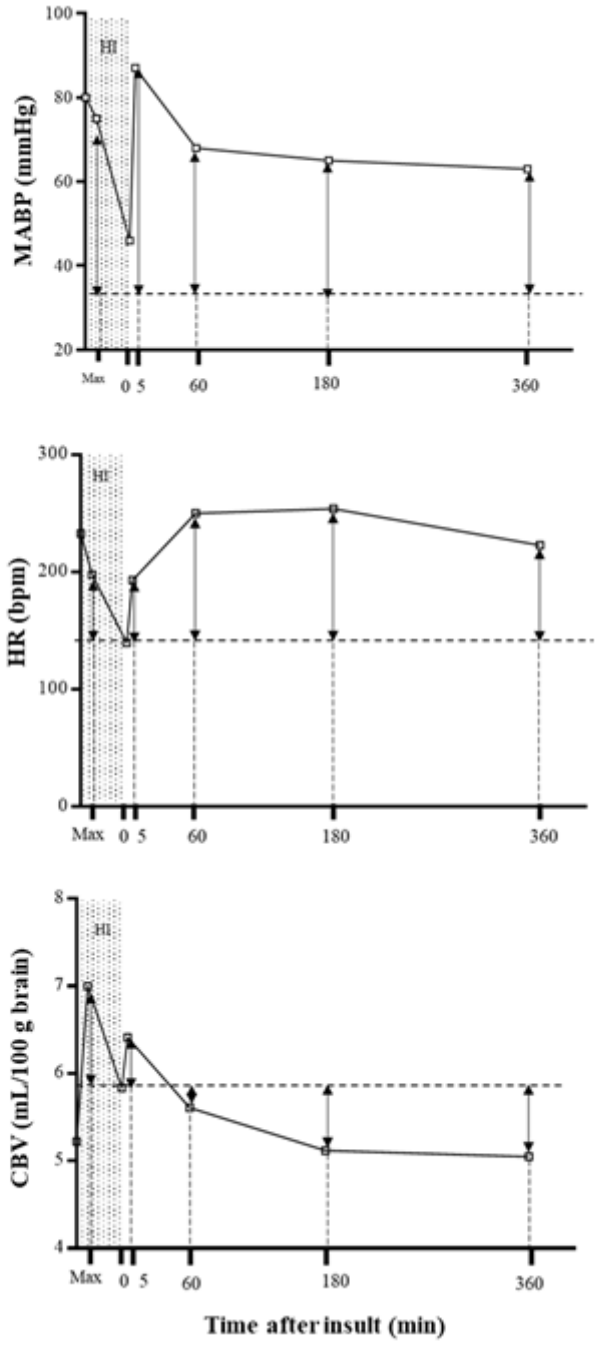

Figure 1

Graphical representation of the increments in CBV, HR, and MABP during HI insult and at 5, 60, 180, and 360 min after insult. CBV increments were calculated as the differences between the CBV value at the end of insult and the maximum CBV value during insult and the CBV at 5 min, 60 min, 180 min, and 360 min after insult. HR increments were calculated as the differences between the HR value at the end of insult and the HR value at the maximum CBV during insult and the HR at 5 min, 60 min, 180 min, and 360 min after insult. MABP increments were calculated as the differences between the MABP value at the end of insult and the MABP value at the maximum CBV during insult and the MABP at 5 min, 60 min, 180 min, and 360 min after insult.

