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Effects of dexmedetomidine on cerebral circulation and systemic hemodynamics after cardiopulmonary resuscitation in dogs

Hiroki Iida[1], Mami Iida[2], Hiroto Ohata[1], Tomohiro Michino[1], and Shuji Dohi[1]

[1] Department of Anesthesiology and Pain Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan
[2] Second Department of Internal Medicine (Cardiology) and Anesthesiology, and Department of Health and Nutrition, Faculty of Home Economics, Gifu Women's University, Gifu, Japan

Abstract
Purpose. Our purpose was to examine the effect of dexmedetomidine, when used with phenylephrine during cardiopulmonary resuscitation (CPR), on the cerebral and systemic circulations.
Methods. In pentobarbital-anesthetized, mechanically ventilated dogs, we evaluated pial vessel diameters, cerebral oxygen extraction, and systemic hemodynamics before and after cardiac arrest (5 min) and resuscitation, in the presence or absence of dexmedetomidine ($n = 7$ each; dexmedetomidine or control group).
Results. In both groups: (a) pial arterioles were dilated at 5 and 15 min after CPR, and had returned to baseline diameters at 30 min; (b) sagittal sinus pressure was significantly raised at 5 and 15 min after CPR; and (c) cerebral oxygen extraction was decreased at 5, 15, and 30 min after CPR, and had returned to baseline level at 60 min after CPR. We could find no differences between the two groups in the cerebral circulation after CPR. However, the number of defibrillation electric shocks required to restore spontaneous circulation (5.5 vs 3.6; $P < 0.05$), the dose of phenylephrine used for CPR (1193 μg vs 409 μg; $P < 0.01$), and the number of postresuscitation ventricular ectopic beats observed during the first 120 min after successful resuscitation (1606 vs 348; $P < 0.05$) were all significantly lower in the dexmedetomidine group.
Conclusion. Although intravenous dexmedetomidine, as used for CPR, does not have a beneficial effect on either cerebral vessels or cerebral oxygen extraction, it may reduce the number of defibrillation shocks needed and the number of postresuscitation ventricular ectopic beats, and help to bring about stable systemic circulation after CPR.

Key words Dexmedetomidine · CPR · Cerebral circulation · Arrhythmia

Address correspondence to: H. Iida
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Introduction

The neurological outcome after cardiac arrest and resuscitation may be greatly affected by whether optimal cerebral perfusion pressure and cerebral blood flow (CBF) are maintained during and after cardiopulmonary resuscitation (CPR). With regard to the effect of dexmedetomidine on CBF, it has been observed to reduce CBF in animal experiments [1,2], and we reported previously that it induced constriction in cerebral vessels in a dog cranial window preparation [3–5].

On the other hand, previous studies have indicated that dexmedetomidine can prevent epinephrine-induced arrhythmias in dog experiments [6–8]. Stabilization of the systemic circulation after CPR (due to a reduction in postcountershock arrhythmias) may contribute to the maintenance of adequate cerebral perfusion pressure. We therefore evaluated the effects of dexmedetomidine, when used with phenylephrine during CPR, on the cerebral and systemic circulations, using a dog cranial window preparation, in in vivo experiments.

Materials and methods

The procedures used in the present study conformed with the Guideline Principles in the Care and Use of Animals as approved by the Council of the American Physiologic Society. The experimental protocols were approved by our Institutional Committee for Animal Care.

The experiments were performed using 14 anesthetized dogs weighing between 6 and 10 kg. Anesthesia was induced with pentobarbital sodium (20 $mg \cdot kg^{-1}$, intravenously) and maintained with a continuous infusion of the same agent (2 $mg \cdot kg^{-1} \cdot min^{-1}$). After tracheal intubation, each dog was mechanically ventilated with oxygen-enriched room air (fraction of inspired oxygen

