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G. 知的財産の出願・登録状況

1. 特許取得

該当なし。

2. 実用新案登録

該当なし。

3. その他

該当なし。

研究成果の刊行に関する一覧表

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Perfusion

Pediatric perfusion in Japan: 2010 practice survey

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H Itoh[1], S Sano[1] and P Pouard[2]

Abstract

We report here Japan's first pediatric perfusion survey. It covers practices from January 2007 through December 2009. Of the 70 congenital heart centers contacted, 53 (76%) completed the survey. They reported performing 3,379 pediatric cardiopulmonary bypass (CPB) procedures in 2009, 3,408 in 2008, and 3,358 in 2007. Twenty-eight percent of all centers used CPB circuits with a priming volume between 151-200 ml. All centers used pre-bypass ultrafiltration and only 6% used retrograde autologous priming. A biomaterial-coated circuit was used by 78% of the centers, a roller pump as the arterial pump by 91%, vacuum-assisted venous drainage by 39%, dilutional ultrafiltration by 48%, and modified ultrafiltration at the end of the procedure by 30%. A regional oxygen saturation monitor was used by 69% of the centers and high flow (150-200 ml/kg/min) management with alpha-stat blood gas control was standard during moderate to normothermic CPBs. Crystalloid cardioplegia solution was used as myocardial protection by 56% of the centers, electronic recording of monitoring data by 51%. The centers performed 98 pediatric extracorporeal membrane oxygenation procedures in 2007, 109 in 2008, and 119 in 2009; 58% of the centers used a centrifugal pump. This survey provides a description of the current practice in Japan. Future surveys will identify trends and rate of change in practice.

Keywords

perfusion; cardiopulmonary bypass; survey; pediatric; congenital heart surgery

Introduction

The history of perfusion is marked by serious challenges and major accomplishments. John Gibbon's development of the cardiopulmonary bypass (CPB) machine in 1953 marked the beginning of cardiopulmonary support during cardiovascular surgery[1]. The technique of CPB was widely implanted by Kirklin, Lillehei, and others[2-4]. It has become an indispensable tool for cardiovascular surgery, whose progress has been astonishing. In congenital heart surgery, the improved results and lower mortality rate that have followed from evidence-based perfusion (EBP) practices are of special note.

In 2005, with the goal of providing an infrastructure for collaboration between healthcare professionals interested in the analysis of outcomes of treatments provided to patients with congenital cardiac disease, and the ultimate aim of improvement in the quality of care provided to these patients[5], the International Consortium for Evidence-Based Perfusion was established as a collaboration of perfusion societies, clinicians, and industry to improve the delivery of care and outcomes for patients worldwide[6]. It should lead to the highest quality of comprehensive care to all congenital heart disease patients[5].

An estimated 9,000 congenital heart surgery procedures are conducted annually in Japan[7]. To date, little is known about actual perfusion management and the organization framework for perfusion in Japan. A clinical database covering multiple congenital heart centers that collects data on perfusion performance would enable us to establish a database that would lead to improved EBP techniques. However, we have, as yet, no basis for a pediatric perfusion database in Japan. The aim of the survey

[1]Department of Cardiovascular Surgery, Okayama University Hospital, Okayama, Japan
[2]Department of Anesthesiology and Pediatric Cardiac Surgery, Hospital Necker-Enfants Malades, Paris, France

Corresponding author:
Hideshi Itoh, Department of Cardiovascular Surgery, Okayama University Hospital, 2-5-1, Shikata, Okayama, 700-8558 Japan
Email: grape@md.okayama-u.ac.jp

was to determine current practice across Japanese centers. The unit of analysis for this study was individual centers.

Materials and Methods

We sent a 45-question perfusion survey in June 2010 by government mail and electronic mail to chief perfusionists in 70 congenital heart centers in Japan. We asked the recipients to fill in blanks and check all applicable boxes based on the predominant practices in their center. We clarified inconsistencies in the survey results by contacting respondents by e-mail or by phone.

The survey, which enquired about perfusion practices from January 2007 through December 2009, covered pediatric caseloads, CPB circuits (priming volume, solution, coating), CPB components (arterial pump, oxygenator, heart-lung machine), CPB monitoring (regional oxygen saturation monitor, in-line monitor, electronic recording), CPB management (perfusion flow, temperature, filtration, vacuum-assisted venous drainage, blood transfusion), blood gas management, hypothermia technique, myocardial protection (cardioplegia solution, temperature), pediatric extracorporeal membrane oxygenation (ECMO) and employment of perfusionists.

