mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–24.
2. Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:293–301.
3. Krafft P, Fridrich P, Fitzgerald RD, Koc D, Steltzer H. Effectiveness of nitric oxide inhalation in septic ARDS. *Chest* 1996;109:486–93.
4. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993;328:399–405.
5. Marcy TW, Marini JJ. Inverse ratio ventilation in ARDS. Rationale and implementation. *Chest* 1991;100:494–504.
6. Puybasset L, Rouby JJ, Mourgeon E, Cluzel P, Souhil Z, Law-Koune JD, Stewart T, Devilliers C, Lu Q, Roche S, Kalfon P, Vicaut E, Viars P. Factors influencing cardiopulmonary effects of inhaled nitric oxide in acute respiratory failure. *Am J Respir Crit Care Med* 1995;152:318–28.
7. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644–55.
8. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988;138:720–3.
9. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG, for the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-Related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996;22:707–10.
10. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
11. Sato T, Okamoto K, Kukita I, Kikuta K, Hamaguchi M, Shihara K, Shibata Y. Nitrogen dioxide production in a nitric oxide inhalation system using the Servo 900C ventilator. *Acta Paediatr Jap* 1997;39:172–5.
12. Sjöstrand UH, Lichtwarck-Aschoff M, Nielsen JB, Markstrom A, Larsson A, Svensson BA, Wegenius GA, Nordgren KA. Different ventilatory approaches to keep the lung open. *Intensive Care Med* 1995;21:310–8.
13. Slutsky AS. Mechanical ventilation. *Chest* 1993;104:1833–59.
14. Okamoto K, Hamaguchi M, Kukita I, Kikuta K, Sato T. Efficacy of inhaled nitric oxide in children with ARDS. *Chest* 1998;114:827–33.
15. Doering EB, Hanson CW, Reily DJ, Marshall C, Marshall BE. Improvement in oxygenation by phenylephrine and nitric oxide in patients with adult respiratory distress syndrome. *Anesthesiology* 1997;87:18–25.
16. Putensen C, Räsänen J, López FA, Downs JB. Continuous positive airway pressure modulates effect of inhaled nitric oxide on the ventilation-perfusion distributions in canine lung injury. *Chest* 1994;106:1563–9.
17. Artigas A, Bernard GR, Carlet J, Dreyfuss D, Gattinoni L, Hudson L, Lamy M, Marini JJ, Matthay MA, Pinsky MR, Spragg R, Suter PM. The American-European consensus conference on ARDS, part 2. Ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. *Intensive Care Med* 1998;24:378–98.
18. Poelaert JI, Vogelaers DP, Colardyn FA. Evaluation of the hemodynamic and respiratory effects of inverse ratio ventilation with a right ventricular ejection fraction catheter. *Chest* 1991;99:1444–50.
19. Puybasset L, Stewart T, Rouby JJ, Cluzel P, Mourgeon E, Belin MF, Arthaud M, Landault C, Viars P. Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome. *Anesthesiology* 1994;80:1254–67.
20. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 1990;16:372–7.

Comparative Analysis of Alpha-stat and pH-stat Strategies with a Membrane Oxygenator During Deep Hypothermic Circulatory Arrest in Young Pigs

Won Gon Kim, Cheong Lim, Hyun Jong Moon, and Yong Jin Kim, Department of Thoracic and Cardiovascular Surgery and Heart Research Institute, BK 21 Human Life Sciences, Seoul National University College of Medicine and Clinical Research Institute, Seoul National University Hospital, Seoul, Korea