$F_{I_{O_2}}$, 0.8–0.9). The tidal volume and respiratory rate were adjusted to maintain an end-tidal CO_2 of 35–40 mmHg. A polyvinyl chloride catheter was placed in a femoral vein for administration of drugs and fluids, and another such catheter was placed in a femoral artery for blood-pressure monitoring and blood sampling. In each animal, a left lateral thoracotomy was performed in the fifth intercostal space, and the pericardial sac was opened. To gain access to the superior sagittal sinus, a burr hole was drilled in the skull 1 cm anterior to lambda over the midline. The sagittal sinus was identified, and the overlying dura was punctured, using a 22-gauge needle. A catheter was introduced so that its tip was positioned anterior to the confluence of the sinuses, to minimize the possibility of contamination from extracerebral venous blood [9]. Rectal temperature was maintained between 36.5° and 37.5°C with the aid of a warming blanket. ECG was monitored via lead II.

A closed cranial window was used to observe the pial microcirculation. The animal was placed in the sphinx position with the head immobilized in a stereotactic frame. The scalp was retracted, the temporal muscle removed, and a hole 2 cm in diameter was made in the parietal bone. After the coagulation of dural vessels, done with the aid of a bipolar electrocoagulator, the dura and arachnoid membrane were cut and retracted over the bone. A ring fitted with a cover glass was placed over the hole and secured with dental acrylic. The ends of three polyvinyl chloride catheters were inserted through the ring. The space under the window was filled with artificial cerebrospinal fluid (aCSF) of the following composition: Na^+, 151 mEq·l^{-1}; K^+, 4 mEq·l^{-1}; Ca^{2+}, 3 mEq·l^{-1}; Mg^{2+}, 1.3 mEq·l^{-1}; Cl^-, 134 mEq·l^{-1}; HCO_3^-, 25 mEq·l^{-1}; urea, 40 mg·dl^{-1}; and glucose, 67 mg·dl^{-1}. The solution was freshly prepared each day and bubbled with 5% CO_2 in air at 37°C. The first catheter was attached to a reservoir bottle containing aCSF. The second catheter was used for the drainage of aCSF, and the final catheter was used for continuous monitoring of intrawindow pressure. The volume below the window was between 0.5 and 1 ml. The intrawindow temperature was monitored using a thermometer (model 6510; Mallinckrodt Medical, St. Louis, MO, USA) and was between 36.5°C and 37.5°C.

Experimental protocols

All in vivo experiments were carried out in the following manner. After instrumentation, dogs were randomly assigned to one of two groups: the control group (normal saline; $n = 7$) or the dexmedetomidine group ($n = 7$). The primary investigators who performed CPR were blinded to treatment group assignments. The animals were allowed to recover from the surgical procedures for at least 30 min. Ventricular fibrillation (VF) was initiated with a DC pulse to the right ventricle. Mechanical ventilation was discontinued after the onset of VF, and animals were left in cardiac arrest for 5 min without treatment. Normal saline (5 ml), in the control group, or dexmedetomidine (2.5 μg·kg^{-1} in 5 ml normal saline) was injected at the start of CPR (blinded to investigators). Coincident with the start of open-chest CPR, each animal was mechanically ventilated at an increased ventilation rate (1.5 times that used before CPR). Each animal was defibrillated by a 20-J DC countershock delivered directly to the heart after 1-min CPR. In both groups, intravenous phenylephrine was administered in 40-μg·kg^{-1} boluses until defibrillation was completed. Restoration of spontaneous circulation was defined as the return of a supraventricular rhythm with a mean arterial blood pressure (MAP) of 60 mmHg. After the recovery of spontaneous beating, sufficient phenylephrine was continuously infused (5–10 μg·kg^{-1}·min^{-1}) to maintain MAP at around the baseline level for the remainder of the experiment. Pial arteriolar diameters, MAP, heart rate (HR), arterial blood gas tensions, pH, blood sugar, and serum electrolytes were measured at the following time-points: just before the cardiac arrest (baseline), and at 5, 15, 30, 60, 90, and 120 min after CPR. Cerebral oxygen extraction was analyzed using the following formula: $[CaO_2 - CvO_2 \text{ (sagittal sinus)}]/CaO_2 = 1 - (CvO_2/CaO_2)$. We also counted the number of ventricular ectopic beats during the first 120 min after CPR (from the electrocardiogram).