Results

Of the 70 centers contacted, 53 (76%) completed the survey.

Program demographics

Procedures. The respondents reported 3,379 pediatric CPB procedures in 2009, 3,408 in 2008, and 3,358 in 2007. The median number of CPB procedures performed per center per year was 50 (range, 4-445) and the mean caseload was 0-50 for 72% of the perfusionists, 51-100 for 21%, and 101-150 for 5%.

CPB circuit

Priming volume. Table 1 shows hospital priming volume of the CPB circuit.

Table 1. Priming volume of CPB circuit used by hospitals during pediatirc cardiac surgery in Japan, 2007-2009.

Priming Volume (mL)	% Hospital share (no. of centers)
100-150	6 (3)
151-200	28 (15)
201-250	21 (11)
251-300	28 (15)
301<	17 (9)

Priming solution. The most frequently used crystalloid priming solutions were Ringer's lactate solution (39% of centers), Ringer's acetate solution (22%), bicarbonated Ringer's solution (18%), bicarbonate replacement fluid (11%), normal saline (4%) and others (6%). For standard colloid priming solutions, usage was 25% albumin (56% of centers), 20% albumin (9%), 5% albumin (18.5%), fresh frozen plasma (2%), low molecular weight dextran (3.7%) and no usage (10.8%). The drugs most frequently added to the priming solution were heparin, mannitol, sodium bicarbonate, antibiotics, and steroids. All centers employed pre-bypass ultrafiltration for blood priming-28% of the centers used 500 mL and 25% used 1000 mL. Only 6% of the centers employed retrograde autologous priming, and 55% used priming solutions at 36-37°C.

Coated circuit. A coated circuit was used by 78% of the centers-49% used poly-2-methoxyethylacrylate coating and 29% used a heparin coating.

CPB components

Arterial pump. A roller pump was used as the arterial pump by 91% of the centers, a centrifugal pump by 9%.

Oxygenator. Table 2 shows hospital usage of oxygenators. The data include plural responses.

Table 2. Oxygenators used by hospitals during pediatric cardiac surgery in Japan, 2007-2009.

	Oxygenator	% Hospital share (no. of centers)
SORIN	D100	2 (1)
	D901	15 (8)
	D902	38 (20)
	D905	8 (4)
TERUMO	RX05	62 (33)
	RX15	21 (11)
	RX25	4 (2)
	FX05	26 (14)
	FX15	13 (7)
	FX25	4 (2)
MAQUET	Quadrox	2 (1)
JMS	Oxia-IC	38 (20)
	Oxia-LP	2 (1)
MERA	Excelung-kids	8 (4)
	HPO-05 RHFC	2 (1)
	HPO-06	2 (1)
NIPRO	Biocube 2000	8 (4)
	Biocube 4000	2 (1)
MEDOS	Hilite 2800	9 (5)

Table 3. Heart-lung machine used by hospitals during pediatric cardiac surgery in Japan, 2007-2009.

	Heart-lung machine	% Hospital share (no. of centers)
SORIN	S3	28.3 (15)
	S5	9.4 (5)
TERUMO	APS-1	5.7 (3)
MAQUET	HL-30	7.5(4)
Technowood	Compo3	17.0 (9)
MERA	HAS	15.1(8)
	AS-R	5.7 (3)
	HAS-2	1.9 (1)
Others (unknown)		9.4 (5)

Heart-lung machine. Table 3 shows hospital usage of a heart-lung machine.

CPB monitoring

Regional oxygen saturation. Regional oxygen saturation monitors such as INVOS (Somanetics, Troy, MI, USA) were used by 69% of the centers; 60% were set in the frontal lobe, 14% in both the frontal lobe and posterior regions.

In-line monitor. Thirty-four percent of the centers used in-line, continuous, arterial blood gas monitoring, 28% used in-line continuous venous blood gas monitoring, 23% used intermittent arterial blood gas monitoring, and 12% used intermittent venous blood gas monitoring and others (no response: 3%).

Electronic recording. Electronic recording was used by 51% of the centers.