Abstract: Using young pigs, this study compared the strategies of alpha-stat and pH-stat during deep hypothermic circulatory arrest (DHCA) for the cooling time of brains during the induction of hypothermia and rewarming time with cardiopulmonary bypass (CPB); the cerebral perfusion rate and metabolism rate, and the ratio of these 2 rates; and the extent of the cerebral edema development after circulatory arrest. Fourteen young pigs were assigned to 1 of 2 strategies of gas management. Cerebral blood flow was measured with a cerebral venous outflow technique. With CPB, core cooling was initiated and continued until the nasopharyngeal temperature fell below 20°C. The flow rate was set at 2,500 ml/min. Once the temperature reached below 20°C, the animals were subjected to DHCA for 40 min. During the cooling period, the acid-base balance was maintained using either alpha-stat or pH-stat strategy. After DHCA, the body was rewarmed to the normal body temperature. The animals then were sacrificed, and we measured the brain water content. The cerebral perfusion and metabolism rates were measured before the onset of CPB, before cooling, before DHCA, 15 min after rewarming, and upon the completion of rewarming. The cooling time was significantly shorter with alpha-stat than with pH-stat strategy while no significant differences were observed in the rewarming time between groups. Also, no significant differences were found in cerebral blood flow volume, metabolic rate, or flow/metabolic rate ratio between groups. In each group, the cerebral blood flow volume, metabolic rate, and flow/metabolic rate ratio showed significant differences in body temperature. Brain water content showed no significant differences between the 2 groups. In summary, this study found no significant differences between alpha-stat and pH-stat strategies, except in the cooling time. The cooling time was rather shorter with the alpha-stat than with the pH-stat strategy. **Key Words:** Deep hypothermic circu-

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Address correspondence and reprint requests to Dr. Won Gon Kim, Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Yongon-Dong 28, Chongno-Gu, Seoul 110-744, Korea. E-mail: wongon@plaza.snu.ac.kr

latory arrest—Acid-base management—Alpha-stat—pH-stat.

Deep hypothermia and circulatory arrest are dramatic applications demonstrating the protective effects of hypothermia in cardiac surgery. However, the human body is unable to maintain normal physiology when exposed to such induced hypothermia, and the maintenance of bodily functions under such a condition, especially that of acid-base balance, remains controversial (1–8). Particularly, controlling the acid-base balance during a circulatory arrest under deep hypothermia strongly influences the function of the central nervous system and thus is an important risk factor for the development of adverse neuropsychiatric complications (9–13). Theoretically, the advantages of the poikilotherm mechanism of acid-base balance control, alpha-stat, are the possible maintenance of intracellular neutral electromechanical states during hypothermia and the close resemblance of coupling pattern of brain perfusion to its metabolic activity to that in the normal temperature state. On the other hand, the advantages of the hibernator mechanism of acid-base balance control, pH-stat, are in stabilizing cerebral hemodynamics and maintaining balanced cerebral perfusion thus providing uniform cooling during hypothermia. The pH-stat approach, however, carries the risk of developing thromboembolism or cerebral edema. Thus, this study aims to compare alpha-stat with pH-stat strategy for the time required to cool brains during the induction of hypothermia and to rewarm with cardiopulmonary bypass; cerebral perfusion rate, brain metabolism rate, and their coupling ratio; and the extent of cerebral edema development after cardiopulmonary bypass (CPB) in an experimental model of hypothermic circulatory arrest in juvenile pigs.

Materials and methods

For this study, juvenile pigs of both sexes weighing 25 to 30 kg were used. The 2 test subject groups of alpha-stat and pH-stat consisted of 7 pigs each. For anesthesia, 0.03 mg/kg of atropine was used as a premedication, and 15 to 20 mg/kg of ketamine and 15 to 20 mg/kg of thiopental sodium were used as inducing agents. Intratracheal intubation was followed by ventilation with a volume-cycled ventilator. For maintenance anesthesia, 0.5 to 1.0% halothane and supplemental oxygen were used. Muscle relaxation was maintained with a continuous infusion of Pancuronium (0.25 mg/kg/h).

A cannula was inserted into the superior sagittal sinus to measure the volume of cerebral blood flow and to take blood sampling of the cerebral vein (14–16). Before the onset of CPB, an incision was made on the scalp followed by the removal of the periosteum and bone overlying the sagittal sinus. To minimize extracranial blood input into the superior sagittal sinus, a 3 cm circular excision was made from the outer cortical layer and spongiosa area surrounding the exposed region. Thereafter, a 24 Fr catheter was inserted (Fig. 1). A Forgarty catheter then was inserted into the sagittal sinus and inflated to prevent the inferior leakage whenever the sagittal sinus outflow was measured. The weight of the brain drained by the catheter was presumed to average 43% of the total brain weight although the study was done in dogs (17). The heart was revealed by a median sternotomy, after which 300 IU/kg of heparin was administered. Ascending-aortic and right-atrial cannulas were then inserted through purse-string sutures with 5-0 prolene sutures. A pediatric membrane oxygenator (Univox-IC, Bentley Laboratories. Inc., Baxter Healthcare Corporation, Irvine, CA, U.S.A.) and a roller pump (American Optical Corporation, Greenwich, CT, U.S.A.) were used. For priming solution, 500 ml of Pentaspan, 160 ml of mannitol, and 700 ml of Hartman's solution were given along with 54 mg of sodium bicarbonate. The total priming volume given was 1,360 ml, and hematocrit was adjusted between 18 and 20%. The perfusion rate was maintained at 2,500 ml/min. During the first 10 to 15 min after the onset of CPB, a normothermic perfusion was maintained while basic tests were performed. Perfusion cooling then was carried out until the body temperature was decreased to 20°C as measured in the nasopharynx. When the

