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Dexmedetomidine in Cardiac Surgery Patients Who Fail Extubation and Present with a Delirium State

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ABSTRACT

Background: We evaluated the use of dexmedetomidine to facilitate the weaning of delirious postoperative patients from mechanical ventilation.

Methods: We included 72 consecutive patients who underwent elective cardiac surgery in this prospective observational study. Each patient had failed at least 1 trial of continuous positive airway pressure (CPAP) and had agitation. Patients were assessed with the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) 12 to 18 hours after their admission to the ICU. Midazolam and fentanyl were then given to all patients according to the sedation protocol. At 36 hours in the ICU, patients who had agitation and an inability to wean were randomly divided into 2 groups: group M, 34 patients who continued to follow the routine sedative protocol; and group D, 38 patients who were given dexmedetomidine. Arterial blood gas measurements, hemodynamic parameters, and time to extubation were recorded. Statistical analysis was performed with GraphPad InStat (version 2.02 for DOS).

Results: All patients tested positive in the CAM-ICU assessment, and all had a delirium diagnosis. The 38 patients in group D tolerated a spontaneous breathing trial with CPAP and were extubated after a mean (±SD) of 49.619 ± 6.96 hours. The 2 groups had significantly different extubation times (58.389 ± 3.958 hours versus 49.619 ± 6.96 hours). The 2 groups had significantly different RASS scores at 48 and 60 hours and significantly different heart rates and PO_2 values at 12 and 24 hours. The 2 groups showed no significant differences with regard to hemodynamic parameters.

Conclusions: Dexmedetomidine may help to eliminate the emergence of agitation and can be a good treatment choice for the delirium state after cardiac surgery.

INTRODUCTION

Mechanical ventilation is often associated with patient agitation that requires sedation to alleviate discomfort, prevent self-destructive behavior, decrease excessive central respiratory drive, and improve patient-ventilator synchrony. Agitation is a common management problem in the intensive care unit (ICU) and is often caused by delirium [Siobal 2006]. Approximately 20% of patients undergoing cardiac surgery are affected by postoperative delirium, with frequencies between 3% and 47% having been reported [van der Mast 2000; Siobal 2006]. This condition has been associated with several perioperative risk factors, although a consistent causal relationship with a single factor has not been demonstrated [van der Mast 2000].

The ideal sedative for use after cardiac surgery would have an immediate onset of action, provide immediate resolution of the anxiety and agitation with a rapid recovery of mental capacity, have minimal adverse effects, and be cost-effective. A number of agents are used for sedation and analgesia; however, none has been proved superior to others with regard to all of the above-mentioned parameters. Midazolam, a benzodiazepine, is an agent commonly used for sedation, often with an opioid analgesic such as fentanyl [Dasta 2006]. α_2-Adrenoreceptor agonists have been used for more than 40 years for anesthesia induction and sedation. Recently, dexmedetomidine, a very selective 2-adrenoreceptor agonist, has received considerable attention in anesthesia practice because of its sedative, hypnotic, anxiolytic, and analgesic effects [Mattila 1991]. The beneficial effects of dexmedetomidine, such as the attenuation of hemodynamic stress secondary to hyperadrenergic overreactivity and delirium-associated agitation, have been reported [Siobal 2006]. This agent has also been used as an adjuvant therapy in complicated delirium states associated with alcohol withdrawal [Rovasalo 2006].

This study evaluated the use of dexmedetomidine to facilitate extubation and weaning from mechanical ventilation of postoperative cardiac surgery patients who have failed prior weaning attempts and are in a delirium state.

MATERIALS AND METHODS

Patients

The study protocol was approved by the institutional review board, and informed consent was obtained from the relatives or legal representatives of all patients. Patients who underwent elective coronary artery bypass grafting, valve

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Table 1. Patient Characteristics*

	Midazolam Group (n = 34)	Dexmedetomidine Group (n = 38)	*P*
Age, y	61.167 ± 9.154	58.905 ± 10.492	.063
Female/male sex, n	20/14	25/13	
Aortic cross-clamping time, min	50.778 ± 9.540	53.714 ± 10.584	.078
CPB time, min	90.722 ± 13.350	88.048 ± 13.385	.082
Time from ICU admission to start of study drug infusion, h	39.833 ± 5.833	37.095 ± 6.745	.091
Time to extubation, h	58.389 ± 3.958	46.619 ± 6.960	<.0001
Postoperative low cardiac output/inotrope use, n	7	8	.093
History of nicotine use, n†	20/30	28/36	.689

*Data are presented as the mean ± SD where indicated. A *P* value <.05 indicates statistical significance. CPB indicates cardiopulmonary bypass; ICU, intensive care unit.