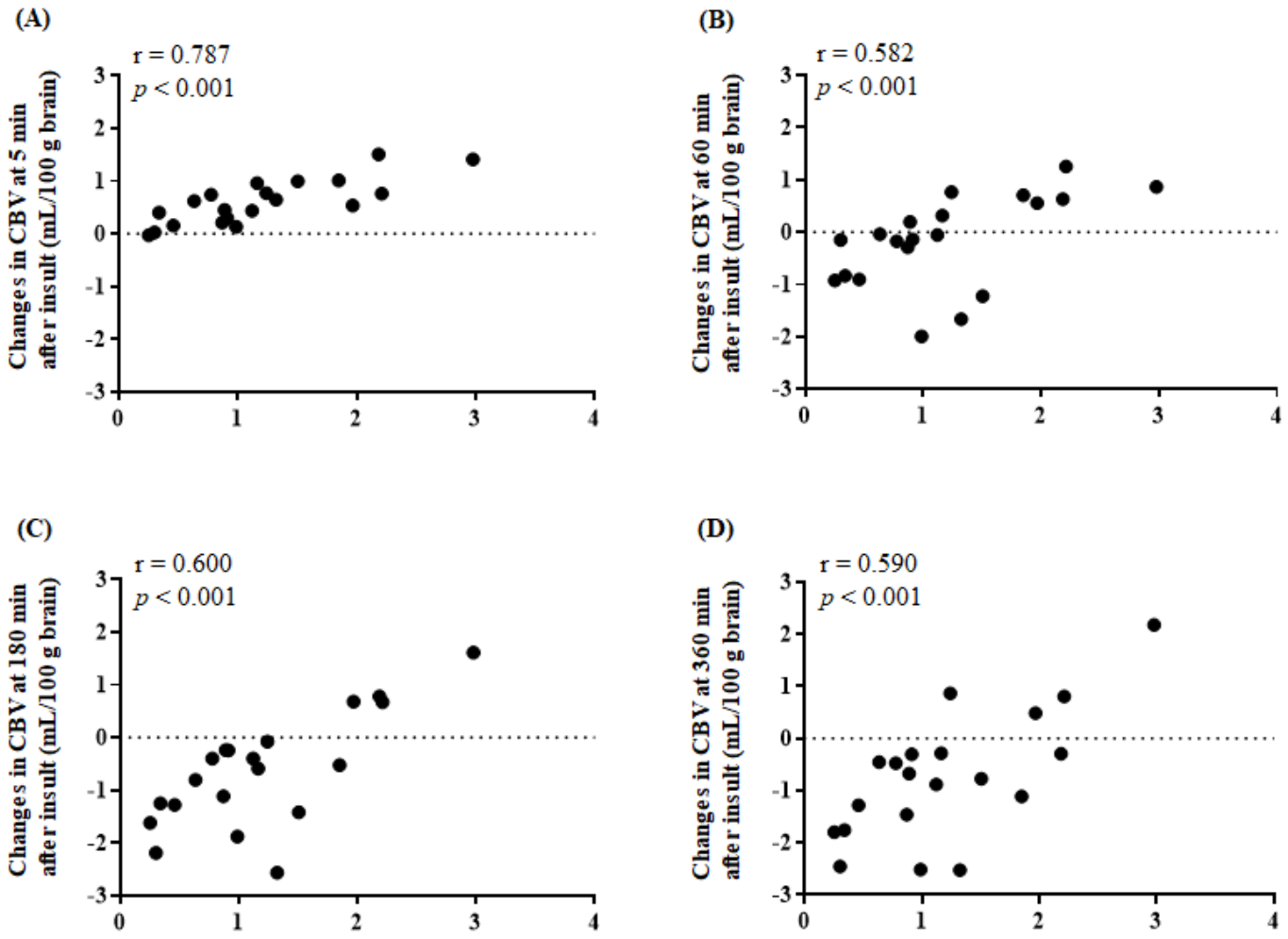

Figure 2.

Figure 2

Correlation between changes in CBV during insult and changes in CBV at (A) 5 min, (B) 60 min, (C) 180 min, and (D) 360 min after insult. CBV changes were defined as the differences between the maximum CBV value during insult and the CBV values 5, 60, 180, and 360 min after insult.