CPB management

CPB flow. For routine normothermic neonatal CPB flow rate, 10% of the centers used 200 ml/kg/min, 12% used 180-200 ml/kg/min, 20% used 180 ml/kg/min, 10% used 150-180 ml/kg/min, 8% used 150 ml/kg/min, 4% used 120ml/kg/min, 8% used 80-120 ml/kg/min, 4% used 3.0 L/min/m^2, 4% used 2.8-3.0 L/min/m^2, 7% used 2.6-2.8 L/min/m^2, 2% used 2.5 L/min/m^2 and others (no response: 11%).

Temperature. For intraoperative temperature monitoring, 39% of centers used the nasopharynx, 86% the rectum, 33% the esophagus, 37% the bladder, 33% the skin, 15% a palmoplantar site, 80% the arterial blood of the circuit, and 78% the venous blood of the circuit. (These data include plural responses).

Filtration. During CPB, 48% of the centers used dilutional ultrafiltration and, at the end of CPB, 30% used modified ultrafiltration.

VAVD. Vacuum-assisted venous drainage was used by 39% of the centers.

Blood transfusion. The minimum acceptable hematocrit level during moderate hypothermia (28-30°C) was reported as 23.5±4.5% (range, 16%-35%), and the minimum acceptable level during deep hypothermia (18-22°C) was reported as 21.9±4.4% (range, 15%-30%).

Blood gas managements

Normothermia to mild hypothermia (34-36°C). Alpha-stat control was used by 88% of the centers, pH-stat control by 12% of the centers.

Moderate hypothermia (28-30°C). Alpha-stat control was used by 81% of the centers, pH-stat control by 19% of the centers.

Deep hypothermia (18-22°C). Alpha-stat control was used by 64% of the centers, pH-stat control by 36% of the centers.

Hypothermia technique (brain protection)

Hypothermia with circulatory arrest was the preferred perfusion technique for complex procedures on neonates in 24% of centers, while 37% of the centers reported also using deep hypothermia with isolated cerebral perfusion. Only one center used mild hypothermia without circulatory arrest, using isolated cerebral and rim perfusion techniques.

Myocardial Protection

Cardioplegia solution. Fifty-eight percent of the centers used crystalloid cardioplegia solution, 32% used blood cardioplegia solution. Ten percent used both crystalloid and blood cardioplegia solution. No center used warm blood cardioplegia.

Temperature. The infusion temperature of the cardioplegia solution was 0-5°C at 46% of the centers, 5-10°C at 24%, 10-15°C at 13%, 15-20°C at 7%, 20-28°C at 3% and others (no response: 7%).

ECMO

Procedures. The number of ECMO procedures performed was 98 in 2007, 109 in 2008, and 119 in 2009.

Pump. The centrifugal pump was used for ECMO by 58% of the centers, the roller pump by 30%, 6% of centers did not use ECMO, and from 6% there was no response.

Oxygenator. For oxygenation, 49% of the centers used the Biocube 2000 (Nipro, Osaka, Japan), 13% the Biocube 4000 (Nipro), 3% the Biocube 6000 (Nipro), 13% the SX-10 (Terumo), 2% the RX-05 (Terumo), 2% the FX-05 (Terumo) 2%, the HSO-05 (Mera, Senko Medical Instrument Mfg., Tokyo, Japan), 2% the excelung-kids (Mera), 2% the 6505R1 (Medtronic, Tokyo, Japan), 6% of centers did not use ECMO, and 6% did not respond.

Staff (perfusionists)

There were 288 pediatric perfusionists — 2 in 10% of the centers, 3 in 15%, 4 in 26%, 5 in 8%, and 6 in 13%. There were 100 certified clinical perfusionists — 1 in 25% of the centers, 2 in 25% of the centers, 3 in 12% of the centers, and none in 22% of the centers. Among the pediatric perfusionists, 49% were 20-30 years old, 33% were 31-40 years old, and 16% were 41-50 years old. Annual income was $25,000-$37,500 for 6% of the perfusionists, $37,501-$62,500 for 49%, $62,501-$87,500 for 27%, and $87,501-$112,500 for 8%.

Discussion

The surgical outcomes for congenital heart disease are influenced by not only surgical managements, but also CPB practices[6,8,9]. Several perfusion surveys have been published on different aspects[8,14]. Groom et al. regularly report pediatric perfusion surveys in North America[10,12-15]. Multicenter organizations such as the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease and the International Consortium for Evidence-Based Perfusion can facilitate collaboration between healthcare providers interested in improving the quality of care delivered to congenital heart disease patients[5,6]. Although we are aware of the importance of evidenced-based "best practices" in perfusion and in initiating quality improvement in Japan[9], we have not yet established a formal community to manage a special database for pediatric perfusion. As an initial step to that end, we report here our first pediatric perfusion survey.