†Number of patients per number of evaluable patients.

replacement, or both between February 2005 and August 2007 were enrolled. We excluded patients according to the following criteria: unstable or uncontrolled diabetes; extreme obesity; an ejection fraction <30% and hemodynamic instability (eg, requirement for dobutamine or dopamine at >10 µg/kg per min, requirement for epinephrine at >0.1 µg/kg per min, or a cardiac index of <2.0 L/min per m^2); prolonged duration of operation (>6 hours), cardiopulmonary bypass (>3 hours), or aortic cross-clamping (>150 minutes); a preoperative history of neurologic events or a psychiatric disorder, as evidenced by preoperative medical records; intraoperative episodes of hypotension, as indicated in the anesthesia chart; postoperative coma; or death. The final 72 patients in the study population were randomly allocated into the study group (group D, n = 38) or the control group (group M, n = 34). The mean (±SD) age of the participants was 60.0 ± 9.80 years. Forty-five of the patients were female, and 27 were male. Age, sex, and history of nicotine and alcohol use were recorded (Table 1).

Definitions and Patient Assessments

All patients underwent elective surgery, and the same anesthesia regimen was used in all patients. Fentanyl (20-50 µg/kg) and midazolam (0.05-0.1 mg/kg) were used for induction, and fentanyl (20-50 µg/kg per hour) and propofol (4-8 mg/kg per hour) were infused for maintenance. None of the patients received any sedative agent after admission to the ICU, and for purposes of analgesia, only opioids (fentanyl, 0.7-10 µg/kg per hour) were administered during the first 8 hours in the ICU. Patients who met the following criteria were extubated and switched to continuous positive airway pressure (CPAP): no evidence of bleeding, patient alertness, stable cardiovascular condition, normal body temperature, an arterial oxygen tension ≥10 kPa with an inspired oxygen concentration ≤35%, a positive end-expiratory pressure <5 cm H_2O, spontaneous respiration with <15 cm H_2O pressure support, a tidal volume >6 mL/kg, and a respiratory rate ≥10 breaths/min but <20 breaths/min. On the basis of these criteria, 903 patients could be extubated. An additional 25 patients were not included because they met the exclusion criteria. Thus, 72 patients (7.2%) remained for inclusion in the study.

After the first 12 to 18 hours in the ICU and after the patient had undergone the Richmond Agitation-Sedation Scale (RASS) and Confusion Assessment Method for the ICU (CAM-ICU) assessments, midazolam (0.05-0.2 mg/kg per hour) and fentanyl (0.7-10 µg/kg per hour) were given to agitated patients who could not be switched to CPAP and thus had failed the first attempt at weaning. At approximately hour 36 in the ICU, patients who still presented with the same condition were randomly divided into 2 groups: 34 patients who continued to receive midazolam (0.05-0.2 mg/kg per hour) (group M) and 38 patients who began an infusion of dexmedetomidine hydrochloride (Precedex; Hospira, Rocky Mount, NC, USA) at a dosage of 0.3-0.7 µg/kg per hour (group D). After the initiation of dexmedetomidine treatment, the background sedation (midazolam) and analgesia (fentanyl) infusions were down-titrated and discontinued. Both groups of patients received nonsteroidal anti-inflammatory drugs or paracetamol infusion for analgesia. The dexmedetomidine dose was titrated on the basis of the patient's blood pressure and heart rate response. Before initiating the infusion, study investigators assessed the neurologic status of the patients by means of a neurologic assessment tool (1-2 minutes in length) that objectively measures arousal and delirium status. The tool classified patients as normal, delirious, or comatose. Arousal was measured with the RASS scale [Ely 2003, 2004], which is a well-validated and highly reliable 10-point scale. Scores from +1 to +4 are assigned to levels of agitation through combativeness, 0 is assigned to an alert and calm state, and –1 to –5 are assigned to successive levels of depressed arousal or coma (see Figure 1 for the RASS scale). RASS assessments were carried out at 12, 24, 36, 48, and 60 hours after the operation.