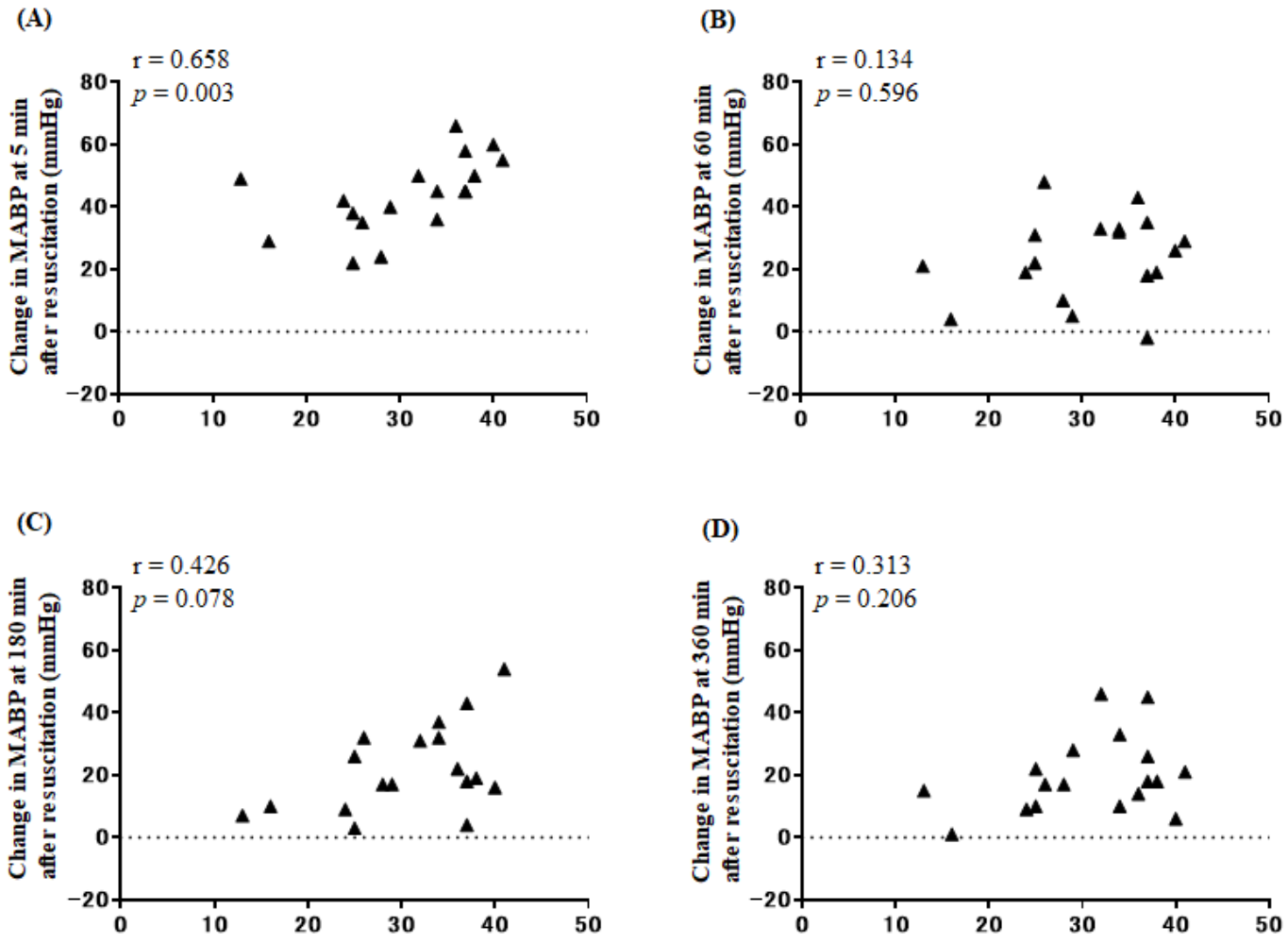

Figure 3.

Figure 3

Correlation between changes in MABP during insult and changes in MABP at (A) 5 min, (B) 60 min, (C) 180 min, and (D) 360 min after insult. MABP changes were defined as the differences between the MABP value at the maximum CBV during insult and the MABP values 5, 60, 180, and 360 min after insult.

