ORIGINAL ARTICLE

The study of systemic general circulation disturbance during the initiation of therapeutic hypothermia: Pit fall of hypothermia

Mitsuru Honda, Kyosuke Yokota, Ryo Ichibayashi, Katsunori Yoshihara, Hiroyuki Masuda[1], Hiroyuki Uekusa[1], Yoshikatsu Seiki[1], Jun Nomoto[1], Takeki Nagao[2], Taichi Kishi[3], Shigeru Sase[4]

Departments of Critical Care Center, and [1]Neurosurgery, Toho University Medical Center, Omori Hospital, [2]Neurosurgery, Toho University Medical Center, Sakura Hospital, [3]Education Planning and Development, School of Medicine, [4]Faculty of Medicine, Toho University, R and D Division, Anzai Medical Co., Ltd, Ota-ku, Tokyo, Japan

ABSTRACT

Aims: Neurointensive care has reduced the mortality and improved the outcome of patients for severe brain damage, over recent decades, and made it possible to perform this therapy in safety. However, we have to understand the complications of this therapy well. The purpose of our study was to determine the systemic circulation disturbance during the initiation of therapeutic hypothermia by using this continuous neurointensive monitoring system.

Materials and Methods: Ten severe brain damage patients treated with hypothermia were enrolled. All patients had Glasgow Coma Scale (GCS) less than or equal to 8, on admission.

Results: We verified that heart rate, cardiac output, and oxygen delivery index (DO2I) decreased with decreasing core temperature. We recognized that depressed cardiac index (CI) was attributed to bradycardia, dehydration, and increased systemic vascular resistance index (SVRI) upon initiation of hypothermia.

Conclusion: Although the hypothermia has a therapeutic role in severe brain damage patients, we have to carry out this therapy while maintaining their cardiac output using multimodality monitoring devices during hypothermia period.

Key words: Hypothermia, severe brain damage, systemic general circulation disturbance

Introduction

Traumatic brain injury is a major cause of disability and death among young people. Neurointensive care has reduced the mortality and improved the outcome after traumatic brain injury, over recent decades.[1-4] The neurological outcome is affected by not only the primary damage at the moment of injury, but also the secondary damage. The primary injury develops into secondary injuries triggered by episodes of intracranial hypertension and systemic hypotension.

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Address for correspondence:
Dr. Mitsuru Honda, Department of Critical Care Center, Toho University Medical Center Omori Hospital, 6-11-1 Omori-Nishi, Ota-ku, Tokyo 143-8541, Japan. E-mail: mhonda@toho-u.ac.jp

Recent neurointensive care has been focusing on the prevention of secondary brain injury. The development of neuromonitoring in neurointensive care units (NICU) has enabled early detection of these secondary episodes, and thereby, reducing the secondary brain damage. NICU has made advances with continuous neuromonitoring. During the past decade, improvements in neurointensive care have been predominantly in intensification and optimization of already established ways to monitor and treat patients.

Although some previous studies showed that mild therapeutic hypothermia was associated with a better clinical outcome,[5-10] the mechanisms by which hypothermia therapy reduces secondary brain injuries were ill-defined. At present, guidelines by the European Resuscitation Council and American Heart Association recommend the use of hypothermia, after cardiac arrest, if the initial rhythm is ventricular tachycardia (VT) or ventricular fibrillation (VF), and to consider its use for other rhythms. Moreover, although mild hypothermia induction at 35-34°C is now applied to control intracranial pressure in the later stage after traumatic brain injury (TBI), no evidence exists to show that neurological outcome is improved by such delayed application of hypothermia. While mild hypothermia protects

the brain, this therapy has side effects, for example, infection, disturbance in the systemic circulation, and hypokalemia. We collected the intracranial and systemic clinical effects of brain injury by using our NICU's advanced monitoring systems. The purpose of our study was to determine the systemic circulation disturbance during initiation of hypothermia, by using this continuous neurointensive monitoring system.

Materials and Methods

The bed side monitoring system

The multimodality monitoring we used continuously measured heart rate (HR), systemic mean arterial pressure (MAP), central venous pressure (CVP), end tidal CO2 (ETCO2), percutaneous artery blood oxygen saturation (SpO2), bladder temperature (Temp B), central vein temperature (Temp V), and continuous cardiac index (CCI). In addition, we measured the intracranial pressure (ICP), jugular vein oxygen saturation (SjO2), and jugular vein temperature (Temp J) as intracranial information. We automatically input this data into a bedside personal computer with a digital signal and collected calculation parameters such as cerebral perfusion pressure (CPP), systemic vascular resistance index (SVRI), oxygen delivery index (DO2I), oxygen consumption index (VO2I), and the oxygen extraction rate (O2ER). We evaluated the disturbance of systemic circulation using these parameters, previously described (Tem V and CVP, MAP, HR, CI, SVRI, DO2I) during initiation in 10 patients with severe brain damage.