In over 70% of the centers, 2 perfusionists worked on each pediatric perfusion procedure, the number recommended for safety management and good clinical outcomes[16]. Moreover, more than 70% of the perfusionists were certified (20% were undergoing clinical training). The median number of CPB procedures performed per center per year in our study was 50, which is about 39% of the number performed in France (128 in 2005), and the mean number performed by each perfusionist in Japan (72% of perfusionists performed less than 50) was less than 1/3 the number performed in France (134 in 2005; range, 22-322)[17]. The difference may be due to Japan having many more congenital heart centers per population than France (1 per 200,000 vs. 1 per 400,000). Alternatively, the number of perfusionists per patient load may be greater in Japan. The low number of procedures performed by each perfusionist in Japan suggests that perfusionists may not gain enough practice to maintain their skills and that could engender a safety risk. For both patient safety and job security, it would be better to have a better balance of employment and caseload.

The use of oxygenators with an integrated arterial filter permits lower priming volumes, but only 1/4 of the Japanese centers used that setup (Table 2). We found that vacuum-assisted venous drainage was not a standard perfusion technique, probably because gaseous microemboli are associated with it and trouble-shooting is difficult[18]. Retrograde autologous priming was also not standard, probably because perfusionists want to avoid the complexity it involves at the start of the CPB. Since the Boston hematocrit trials suggested the potential advantage of a higher hematocrit level during hypothermic CPB[19-21], the trend in Japan has been to maintain hematocrit levels at over 25% during hypothermic CPB, especially during complex congenital heart surgery. Thus, most pediatric perfusionists avoid the non-transfusion CPB technique and vacuum-assisted venous drainage and retrograde autologous priming are not necessary for non-transfusion CPB techniques for young children. Hence, reducing the priming volume of the CPB circuit may not be important in the management of perfusion safety, especially in complex cases.

Concerning CPB components and circuits, the Terumo RX-05 oxygenator was popular because of its low priming volume, and the Sorin heart-lung machine was used predominantly. In General, products made in Japan were preferred, probably because of their easy maintenances and customizability.

We found that high flow management with alpha-stat blood gas control was standard during moderate to normothermic CPB. A North American survey taken in 2002, however, reported an increase in the use of pH-stat control[15], a technique that had become standard after 1993[16,22], but shifted to alpha-stat management to avoid deep hypothermic circulatory arrest in the presence of moderate to mild hypothermia. Related to that was the aggressive use of ultrafiltration methods such as prebypass, dilutional, and modified ultrafiltration, which may elevate the metabolic rate and increase collateral flow, to manage higher temperatures settings. Both high

flow management and ultrafiltration methods might help acid-base management.

Crystalloid cardioplegia was the predominant solution used for myocardial protection. In North America, 67% of centers used blood cardioplegia in 2002[15]. Future surveys will track how this changes.

In-line continuous blood gas monitoring, which is recommended by the Japanese Society of Extra-corporeal Technology, was used at over 50% of the centers and is increasing due to a keen awareness of perfusion safety management in Japan. In Australia and New Zealand, in contrast, only 5.2% of centers reported in-line blood gas monitoring routinely in 2006[9]. The technique is costly, so differences in usage may follow from differences in medical insurance systems (in-line monitoring is covered by medical insurance in Japan).

In conclusion, we have outlined the results of the first pediatric perfusion survey in Japan and compared some of the results with those of similar surveys conducted in other countries. Our survey lays the foundation for a Japanese pediatric perfusion database. Although we recognize the importance of "experience-based" practices to congenital heart surgery, we believe that data are also important and are necessary if we are to place perfusion on a sound scientific footing. We will update the survey at regular intervals so as to detail the progression of changes of pediatric perfusion practices in Japan.