Delirium, the independent variable, was measured with a well-validated and highly reliable instrument, the CAM-ICU [Truman 2003; Ely 2004]. CAM-ICU was developed as a tool for use by nonpsychiatrists, such as ICU nurses or intensivists, to diagnose delirium. Three different persons (1 nurse and 2 intensivists) independently translated the tool into the Turkish language. The 3 translations were

Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressively vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert but has sustained awakening (eye opening/eye contact) to *voice* (≥10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens to *voice* with eye contact (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)	
-4	Deep sedation	No response to voice but movement or eye opening to *physical* stimulation	Physical Stimulation
-5	Unarousable	No response to *voice* or *physical* stimulation	

Figure 1. Richmond Agitation-Sedation Scale (RASS).

compared and the differences resolved before the test was performed. An intensivist performed the test daily; a psychiatrist then evaluated the patients. The CAM-ICU assessment was positive if the patient demonstrated an acute change or fluctuation in mental status (as determined by abnormalities or fluctuations in the RASS scores) plus inattention and either disorganized thinking or an altered level of consciousness. Delirium was diagnosed only if symptoms had been present for at least 24 hours. The first postoperative day was excluded because true delirium and possible residual anesthesia effects may not be differentiated early after an operation.

Each study patient failed at least 1 CPAP trial over several days because of respiratory and/or hemodynamic changes associated with agitation. The study patients received respiratory therapy, such as ipratropium, salbutamol, and N-acetylcysteine, before and after weaning. Some patients in group M received 5 mg haloperidol intramuscularly 4 times a day for the treatment of excessive agitation. Soon after the dexmedetomidine infusion was started, pressure support was commenced at 15 cm H_2O greater than a positive end-expiratory pressure of 5 cm H_2O. Patients were weaned to CPAP and evaluated for extubation by calculating the rapid shallow breathing index. During preparation for extubation, sedative infusion was discontinued in group M and down-titrated in group D. Patients were extubated after successfully switching to CPAP, which was confirmed by arterial blood gas analysis. Samples for arterial blood gas analyses were obtained at 4 times: just before and 6, 12, and 24 hours after the initiation of dexmedetomidine infusion. Heart rate, mean arterial blood pressure, central venous pressure, respiratory rate, and lactate measurements were made at the same time intervals. Operation and cardiopulmonary bypass durations, times to extubation, and medications administered during anesthesia were recorded.

Statistics

All statistical analyses were performed with GraphPad InStat software (version 2.02 for DOS; GraphPad Software, La Jolla, CA, USA). All values are expressed as the mean ± SD. For comparisons of groups involving repeated measurements, we used the Friedman test with the Dunn multiple comparisons test. The Mann-Whitney *U* test was used for intergroup comparisons of continuous variables. A P value <.05 was considered statistically significant.

RESULTS

All of the study patients had failed weaning trials prior to inclusion (group M, 42.83 ± 5.833 hours; group D, 40.68 ± 4.98 hours). Weaning failures on low levels of pressure support after the reduction of sedation were associated with agitation, hypertension, and varying degrees of tachycardia and tachypnea.

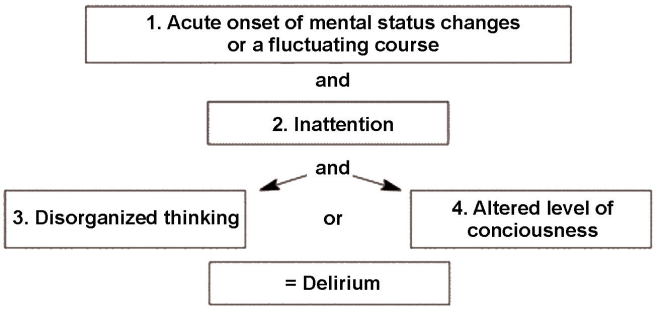

Figure 2. The Confusion Assessment Method for the Intensive Care Unit. The diagnosis of delirium requires the presence of both an acute onset of changes or fluctuations in the course of mental status (feature 1) and inattention (feature 2), and either disorganized thinking (feature 3) or an altered level of consciousness (feature 4). Figure adapted from Ely et al [2001].

Table 2. Results of Confusion Assessment Method for Intensive Care Unit (CAM-ICU) Evaluations*

	Positive CAM-ICU Result (Features 1 and 2 plus Feature 3 or 4)		
	All Patients (n = 72)	Group D (n = 37)	Group M (n = 34)
Postoperative hour 36, n	72 (7.2%)	—	—
Postoperative hour 60, n	8 (11.1%)	1 (2.7%)	7 (21%)*

*P < .05.