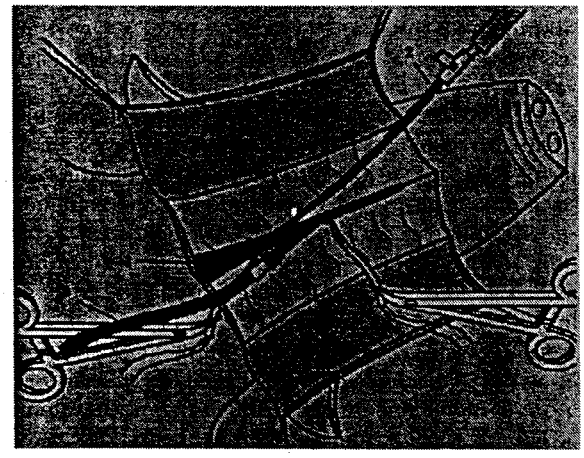

FIG. 1. The schematic drawing shows the superior sagittal sinus outflow measurement.(superior sagittal sinus [1], Fogarty catheter [2], and sampling catheter [3]).

TABLE 1. *Criteria of alpha-stat and pH-stat acid-base managements*

In vivo temp (°C)	Measured and reported at 37				Corrected to in vivo temp			
	pH		P_{CO_2}		pH		P_{CO_2}	
	Alpha	pH	Alpha	pH	Alpha	pH	Alpha	pH
37	7.40	7.40	40	40	7.40	7.40	40	40
33	7.40	7.34	40	47	7.44	7.40	35	40
30	7.40	7.30	40	54	7.50	7.40	29	40
27	7.40	7.26	40	62	7.55	7.40	26	40
23	7.40	7.21	40	74	7.60	7.40	22	40
20	7.40	7.18	40	84	7.65	7.40	19	40
17	7.40	7.14	40	96	7.69	7.40	17	40

body temperature fell to 20°C, the circulation was stopped for 40 min. After the arrest period, the body was rewarmed to normal body temperature. During the cooling and rewarming period, the acid-base balance was maintained according to either the alpha-stat or the pH-stat strategy (Tables 1 and 2). The animals then were sacrificed, and their brains were removed and examined for edema. The brains also were microscopically analyzed for signs of cerebral thromboembolism.

The cerebral perfusion and metabolism rates were measured before the onset of CPB, before perfusion cooling, before circulatory arrest, 15 min after rewarming, upon the completion of rewarming, and 1 h after rewarming. The cerebral metabolism rate was calculated according to the following equation: *metabolic rate = cerebral blood flow × (arterial blood oxygen content − sagittal sinus blood oxygen content)/* 100. Arterial blood gas analyses were regularly carried out as needed. Body temperature was measured from the nasopharynx and the rectum. The extent of cerebral edema was calculated by subtracting the dry weight of the brain from its wet weight and then dividing this value by the wet weight. The dry weight of the brain was measured after subjecting the brain to 72 h of dehydration at 60°C in a dryer machine.

The measurements obtained from the 2 groups were compared with the Wilcoxon rank sum test while the variations with each group were analyzed with repeated measures ANOVA. A p value less than 0.05 was considered statistically significant.