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Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE
Hypertension and Circulatory Control

Medetomidine, an α2-Adrenergic Agonist, Activates Cardiac Vagal Nerve Through Modulation of Baroreflex Control

Shuji Shimizu, MD, PhD; Tsuyoshi Akiyama, MD, PhD; Toru Kawada, MD, PhD; Yusuke Sata, MD; Masaki Mizuno, PhD; Atsunori Kamiya, MD, PhD; Toshiaki Shishido, MD, PhD; Masashi Inagaki, MD; Mikiyasu Shirai, MD, PhD; Shunji Sano, MD, PhD; Masaru Sugimachi, MD, PhD

Background: Although α2-adrenergic agonists have been reported to induce a vagal-dominant condition through suppression of sympathetic nerve activity, there is little direct evidence that they directly increase cardiac vagal nerve activity. Using a cardiac microdialysis technique, we investigated the effects of medetomidine, an α2-adrenergic agonist, on norepinephrine (NE) and acetylcholine (ACh) release from cardiac nerve endings.

Methods and Results: A microdialysis probe was implanted into the right atrial wall near the sinoatrial node in anesthetized rabbits and perfused with Ringer's solution containing eserine. Dialysate NE and ACh concentrations were measured using high-performance liquid chromatography. Both 10 and 100 μg/kg of intravenous medetomidine significantly decreased mean blood pressure (BP) and the dialysate NE concentration, but only 100 μg/kg of medetomidine enhanced ACh release. Combined administration of medetomidine and phenylephrine maintained mean BP at baseline level, and augmented the medetomidine-induced ACh release. When we varied the mean BP using intravenous administration of phenylephrine, treatment with medetomidine significantly steepened the slope of the regression line between mean BP and log ACh concentration.

Conclusions: Medetomidine increased ACh release from cardiac vagal nerve endings and augmented baroreflex control of vagal nerve activity. (*Circ J* 2012; **76:** 152–159)

Key Words: Acetylcholine; Norepinephrine; Sinoatrial node; Sympathetic nervous system; Vagus nerve

The selective α2-adrenergic agonist, dexmedetomidine, is widely used for sedation in intensive care units because it has a less respiratory depressive effect.[1] In addition, several benefits of dexmedetomidine that favor its use in intensive care have been reported, such as reduced opioid dosage requirement. In animal studies, Hayashi et al reported that dexmedetomidine prevented epinephrine-induced arrhythmias in halothane-anesthetized dogs.[2] This antiarrhythmic effect of α2-adrenergic agonists may be partly ascribed to vagal activation.[3] It has already been reported that central sympathetic inhibition by an α2-adrenergic agonist, guanfacine, augmented the sleep-related ultradian rhythm of parasympathetic tone in patients with chronic heart failure.[4] Although α2-adrenergic agonists are widely recognized as inducing a vagal-dominant condition through the suppression of sympathetic nerve, there is little direct evidence that they directly increase cardiac vagal nerve activity, because such activity has been assessed only by indirect methods, such as heart rate variability, in most studies.[5]

Vanoli et al[6] reported that vagal stimulation after an acute ischemic episode effectively prevented ventricular fibrillation in dogs. Their group also indicated that the dogs that developed ventricular fibrillation during the acute ischemic episode had a significantly lower baroreflex-mediated heart rate response,[7] suggesting the importance of the baroreflex in controlling vagal function. If an α2-adrenergic agonist is able to activate the cardiac vagal nerve directly or via modulation of the baroreflex function, it will provide a new therapeutic option for life-threatening arrhythmias after myocardial ischemia.

Medetomidine is a racemic mixture of 2 stereoisomers, dexmedetomidine and levomedetomidine. However, because it has already been reported that levomedetomidine has no effect on cardiovascular parameters and causes no apparent sedation or analgesia,[8] the pharmacokinetics of dexmedetomidine and racemic medetomidine are almost similar. We hypothesized that medetomidine can activate the cardiac vagal nerve

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Department of Cardiovascular Dynamics (S. Shimizu, T.K., Y.S., M.M., A.K., T.S., M.I., M. Sugimachi), Department of Cardiac Physiology (T.A., M. Shirai), National Cerebral and Cardiovascular Center Research Institute, Suita; and Department of Cardiovascular Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama (S. Sano), Japan
Mailing address: Shuji Shimizu, MD, PhD, Department of Cardiovascular Dynamics, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: shujismz@ri.ncvc.go.jp

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through a central action and improve the baroreflex control of vagal nerve activity. We have established a cardiac microdialysis technique for separate monitoring of neuronal norepinephrine (NE) and acetylcholine (ACh) release to the rabbit sinoatrial (SA) node in vivo.[9–11] Using this microdialysis technique, we investigated the effects of medetomidine on cardiac autonomic nerve activities innervating the SA node.