In each dog, the diameters of four pial arterioles (two ≥100 μm and two <100 μm) were measured. The data from each view were stored on videotape for later playback and analysis, and diameter measurements were made using a videomicrometer (Olympus Flovel videomicrometer, model VM-20; Flovel, Tokyo, Japan) attached to a microscope (model SZH-10; Olympus, Tokyo, Japan).

Statistical analysis

Changes in all variables (time-dependent effects in the presence or absence of dexmedetomidine) were examined by one-way analysis of variance (ANOVA) for repeated measurements, a paired *t*-test with a Bonferroni correction being used for post-hoc comparisons. The changes in pial arteriolar diameter, cerebral oxygen extraction, and other variables (hemodynamic and physiologic) observed in the dexmedetomidine group were compared with those in the control group by means of two-way ANOVA. The Mann-Whitney U-test was used to examine differences between the two groups. Significance was set at $P < 0.05$. Values for all results are expressed as means ± SD.

Table 1. Comparison of hemodynamic variables between control and dexmedetomidine groups

	Baseline	5 Min	15 Min	30 Min	60 Min	90 Min	120 Min
MAP (mmHg)							
Control	124 ± 25	138 ± 37	134 ± 23	140 ± 18	140 ± 20	131 ± 20	124 ± 24
Dexmedetomidine	126 ± 13	123 ± 30	137 ± 27	148 ± 21	154 ± 20	146 ± 11	137 ± 7
HR (beats·min^{-1})							
Control	160 ± 29	145 ± 54	169 ± 30	169 ± 25	167 ± 26	152 ± 35	165 ± 27
Dexmedetomidine	165 ± 14	145 ± 14	155 ± 23	165 ± 31	176 ± 40	181 ± 35	176 ± 33
SSP (mmHg)							
Control	3.8 ± 1.9	14.8 ± 5.3*	10.5 ± 6.3*	6.0 ± 3.3	3.7 ± 1.4	3.2 ± 1.7	3.0 ± 2.0
Dexmedetomidine	4.4 ± 3.5	21.9 ± 7.4*	14.3 ± 5.2*	10.6 ± 4.5	7.9 ± 2.8	7.4 ± 2.3	7.0 ± 2.4

* $P < 0.05$ versus baseline value
Values are means ± SD
MAP, mean arterial blood pressure (mmHg); HR, heart rate (beats·min^{-1}); SSP, sagittal sinus pressure

Table 2. Comparison of physiologic variables between control and dexmedetomidine groups

	Baseline	5 Min	15 Min	30 Min	60 Min	90 Min	120 Min
pHa							
Control	7.39 ± 0.03	7.24 ± 0.09**	7.30 ± 0.04	7.31 ± 0.02	7.33 ± 0.02	7.35 ± 0.07	7.33 ± 0.05
Dexmedetomidine	7.37 ± 0.02	7.24 ± 0.07**	7.30 ± 0.04**	7.32 ± 0.03	7.33 ± 0.01	7.33 ± 0.03	7.34 ± 0.05
Pa_{CO_2} (mmHg)							
Control	41 ± 4	39 ± 12	32 ± 4	31 ± 3	30 ± 5	30 ± 4	31 ± 4
Dexmedetomidine	41 ± 4	40 ± 9	31 ± 4**	30 ± 4**	31 ± 6**	32 ± 5	32 ± 5
Pa_{O_2} (mmHg)							
Control	326 ± 67	285 ± 136	307 ± 109	302 ± 99	335 ± 131	364 ± 138	351 ± 136
Dexmedetomidine	338 ± 48	161 ± 58*;**	266 ± 83	309 ± 122	289 ± 157	238 ± 127*	224 ± 103*
Na (mEq·l^{-1})							
Control	145 ± 6	143 ± 5	141 ± 5	142 ± 5	142 ± 5	143 ± 7	145 ± 6
Dexmedetomidine	145 ± 2	144 ± 2	144 ± 2	145 ± 4	145 ± 4	144 ± 1	145 ± 2
K (mEq·l^{-1})							
Control	4.2 ± 0.5	6.2 ± 1.6	5.5 ± 1.2	4.8 ± 0.8	4.8 ± 1.2	4.5 ± 1.3	4.5 ± 1.1
Dexmedetomidine	3.7 ± 0.2	4.5 ± 0.7	4.3 ± 0.4	4.4 ± 0.3	4.4 ± 0.4	4.1 ± 0.6	3.9 ± 0.5
BS (mg·dl^{-1})							
Control	143 ± 28	327 ± 80**	375 ± 67**	374 ± 73**	329 ± 72**	261 ± 106	276 ± 91
Dexmedetomidine	131 ± 36	288 ± 81**	286 ± 89*;**	278 ± 65*;**	244 ± 63*;**	214 ± 71	186 ± 68*
BT (°C)							
Control	36.3 ± 1.5	36.1 ± 1.4	35.9 ± 1.4	35.9 ± 1.4	36.0 ± 1.4	35.7 ± 1.3	36.0 ± 1.4
Dexmedetomidine	36.9 ± 0.7	36.8 ± 0.6	36.8 ± 0.6	36.8 ± 0.7	36.8 ± 0.8	36.7 ± 0.7	36.6 ± 0.7