Results

The cooling time was considered to be the time taken for the nasopharynx temperature to reach 20°C after CPB cooling was started. The rewarming time was considered to be the time taken for the nasopharynx temperature to reach 38°C after the onset of rewarming. The cooling time for the alpha-stat group was 16.57 ± 5.13 min, which was significantly shorter than that of the pH-stat group, 22.83 ± 2.14 min ($p < 0.05$). However, no significant difference was observed in the rewarming time, which was 40.0 ± 5.07 min for the alpha-stat group and 46.5 ± 6.32 min for the pH-stat group. While the values of the cerebral metabolic rate and cerebral perfusion as estimated from the sagittal sinus outflow measurement were higher in the pH-stat group than those in the alpha-stat group, the values were not statistically significant (Fig. 2). The perfusion-to-metabolic-rate ratios also showed no statistically significant difference. However, a significant change was observed in the cerebral perfusion and metabolic rate within each group over the course of the experiment. Particularly at 20°C, the brain metabolic rate fell more

TABLE 2. *Gas amounts administered in alpha-stat and pH-stat acid-base managements*

	Cooling				Rewarming			
	Temp (°C)	O_2 L/min	Fio_2	CO_2	Temp (°C)	O_2 L/min	Fio_2	CO_2
Alpha-stat	37	4.0	0.75	0	20	1.8	0.45	0
	31	3.0	0.60	0	24	2.0	0.50	0
	27	2.5	0.55	0	27	2.3	0.60	0
	24	2.0	0.50	0	31	2.5	0.65	0
	20	1.8	0.45	0	37	3.0	0.75	0
pH-stat	37	3.0	0.70	5.0	20	1.0	0.45	4.5
	31	2.0	0.65	5.0	24	2.0	0.50	4.0
	27	1.8	0.60	5.0	27	2.0	0.60	3.5
	24	1.5	0.50	5.5	31	3.0	0.65	3.0
	20	0.5	0.40	5.5	37	3.0	0.70	3.0

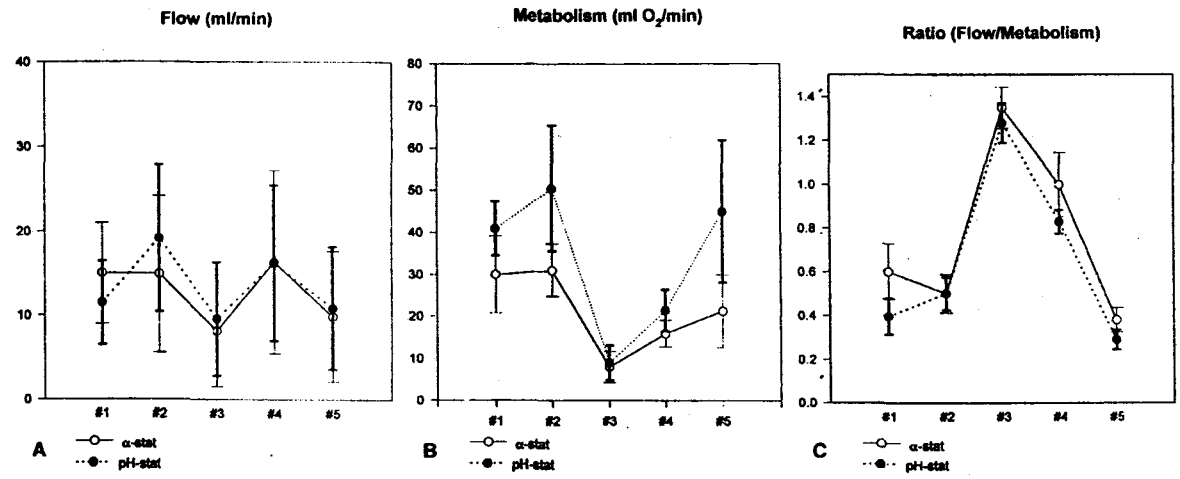

FIG. 2. Shown are cerebral flow (A), metabolism (B), and cerebral blood flow/metabolism (C) before the onset of cardiopulmonary bypass (#1), before cooling (#2), before deep hypothermic circulatory arrest (#3), 15 min after rewarming (#4), and on completion of rewarming (#5).

than the cerebral perfusion, so that the perfusion-to-metabolic-rate recorded was greater than 1. No significant difference was observed between groups in brain water content (78.4 ± 5.56% for pH-stat, 81.93 ± 3.70% for alpha-stat). No signs of cerebral embolism were observed microscopically.