Methods

Surgical Preparation

Animal care was provided in accordance with the "Guiding principles for the care and use of animals in the field of physiological sciences" published by the Physiological Society of Japan. All protocols were approved by the Animal Subject Committee of the National Cerebral and Cardiovascular Center.

In this study, 31 Japanese white rabbits weighing 2.3–3.0 kg were used. Anesthesia was initiated by an intravenous injection of pentobarbital sodium (50 mg/kg) via the marginal ear vein, and then maintained at an appropriate level by continuous intravenous infusion of α-chloralose and urethane (16 mg·kg^{-1}·h^{-1} and 100 mg·kg^{-1}·h^{-1}) through a catheter inserted into the femoral vein. The animals were intubated and ventilated mechanically with room air mixed with oxygen. Respiratory rate and tidal volume were set at 30 cycles/min and 15 ml/kg, respectively. Systemic arterial pressure was monitored by a catheter inserted into the femoral artery. Esophageal temperature, which was measured by a thermometer (CTM-303, Terumo, Japan), was maintained between 38°C and 39°C using a heating pad.

With the animal in lateral position, a right lateral thoracotomy was performed and the right 3rd to 5th ribs were partially resected to expose the heart. After incising the pericardium, a dialysis probe was implanted as described below. Three stainless steel electrodes were attached around the thoracotomy incision for recording body surface electrocardiogram (ECG). The heart rate was determined from the ECG using a cardiotachometer. Heparin sodium (100 IU/kg) was administered intravenously to prevent blood coagulation. At the end of the experiment, the animal was killed humanely by injecting an overdose of pentobarbital sodium. In the postmortem examination, the right atrial wall was resected en bloc with the dialysis probe. The inside of the atrial wall was observed macroscopically to confirm that the dialysis membrane was not exposed to the right atrial lumen.

Dialysis Technique

The materials and properties of the dialysis probe have been described previously.[9–12] A dialysis fiber of semipermeable membrane (length 4 mm, outer diameter 310 μm, inner diameter 200 μm, PAN-1200, molecular weight cutoff 50,000; Asahi Chemical, Tokyo, Japan) was attached at both ends to polyethylene tubes (length 25 cm, outer diameter 500 μm, inner diameter 200 μm). A fine guiding needle (length 30 mm, outer diameter 510 μm, inner diameter 250 μm) with a stainless steel rod (length 5 mm, outer diameter 250 μm) was used for the implantation of the dialysis probe. A dialysis probe was implanted into the right atrial myocardium near the junction of the superior vena cava and the right atrium. After implantation, the dialysis probe was perfused with Ringer's solution (in mmol/L: NaCl 147, KCl 4, $CaCl_2$ 3) containing a cholinesterase inhibitor eserine (100 μmol/L), at a speed of 2 μl/min using a microinjection pump (CMA/102, Carnegie Medicin, Sweden). Experimental protocols were started 120 min after implantation of the dialysis probe. The dead space between the dialysis membrane and the sample tube was taken into account at the beginning of each dialysate sampling. In protocols 1 and 2 as described below, 8 μl of phosphate buffer (pH 3.5) was added to each sample tube before dialysate sampling, and each dialysate sampling period was set at 20 min (1 sample volume=40 μl). Half of the dialysate sample was used for ACh and the other half for NE measurements. In protocol 3, 2 μl of phosphate buffer was added to each sample tube before dialysate sampling, and each dialysate sampling period was set at 5 min (1 sample volume=10 μl). In protocol 4, 4 μl of phosphate buffer was added to each sample tube before dialysate sampling, and each dialysate sampling period was set at 10 min (1 sample volume=20 μl). Dialysate NE and ACh concentrations were analyzed separately by high-performance liquid chromatography as described previously.[12,13]

Experimental Protocols

Protocol 1 (n=7) Baseline dialysate was sampled before the injection of medetomidine. Thereafter, a low dose (10 μg/kg) of medetomidine was injected intravenously via the femoral vein. After allowing 20 min for hemodynamic stabilization, dialysate was sampled for 20 min (40 μl). When the hemodynamics had recovered to the baseline level, a high dose (100 μg/kg) of medetomidine was injected intravenously and another 20-min dialysate sample was collected after hemodynamic stabilization. Finally, the vagal nerves were sectioned bilaterally at the neck and a dialysate sample was collected immediately after vagotomy. In 4 rabbits, an α_2-adrenergic antagonist, atipamezole (2.5 mg/kg), was intravenously administered before euthanasia and hemodynamic responses were recorded.