* $P < 0.05$ versus control group; ** $P < 0.05$ versus baseline value
Values are means ± SD
Pa_{CO_2}, arterial blood carbon dioxide tension; Pa_{O_2}, arterial blood oxygen tension; Na, plasma sodium concentration; K, plasma potassium concentration; BS, blood sugar; BT, body temperature

Results

Hemodynamic and physiologic data

All animals were successfully resuscitated after electrical defibrillation. Neither MAP nor HR changed significantly throughout the experiments in either group. Sagittal sinus pressure was significantly raised at 5 and 15 min after CPR in both groups (Table 1). There were no significant differences between the two groups in either arterial pH or Pa_{CO_2}, although arterial PH decreased at an early stage after CPR. Pa_{O_2} was decreased significantly at 5 min after CPR in the dexmedetomidine group. Serum electrolytes showed alterations during the experiments in both groups. The blood sugar concentration was increased after CPR in both groups, but the values were lower in the dexmedetomidine group than in the control group from 15 min after CPR. Body temperature was unchanged throughout the experiment in both groups (Table 2).

Cerebral circulation

There were no significant differences between the groups in the baseline diameters of the large or small

arterioles. In both groups, large and small arterioles were dilated at both 5 and 15 min after CPR, and had returned to baseline diameters at 30 min. However, there was a tendency (nonsignificant) for a smaller vasodilation at 5 and 15 min in the dexmedetomidine group (Fig. 1). In both groups, cerebral oxygen extraction was decreased at 5, 15, and 30 min after CPR, and had returned to the baseline level at 60 min after CPR (Fig. 2).

Other parameters

The number of electric shocks required for the restoration of spontaneous circulation was significantly greater in the control group. Both the dose of phenylephrine used for CPR and the number of postresuscitation ventricular ectopic beats observed in the first 120 min after successful resuscitation were significantly lower in the dexmedetomidine group (Table 3).

Discussion

The major finding made in the present study was that the use of intravenous dexmedetomidine during CPR did not alter the changes in cerebral arteriolar diameters and cerebral oxygen extraction that occurred after cardiac arrest and resuscitation. However, dexmedetomidine did reduce the dose of phenylephrine used to complete CPR, and it also reduced the number of ventricular ectopic beats observed after CPR. Thus, it is possible that dexmedetomidine-induced stabilization of the systemic circulation and maintenance of optimal cerebral perfusion pressure after CPR may lead to a good outcome after CPR.