This research project was approved by the Ethics committee, and written informed consent was given by the patient's next kin. Since recent five years, 10 patients admitted to the NICU, Toho University Omori medical center, with severe brain damage, were prospectively enrolled (Glasgow Coma Scale score $\leqq$8, on admission). Their ages ranged from 34 to 75 years (mean of 55.5 years). The 10 patients consisted of 5 subarachnoid hemorrhage patients, 2 traumatic brain injury patients, 2 cardiopulmonary arrest patients, and 1 cerebral infarction patient [Table 1]. The exclusion criteria for the present study were (1) patients resuscitated from cardiac arrest with hypotension and (2) hypotensive patients with Takotsubo cardiomyopathy. Neurosurgical interventions were undertaken, when necessary, to evacuate mass lesions or to treat aneurysms. Hypothermia was initiated promptly after surgery for patients with subarachnoid hemorrhage (SAH) and TBI. The other patients were initiated promptly after admission to the NICU. Routine monitoring, previously described, was carried out during hypothermia. All patients were intubated and ventilated to maintain arterial partial pressure of oxygen (PO2) >100 mmHg and arterial partial pressure of carbon dioxide (PCO2) at 35-40 mmHg. The hypothermia was carried out under anesthesia. They received propofol (3.0-5.0 mg/kg/hr), continuously, as sedation, buprenorphine (1.0-2.0 mg/kg/hr) as analgesia, and pancuronium (0.05 mg/kg/hr) as muscle relaxants. The primary goals of hypothermia were

Table 1: Case of summary

Age	Gender	Diagnosis	Outcome (GOS)
38	Male	Cardiac arrest	GR
61	Female	SAH	D
75	Female	Cerebral infarction	D
47	Male	TBI	GR
72	Female	SAH	SD
49	Female	SAH	D
59	Male	SAH	VS
60	Female	TBI	D
34	Female	Cardiac arrest	D
60	Female	SAH	MD

SAH: Subarachnoid hemorrhage, TBI: Traumatic brain injury; GOS: Glasgow outcome scale; GR: Good recovery; MD: Moderate disability; SD: Severe disability; VS: Vegetative state; D: Death

stabilization or improvement of the patients with neurological conditions, and maintenance of a mean arterial pressure (MAP) 90 mmHg or more, with vasoactive mediators (dobutamine and dopamine), and adequate volume expansion to maintain a cerebral perfusion pressure during the initiation; because, not only the hypothermia, but also, sedative agents such as propofol reduce MAP. We closely monitored MAP and cardiac index in real time, and corrected hypotension immediately, if needed. We used the cold water blanket technique to reduce brain temperature, until it reached the target value. A computed tomographic (CT) scan was performed at admission, and liberally, thereafter, whenever clinically indicated.

We examined analysis of correlation using parameter's values obtained once per minute from computer system. The analysis of Pearson's correlation was used to assess the correlation between core temperature and parameters of systemic circulation. In this study, we regarded statistical significant Pearson's correlation coefficients that are less than −0.4 ($P<0.05$) or more than 0.4 ($P<0.05$) as clinically significant correlation.

Results

It took an average of 5 hours 24 minutes to reach the target temperature. We examined the relationship between the correlation of change of temperature and CVP. CVP lowered significantly in two cases, with decreasing temperature. Although CVP was kept relatively constant in eight cases, the water balance was negative in four cases. With decreasing temperature, urinary volume increased during the initiation of hypothermia. Consequently, mean water balance was −173 ml/5.4 hr, inspite of volume replacement. We recognized dehydration until it reached the target temperature [Table 2].

We examined the correlation between the change in temperature and MAP, HR, SVRI, CI, and DO2. With decreasing temperature, the MAP was raised in five cases and lowered

in one case. HR decreased in nine cases. CI decreased in five cases, and increased in no cases. SVRI increased in five cases, and decreased in no cases. DO2 decreased in six cases, and increased in one case [Table 3].