Protocol 2 (n=7) To prevent possible interference of medetomidine-induced hypotension with vagal nerve activity, intravenous infusion of an α_1-adrenergic agonist, phenylephrine, was started simultaneous to intravenous injection of medetomidine. Baseline dialysate sample was collected for 20 min before medetomidine injection. Simultaneous to intravenous injection of high-dose (100 μg/kg) medetomidine, intravenous infusion of phenylephrine was started (6.6±1.2 μg·kg^{-1}·min^{-1}) to maintain the mean blood pressure (BP) at baseline level. After hemodynamic stabilization, dialysate was sampled for 20 min. Finally, dialysate was again sampled immediately after bilateral cervical vagotomy.

Protocol 3 To investigate the effect of medetomidine on baroreflex-induced vagal ACh release, we varied the mean BP by changing the dose of intravenous phenylephrine in both the control (n=5) and medetomidine-treated (n=7) groups. In the control group, Ringer's solution was infused intravenously at 1.0 ml·kg^{-1}·h^{-1} throughout the experiment. In the medetomidine-treated group, medetomidine was initially injected intravenously at a dose of 60 μg/kg, and thereafter continuously infused at a dose of 60 μg·kg^{-1}·h^{-1} or a rate of 1.0 ml·kg^{-1}·h^{-1}. After baseline dialysate sampling, mean BP was increased in a stepwise manner by altering the dose of intravenous phenylephrine (maximal dose: 32.2±5.5 μg·kg^{-1}·min^{-1} in the control group and 18.6±2.1 μg·kg^{-1}·min^{-1} in the medetomidine-treated group). Dialysate samples were collected for 5 min at 4–7 different mean BP levels. Relations of log ACh concentrations vs. mean BP were plotted and regression lines for each animal were calculated.

Protocol 4 (n=5) We investigated the peripheral effects of medetomidine on heart rate and dialysate ACh concentration under electrical stimulation of the right cervical vagal nerve. Bilateral vagal nerves were exposed through a midline cervical incision and sectioned at the neck. A pair of bipolar stainless steel electrodes was attached to the efferent side of the

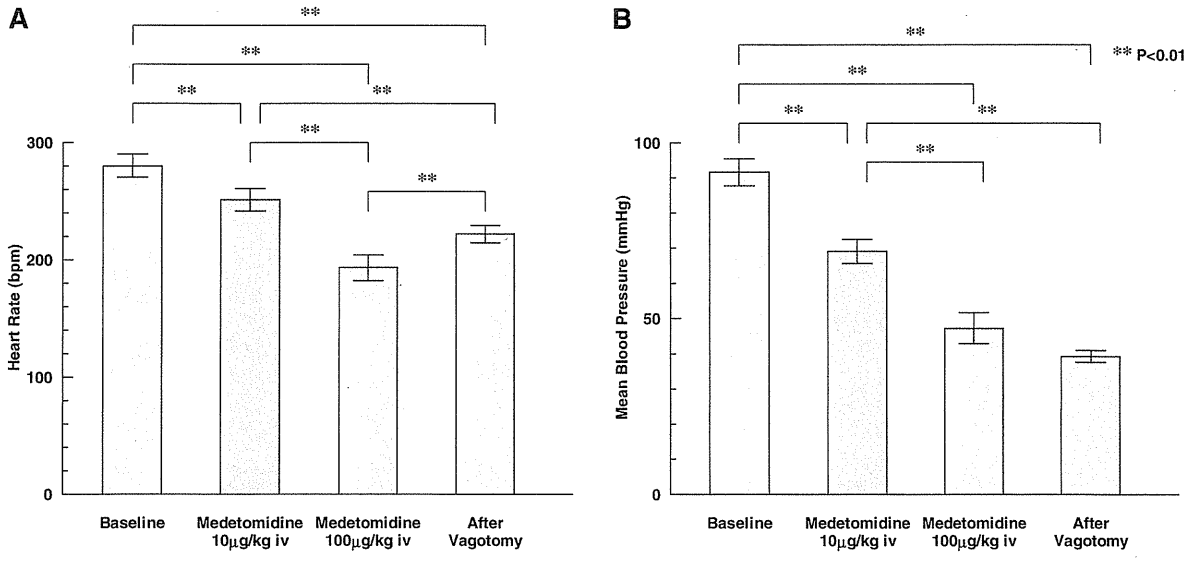

Figure 1. Intravenous administration of low and high doses of medetomidine decreased heart rate (A) and mean blood pressure (B). Medetomidine decreased heart rate in a dose-dependent manner. Vagotomy partially restored the decrease in heart rate but had no effect on mean blood pressure under administration of 100 μg/kg of medetomidine. **P<0.01.