Although previous reports have demonstrated that alpha-2 agonists may improve the neurologic outcome after several types of cerebral ischemia [10–14], including the transient global type, the mechanism underlying this neuroprotective action is not fully understood. However, it has been suggested that a blockade of sympathetic activity (decrease in the release and turnover of

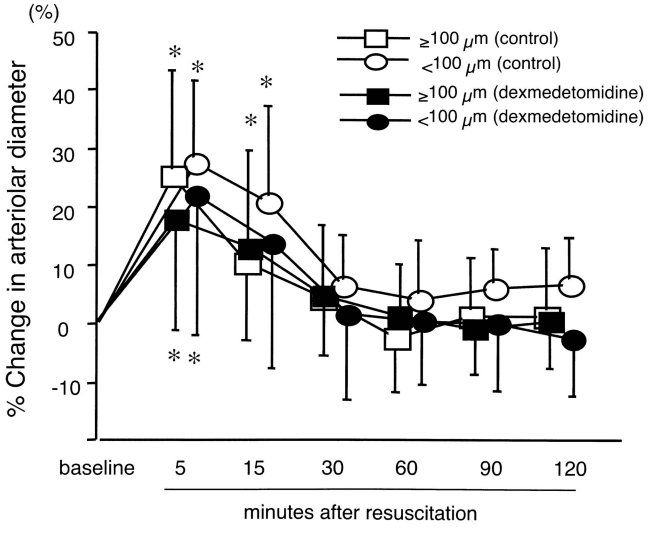

Fig. 1. Time-course data of changes in arteriolar diameter after cardiopulmonary resuscitation in dogs. Each *data point* indicates percentage change in diameter (mean ± SD) from the baseline value. *Open squares* (arterioles ≥100 μm in diameter) and *open circles* (<100 μm in diameter) represent the control group. *Closed squares* (≥100 μm) and *closed circles* (<100 μm) represent the dexmedetomidine group. *: $P < 0.05$ versus baseline

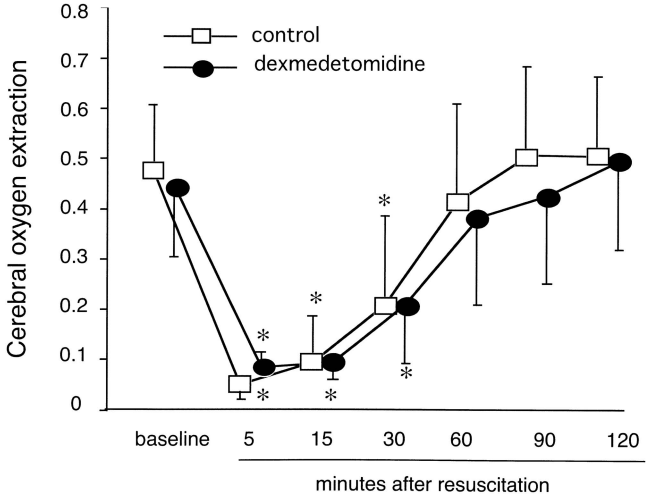

Fig. 2. Time-course data of changes in cerebral oxygen extraction after cardiopulmonary resuscitation in dogs. *Open squares* represent the control group, *closed circles* the dexmedetomidine group. Each *data point* and *bar* show mean ± SD. *: $P < 0.05$ versus baseline

Table 3. Comparison of other parameters between control and dexmedetomidine groups

	Control	Dexmedetomidine	*P* value
Dose of phenylephrine used during CPR (μg)	1193 ± 640	409 ± 308	<0.01
Number of defibrillations (electric shocks)	5.5 ± 1.9	3.6 ± 1.3	<0.05
Number of ventricular ectopic beats during 120 min after successful CPR	1606 ± 281	348 ± 193	<0.05

Values are means ± SD
CPR, cardiopulmonary resuscitation

norepinephrine in the brain), and/or a decrease in the release of excitatory neurotransmitters (such as glutamate) may account for the neuroprotective effects of these agonists during and after ischemic insults [10–14]. In addition, it has been suggested that the cerebrovascular or cerebral metabolic effect of dexmedetomidine may contribute, in part, to its neuroprotective action [10–14]. Therefore, we initially speculated that cerebrovascular alterations induced by dexmedetomidine might account for the decreased neurologic injury observed after cerebral ischemia when this drug was used, because its vasoconstrictor property might bring about a favorable effect on cerebral circulation in the reperfusion period after cardiac arrest and resuscitation. However, we could find no evidence of a significant effect of dexmedetomidine on cerebrovascular reactivity after CPR in the present study.