In five cases that had depressed CI, we examined the correlation between change of CI and CVP, HR, and SVRI. There were negative correlations between CI and CVP, in two cases. There were negative correlations between CI and SVRI, in four cases. There were positive correlations between CI and HR, in four cases. We recognized that depressed CI was attributed to bradycardia, dehydration, and increased SVRI, upon initiation of hypothermia [Table 4]. It is necessary to control the systemic circulation in order to deliver enough oxygenated blood to the brain. Especially, when there is dehydration, we must monitor the intracranial environment and treat by improving the volume in the systemic circulation.

Table 2: Water balance until reaching target temperature

No. of the case	Water balance	CVP
1	−	~
2	−	~
3	+	~
4	−	~
5	−	~
6	±0	~
7	+	~
8	−	~
9	−	↓
10	−	↓

(mean −173 ml/5.4 hr). CVP: Central venous pressure; ↓: r≧−0.4; ~: No significant difference (r: Correlation coefficient)

Table 3: Relationship between temp V and parameters of systemic general circulation (r<-0.4, r>0.4)

No. of the case	MAP	HR	CI	SVRI	DO2
1	↑	↓	~	↑	~
2	~	↓	↓	~	↓
3	~	↓	↓	↓	
4	~	↓	~	~	
5	↑	↓	~	↑	↓
6	↑	↓	↓	↑	↓
7	~	~	~	~	
8	↑	↓	~	↑	↑
9	↑	↓	↓	↑	↓
10	↓	↓	↓	~	↓

MAP: Mean artery pressure; HR: Heart rate; CI: Cardiac index; SVRI: Systemic vascular resistance index; DO2I: Delivery oxygen index; ↓: r≧−0.4; ↑: r≦0.4; ~: No significant difference (r: Correlation coefficient)

Table 4: Relationship between CI and CVP, HR, and SVRI (r<−0.4, r>0.4)

No. of the case	CVP	HR	SVRI
2	~	↓	↑
3	↓		
6	~	↓	↑
9	↓	↓	↑
10	~	↓	↑

CI: Cardiac index; CVP: Central venous pressure; HR: Heart rate; SVRI: Systemic vascular resistance index; ↓: r≧−0.4; ↑: r≦0.4; ~: No significant difference (r: Correlation coefficient)

Illustrative case

Case: 56-year-old male

He sustained traumatic brain injury in a traffic accident. On admission, his consciousness level was GCS 8 (E1, V2, M5). Emergency CT demonstrated brain contusion and intracerebral hematoma. Emergency craniectomy and hematoma removal was performed. Hypothermia was followed after surgery. The trend graph is shown in Figure 1. MAP was kept constant during initiation, but with decreasing temperature, SVRI rose, and cardiac output deteriorated. Although elevation of SVRI compensated for deterioration in blood pressure on the surface, the systemic circulation disturbance was elicited by cardiac dysfunction and might reduce the cerebral blood flow. This case illustrates the disturbance of systemic circulation which occurs during initiation of hypothermia. The disturbance of systemic circulation may contribute to secondary brain damage.

Discussion

Recently, two large studies have demonstrated that therapeutic hypothermia can improve outcome in patients with post-anoxic brain injury, following cardiac arrest.[11,12] On the other hand, although some previous studies for TBI showed that mild hypothermia therapy was associated with a better clinical outcome, this treatment remains highly controversial, especially in patients with severe traumatic head injury. One

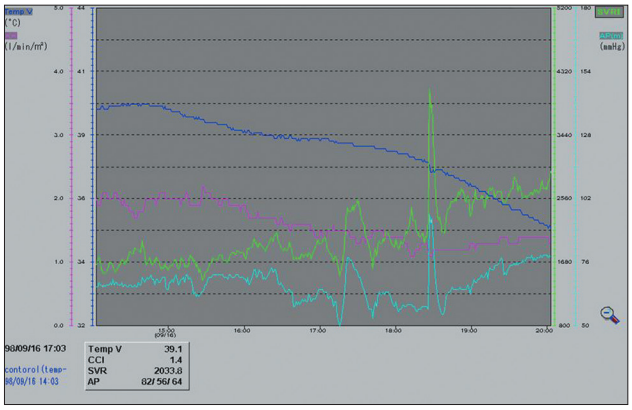

Figure 1: The trend graph of the monitoring system. The trend graph demonstrated that mean arterial pressure (MAP) was kept constant during initiation, but, with decreasing of temperature, systemic vascular resistance index (SVRI) rose, and cardiac output index (CI) deteriorated. Blue line: Temp V; pink line: CI; green line: SVRI; light-blue: MAP