right vagal nerve. The nerve and electrode were covered with warmed mineral oil for insulation. After the baseline dialysate sampling, the right efferent vagal nerve was stimulated at the frequency of 20 Hz by a digital stimulator (SEN-7203, Nihon Kohden, Japan). The pulse duration and amplitude of nerve stimulation were set at 1 ms and 10 V. Thereafter, a low dose (10 μg/kg) of medetomidine was injected intravenously via the femoral vein. After hemodynamic stabilization, dialysate was sampled for 10 min under the 20-Hz electrical stimulation of vagal nerve. Finally, a high dose (100 μg/kg) of medetomidine was injected intravenously and another 10-min dialysate sample was collected under the 20-Hz electrical stimulation.

Statistical Analysis

All data are presented as mean ± standard error. Heart rate and mean BP were compared by 1-way repeated measures analysis of variance (ANOVA) followed by a Tukey's test.[14] Dialysate NE and ACh concentrations were also compared by 1-way repeated measures ANOVA followed by a Tukey's test. Comparisons of data between protocols 1 and 2 were conducted using unpaired t-test (Student's or Welch's t-test). In protocol 3, the average slopes and intercepts of the regression lines were compared using unpaired t-test. Differences were considered significant at P<0.05.

Results

Protocol 1

Intravenous injection of medetomidine significantly decreased heart rate (Figure 1A) and mean BP (Figure 1B) in a dose-dependent manner (280±10 beats/min and 92±4 mmHg, respectively, at baseline; 251±10 beats/min and 69±3 mmHg at 10 μg/kg; and 193±11 beats/min and 47±4 mmHg at 100 μg/kg, P<0.01 for all comparisons). Vagotomy increased heart rate to 222±7 beats/min but did not affect mean BP (Figures 1A,B).

Low-dose medetomidine significantly decreased dialysate NE concentration (Figure 2A) from 0.72±0.06 to 0.59±0.04 nmol/L (P<0.01) but did not affect dialysate ACh concentration (Figure 2B) compared with baseline. High-dose medetomidine also decreased dialysate NE concentration (to 0.52±0.05 nmol/L) similar to low-dose medetomidine (Figure 2A) and significantly increased dialysate ACh concentration from 7.2±1.3 nmol/L at baseline to 12.1±1.6 nmol/L (P<0.01, Figure 2B). Dialysate NE concentration was not changed by vagotomy, whereas dialysate ACh concentration recovered to the baseline level immediately after vagotomy (Figures 2A,B).

In 4 rabbits treated with atipamezole, heart rate and mean BP recovered to the baseline levels immediately after the injection (276±18 beats/min and 88±6 mmHg, respectively, at baseline; and 280±11 beats/min and 83±6 mmHg after the injection).

Protocol 2

Intravenous injection of high-dose medetomidine combined with phenylephrine decreased heart rate (Figure 3A) and the decrease was significantly greater than that observed in protocol 1 (140±9 vs. 193±11 beats/min, P<0.01), while mean BP was maintained at the same level as baseline (Figure 3B). Medetomidine combined with phenylephrine decreased dialysate NE concentration from 0.85±0.09 at baseline to 0.68±0.10 nmol/L (Figure 4A), and the decrease was not significantly different from that of medetomidine alone (protocol 1). However, medetomidine combined with phenylephrine increased dialysate ACh concentration (Figure 4B) to a significantly and markedly higher level than that observed in protocol 1 (26.8±5.4 vs. 12.1±1.6 nmol/L, P<0.05). Dialysate ACh concentration recovered to the baseline level immediately after vagotomy.

Protocol 3

The change in mean BP by phenylephrine administration affected dialysate ACh concentration only slightly in the control group (Figure 5A), whereas the elevation of mean BP