Recent experimental studies have provided evidence favoring the use of alpha-2 agonists during CPR [15–17]. In an experimental animal model, it has been reported that the use of epinephrine during CPR may increase the severity of postresuscitation myocardial dysfunction [18], and this undesirable effect seems to be associated with its beta-adrenergic actions, which provoke disproportionate increases in myocardial oxygen consumption. For this reason, the use of an alpha-2 adrenergic agonist such as dexmedetomidine as a primary or additive drug for CPR may provide unique advantages over epinephrine. In the present study, electrical defibrillation was achieved with greater ease and with apparently less application of total electrical energy in the dexmedetomidine group. These beneficial effects are consistent with the results of an earlier experimental study in rats [15]. Moreover, massive endogeneous catecholamine release after CPR and administration of catecholamines for CPR could induce dysrhythmias and an unstable systemic circulation, leading to unstable cerebral perfusion pressure. A number of previous reports have demonstrated the antiarrhythmic effects of dexmedetomidine in experimental studies on dogs [11–13]. In the present study, after successful resuscitation the incidence of postresuscitation ventricular ectopic beats was significantly reduced in the dexmedetomidine group. Interestingly, Tang et al. [19] indicated that ATP-sensitive K^+-channel activation decreased the number of postresuscitation ventricular ectopic beats in rats. We previously demonstrated that dexmedetomidine activated ATP-sensitive K^+-channels in cerebral vessels in dogs [3]. Such an action of dexmedetomidine may support the notion of favorable effects following its use in CPR, and thus, the possibility of an improved outcome of CPR.

A number of previous studies have demonstrated interactions between alpha-2 agonists and other adrenergic agonists, such as phenylephrine and epinephrine [20–22]. The main mechanism underlying a potentiation of the effects of adrenergic agonists during alpha-2 agonist administration is thought to be an immediate upregulatory effect through a reduction in central sympathetic outflow by the alpha-2 agonist. In the present study, the dose of phenylephrine used for successful CPR was much lower in the dexmedetomidine group. Although it is well known that oral premedication with clonidine can enhance the response to adrenergic agonists [20–22], it is unclear whether or not concomitantly administered dexmedetomidine might have a similar effect. However, from the present results, it seems that simultaneously administered dexmedetomidine may potentiate the effect of phenylephrine during CPR, and we think that such an interaction could be advantageous if these drugs are used during CPR.

In general, an increased blood sugar concentration before and during ischemia worsens the neurologic outcome [23]. It has been reported that dexmedetomidine can induce hyperglycemia [24,25]. If that were so, dexmedetomidine would be an unsuitable agent for CPR. However, in the present study, the blood sugar concentration was lower in the dexmedetomidine group than in the control group, and this was, perhaps, a reflection of a dexmedetomidine-induced reduction in the release of endogeneous catecholamines. Such an effect of dexmedetomidine might be favorable for its use during CPR. An apparent disadvantage observed in the present study was that Pa_{O_2} after CPR was lower in the dexmedetomidine group, although the level was not so low as to constitute a clear risk. However, as the reason for this finding remains unclear, further study is needed.

A limitation of our study is that we tested only a single dose of dexmedetomidine. Therefore, we cannot exclude the possibility that a higher dose of dexmedetomidine could induce changes in cerebral circulation and metabolism in this model. However, the dose we used ($2.5\,\mu g^{-1}\,kg^{-1}$) is relatively high, but within the clinical range as a one-shot dose [26]. In addition, because we did not perform histological evaluation in the present study, we cannot comment on the neuroprotective effect of dexmedetomidine.

In conclusion, although the use of intravenous dexmedetomidine for CPR in our dogs did not have a beneficial effect on either cerebral vessels or oxygen extraction, it reduced the number of defibrillation shocks required and the number of postcountershock ventricular ectopic beats. The improved stability of the systemic circulation induced by dexmedetomidine may contribute to the maintenance of optimal cerebral perfusion pressure.

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