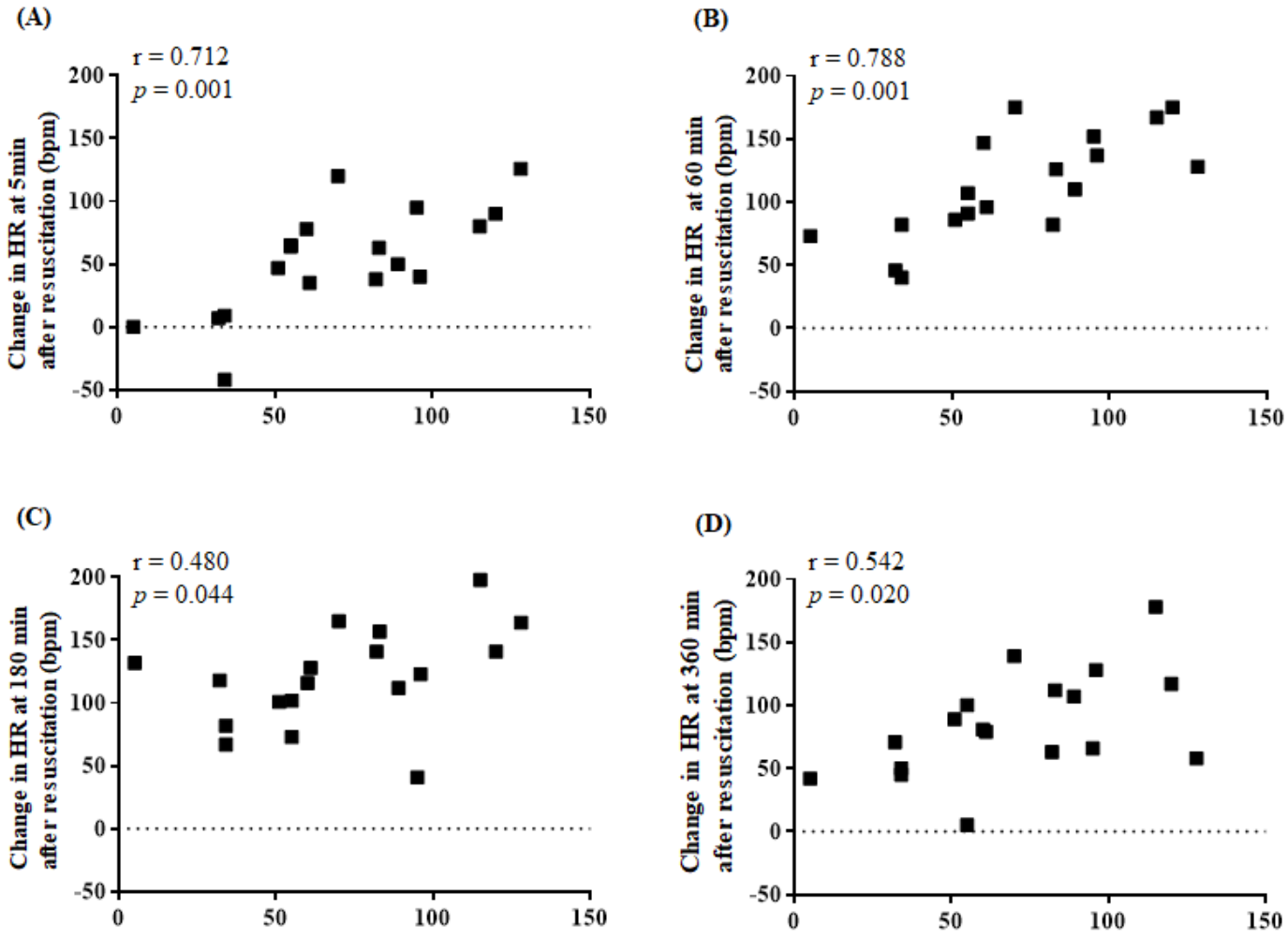

Figure 4.

Figure 4

Correlation between change in HR during insult and change in HR at (A) 5 min, (B) 60 min, (C) 180 min, and (D) 360 min after insult. HR changes were defined as the differences between the HR value at peak CBV during insult and the HR value immediately before resuscitation 5, 60, 180, and 360 min after insult.

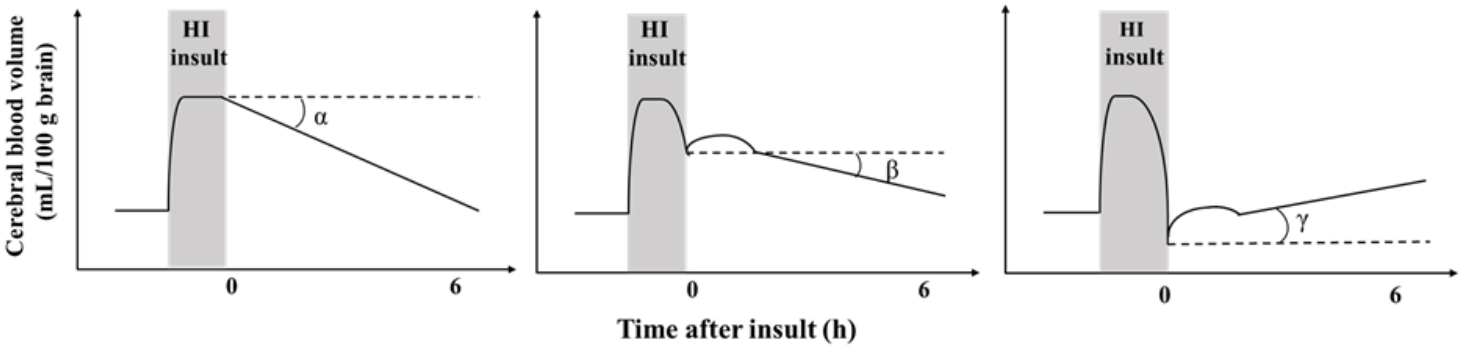

Figure 5.

Figure 5

Schematic representation of the three types of changes in CBV during HI insult and after insult according to severity of insult. (A) in mild insults, CBV falls slightly during the insult and decreases to baseline after resuscitation. (B) In moderately severe insults, CBV decreases during the insult above the baseline and decreases after resuscitation to a smaller extent than in (A). (C) In severe insults, CBV falls during the insult to below the baseline and increases after resuscitation. The angles of the CBV changes from the basal horizontal line after resuscitation are α < β < γ (the angle values of α and β are negative, whereas that of γ is positive).