Discussion

Despite theoretical advantages and disadvantages of alpha-stat and pH-stat, current studies revealed no significant difference between these 2 acid-base management systems in terms of postoperative neuropsychiatric complications after CPB under moderate hypothermia (13). However, extrapolating the results obtained using either of these systems under moderate hypothermia directly into pediatric patients under profound hypothermia is not reasonable and led us to compare alpha-stat and pH-stat under profound hypothermia in young pigs. Until now, only limited experimental data were available on which of these 2 gas management systems would give better protection for brain metabolism, and no studies compared the alpha-stat and pH-stat under profound hypothermia in the human body. However, there is a general consensus that a difference does exist between the 2 mechanisms since values of the pH and $Paco_2$ balance deviate far from their normal values. The results of this experiment showed no difference between alpha-stat and pH-stat in the cerebral metabolic rate at 20°C. While the cerebral perfusion rate decreased along with the rate of metabolism at low temperatures, the cerebral blood vessels remained responsive to $PaCO_2$. Thus, the relative hypercarbia under pH-stat allowed the dilatation of cerebral vessels and a better perfusion rate than under alpha-stat. While not statistically significant, a higher cerebral blood flow volume appeared to have been maintained in the pH-stat test group than in the alpha-stat test group. In an alert healthy animal, brain perfusion and metabolism are determined by regional metabolic demands. Such cerebral coupling plays an important role in cerebral homeostasis. Under hypothermia, cerebral blood flow falls proportionately, but brain metabolic rate falls exponentially. The perfusion-to-metabolic-rate ratio thus increases with a fall in temperature. This experiment also revealed the highest perfusion-to-metabolic-rate ratio at 20°C. However, there was no significant difference in the perfusion-to-metabolic-rate ratios between the 2 groups. The cerebral water content, used as a measure of edema, also showed no difference. We did not observe any evidence of thromboembolism in the brain specimens of the groups. As previously described, pH-stat has the theoretical advantage of better cooling through luxuriant cerebral perfusion, which led us to anticipate that the pH-stat would show shorter cooling and rewarming times compared to alpha-stat. However, alpha-stat showed the statistically faster cooling time. While not statistically significant, alpha-stat also showed the tendency for a faster rewarming time. One possible explanation for these results is that more uniform cooling provided theoretically by pH-stat does not necessarily mean fast cooling. Another possibility is that the nasopharyngeal temperature measurement, which acts as a monitor to measure cerebral temperature, does not adequately reflect the global temperature of the brain in the pig. Further work with

direct temperature measurement at multiple sites in the brain of the animal may be needed to clarify the latter problem although a small difference of cooling time to induce deep hypothermic circulatory arrest is not considered to offer a practical problem in clinical situations.