well designed, multi-centered, randomized controlled trial (RCT), in 2001, did not show any effect on the outcome, in the overall patient group, although decreases in intracranial pressure were noted in the hypothermia group.[13] This study has been criticized based on its methodology: Treatment was started late, and cooling was slow (average time to target temperature >8 h).[14] Furthermore, there were problems with hypotension, hypovolemia, electrolyte imbalance, and hyperglycemia in the treatment group. Marshall[15] criticized the study for inter-center inconsistencies in patient management and the lack of specialized neurointensive care at some of the study centers. Based on these problems, a new study has been initiated that includes hypothermic and normothermic groups of patients with severe TBI (GCS3-8), in whom, hypothermia of 33°C is being achieved within 4 h after injury, and maintained for 48 h, in patients who are 16-45 years old. Rewarming is being initiated in 48 h, after reaching the target temperature. Hypotension will be promptly treated with vasopressors.[16]

It has been shown that even very brief episodes of mild hypotension and/or hypovolemia can adversely affect the outcome.[17] Great care should be taken to avoid all the potentially harmful effects of hypothermia and to prevent even the briefest episodes of hypovolemia and hypotension. Indeed, in this study, CVP was kept relatively constant during initiation, but with decreasing temperature, urinary volume increased, and dehydration deteriorated. In addition, AP was kept relatively constant during initiation, but with decreasing temperature, SVRI increased, and cardiac output deteriorated. CPP is the difference between the MAP and ICP. Therefore, similarly, CPP was kept relatively constant during initiation, but with decreasing temperature, SVRI increased, and cardiac output deteriolated. During the initiation of hypothermia, systemic circulation disturbance might result in cerebral ischemia. It is thought that we have to monitor these parameters carefully. If we recognize abnormal value in these parameters, we are able to treat systemic circulation disturbance with volume displacement and vasopressors or vasodilators.

It has been well known that the cardiac output decreases linearly with hypothermia, to approximately 60% of control values at a body temperature of 32-33°C.[18,19] The reduction in cardiac output was due mainly to the decrease in heart rate and the volume of circulating blood, since the stroke volume was decreased to a much lesser extent.[19] The causes for bradycardia during hypothermia are thought to be the direct effects of cooling on sinus nodes or the atrium of the heart, metabolic reduction in accordance with body temperature drop, and a possible mediation of vagal nerves. It was found that a suppression of the baroreflex of HR, but not sympathetic nerve activity, during hypothermia, may indicate the direct effects of hypothermia on the heart.[20] Therefore, there is less possibility that a decrease in HR, during hypothermia, results from metabolic reduction. These adverse events can occur as side effects of cooling, but are quite easily preventable, with proper intensive care, and thus, should not be regarded as inevitable consequences of hypothermic treatment. Actually, it was reported that moderate hypothermia improved neurological outcome of severe TBI patients so far, as their cardiac output was maintained in normal-hyperdynamic range.[21]

Recently, from experimental and clinical research, we have learned that the neurological outcome is not an effect of the primary damage occurring at the moment of injury. The primary injury develops into secondary injuries triggered by various biochemical and hemodynamic processes influenced, for example, by episodes of intracranial hypertension, systemic hypotension, and hypoxia.[22] And so, in addition to the intracranial environment monitoring, monitoring of systemic circulation are mandatory for adequate treatment of patients with severe brain damage. But each of these monitoring devices is separate and independent making simultaneous evaluation of blood flow and metabolic changes in both cerebral and systemic circulation not feasible. We have used the monitoring system using a personal computer system.[23] With this system in real time, we can manage intaracranial and systemic changes instantaneously, by a way of combined monitoring of brain damage setting. There are many parameters provided by using these multimodality monitoring devices. It is important clinically to observe a trend change of parameters with time. Our monitoring system allows by way of a trend graph to display trend changes on the same screen at the same time. In particular, this becomes important during on-going hypothermia treatment. As a result, we are able to detect an abnormality while monitoring, and treat promptly.

Conclusion

There are systemic general circulation disturbances during the initiation of hypothermic therapy. It was suggested that general systemic circulation disturbance might deteriorate the cerebral circulation and result in ischemic brain. We have to carry out this therapy to avoid secondary brain damage while maintaining the cardiac output with using multimodality monitoring devices.

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