References

1. White FN. A comparative physiological approach to hypothermia. *J Thorac Cardiovasc Surg* 1981;82:821–31.
2. Malan A, Wilson TL, Reeves RB. Intracellular pH in cold-blooded vertebrates as a function of body temperature. *Respir Physiol* 1976;28:29–47.
3. Swan H. The importance of acid-base management for cardiac and cerebral preservation during open-heart operations. *Surg Gyn Obstet* 1984;158:391–414.
4. Dickinson D, Sambrooks J. Intellectual performance in children after circulatory arrest with profound hypothermia in infancy. *Arch Dis Child* 1979;54:1–6.
5. Jonas RA, Wernovsky G, Ware J. The Boston circulatory arrest study: perioperative neurologic outcome after the arterial switch operation. *Circulation* 1992;86(Suppl 1):360A.
6. Grote CL, Shanahan PT, Salmon P, Meyer RG, Barrett C, Lansing A. Cognitive outcome after cardiac operations. *J Thorac Cardiovasc Surg* 1992;104:1405–9.
7. Ferry PC. Neurologic sequelae of open-heart surgery in children. An irritating question. *Am J Dis Child* 1990;144:369–73.
8. Wright J, Hicks R. Deep hypothermic arrest. Observation on later development in children. *J Thorac Cardiovasc Surg* 1979;86:466–8.
9. Nattie EE. The alpha-stat hypothesis in respiratory control and acid-base balance. *J Appl Physiol* 1990;69:1201–7.
10. Treasure T, Naftel DC, Conger KA, Garcia JH, Kirklin JW, Blackstone EH. The effect of hypothermic circulatory arrest time on cerebral function, morphology, and biochemistry. An experimental study. *J Thorac Cardiovasc Surg* 1983;86:761–70.
11. Watanabe T, Miura M, Inui K, Minowa T, Shimanuki T, Nishimura K, Washio M. Blood and brain tissue gaseous strategy for profoundly hypothermic total circulatory arrest. *J Thorac Cardiovasc Surg* 1991;102:497–504.
12. Lundar T, Lindegaard KF, Froysaker T, Grip A, Bergman M, Ami-Holen E, Nornes H. Cerebral carbon dioxide reactivity during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg* 1986;41:525–30.
13. Hindman BJ. Cerebral physiology of hypothermia and hypothermic acid-base management during cardiopulmonary bypass. *Cardiol Young* 1993;3:273–80.
14. Upton R, Grant C, Ludbrook G. An ultrasonic Doppler venous outflow method for the continuous measurement of cerebral blood flow in conscious sheep. *J Cereb Blood Flow Metab* 1994;14:680–8.
15. Takeshita H, Michenfelder JD, Theye R. The effects of morphine and N-allylnormorphine on canine cerebral metabolism and circulation. *Anesthesiology* 1972;37:605–12.
16. Stange K, Lagerkranser M, Sollevi A. Effect of adenosine-induced hypotension on the cerebral autoregulation in the anesthetized pig. *Acta Anesthesiol Scand* 1989;33:450–7.
17. Michenfelder JD, Messick JM Jr, Theye RA. Simultaneous cerebral blood flow measured by direct and indirect methods. *J Surg Res* 1968;8:475–81.

Experimental Use of a Compact Centrifugal Pump and Membrane Oxygenator as a Cardiopulmonary Support System

Etsuro Suenaga, Kozo Naito, Zhi-Li Cao, Hisao Suda, Tetsuya Ueno, Masafumi Natsuaki, and Tsuyoshi Itoh, Department of Thoracic and Cardiovascular Surgery, Saga Medical School, Saga, Japan

Abstract: Compactness and high performance are the most important requirements for a cardiopulmonary support system. The Nikkiso (HPM-15) centrifugal pump is the smallest (priming volume; 25 ml, impeller diameter; 50 mm) in clinically available centrifugal pumps. The Kuraray Menox (AL-2000) membrane oxygenator, made of double-layer polyolefin hollow fiber, has a minimum priming volume (80 ml) and a low pressure loss (65 mm Hg at 2.0 L/min of blood flow) compared with other oxygenators. The aim of this study was to evaluate the performance of the most compact cardiopulmonary support system (total priming volume: 125 ml) in animal experiments. The cardiopulmonary bypass was constructed in a canine model with the Nikkiso pump and Menox oxygenator in comparison with a conventional cardiopulmonary support system. The partial cardiopulmonary bypass was performed for 4 h to evaluate the gas exchange ability, blood trauma, serum leakage, hemodynamics, and blood coagulative parameters. The postoperative plasma free hemoglobin level of the compact cardiopulmonary system was 29.5 ± 10.21 mg/dl (mean ± SD), which was lower than that of the conventional cardiopulmonary system, 48.75 ± 27.39 mg/dl (mean ± SD). This compact cardiopulmonary system provided the advantage in terms of reduction of the priming volume and less blood damage. These results suggested the possibility of miniaturization for the cardiopulmonary bypass support system in open-heart surgery in the near future. **Key Words:** Compact cardiopulmonary system—Centrifugal pump—Membrane oxygenator—Hemolysis—Coagulation parameters.

In open-heart surgery, a majority of cardiopulmonary bypass (CPB) systems still utilize bulky roller pumps. The continuous invasion of the CPB to the patient is related to the CPB time, flow rate, total internal surface area, pressure gradient of the circuit, and biocompatibility of the material (1).

Currently, a compact atraumatic centrifugal pump and membrane oxygenator are available for clinical use (2,3). The combination of these 2 devices is ex-

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Address correspondence and reprint requests to Dr. Etsuro Suenaga, Department of Thoracic and Cardiovascular Surgery 5-1-1, Nabeshima, Saga 849, Japan.