All patients had positive results in CAM-ICU assessments (Figure 2: features 1 and 2 plus feature 3 or 4) and received a delirium diagnosis in the first 36 hours of the ICU stay (P > .05) (Table 2).

Of the 38 patients in group D, 34 (94%) tolerated a spontaneous breathing trial with CPAP and could be extubated after a mean duration of 49.619 ± 6.96 hours. Two patients in group D and 7 patients in group M failed 4 or more CPAP trials and were assessed as delirious.

The mean maintenance dosages of dexmedetomidine and midazolam were 0.36 ± 0.09 µg/kg per hour and 0.03 mg/kg per hour, respectively. The dosages of both drugs were titrated to maintain the level of sedation within a predefined range of 10% increases or decreases in infusion rate. The mean total fentanyl dose was 75 ± 15 µg in the M group and 15 ± 10.5 µg in the D group. Patients were extubated at a mean dexmedetomidine dosage of 0.20 ± 0.01 µg/kg per hour and continued to receive dexmedetomidine infusion for a mean of 75 ± 38 minutes after extubation. Nine patients in group M failed extubation and required tracheostomy. The 2 groups had significantly different mean times to extubation (M group, 58.389 ± 3.958 hours; D group, 49.619 ± 6.96 hours). RASS scores at 48 and 60 hours were significantly different (P = .0003, and P < .0001, respectively; Table 3). The 2 groups had significantly different heart rates and PO_2 values at 12 and 24 hours (Table 4). The 2 groups did not differ with regard to other hemodynamic parameters or arterial blood gas measurements.

Table 3. Richmond Agitation-Sedation Scale (RASS) Scores*

A. RASS Scores for all 72 Patients in the ICU (at 12, 24, and 36 h)

	RASS Score	P
Time of RASS assessment		
12 h	2.11 ± 0.81	
24 h	1.43 ± 0.62	
36 h	0.46 ± 0.67	<.0001
RASS comparisons		
12 h versus 24 h		<.001
12 h versus 36 h		<.001
24 h versus 36 h		<.001

B. RASS Scores for Patients in Group D and Group M (at 48 and 60 h)

	RASS Score	P
Time of RASS assessment/group		
48 h/D	−1.66 ± 0.58	
60 h/D	−0.53 ± 0.51	
48 h/M	−1.03 ± 0.58	
60 h/M	−1.29 ± 0.63	
RASS comparisons		
48 h/D versus 60 h/D		<.0001
48 h/M versus 60 h/M		.0039
48 h/D versus 48 h/M		.0003
60 h/D versus 60 h/M		<.0001

*RASS data are presented as the mean ± SD. P values <.05 are statistically significant. ICU indicates intensive care unit; group D, dexmedetomidine group; group M, midazolam (control) group.

DISCUSSION

Sedatives are used during the postoperative period in most patients undergoing cardiac surgery to reduce anxiety during weaning and to avoid cardiovascular instability. Although recent articles have demonstrated that reductions in both mechanical ventilation times and ICU stays are associated with the use of protocols guiding sedation in various groups of critically ill patients, limited specific information is currently available for patients undergoing cardiac surgery [Dasta 2006].

Dexmedetomidine is used clinically to induce sedation in ICU patients, particularly during the early postoperative period [Venn 2002]. Unlike other anesthetics, dexmedetomidine induces a sedative response that has properties similar to those of natural sleep. Patients receiving dexmedetomidine experience a clinically effective sedation, yet are easily stilled and uniquely arousable, an effect not observed with any other clinically available sedative. Very little is known about the effects of α_2-adrenoreceptor agonists and antagonists, particularly dexmedetomidine, on aggression and anxiety [Mattila 1991].

Table 4. Hemodynamic Parameters and Blood Gases*

	Midazolam Group	Dexmedetomidine Group	*P*
PO_2, mm Hg			
0 h	67.49 ± 4.93	68.19 ± 5.03	.7996
6 h	76.06 ± 7.46	82.71 ± 9.33	.0311
12 h	75.75 ± 8.29	88.12 ± 5.87	<.0001
24 h	83.52 ± 9.67	98.53 ± 7.71	<.0001
Heart rate, beats/min			
0 h	99.167 ± 10.815	98.143 ± 9.866	.7033
6 h	94.556 ± 16.325	92.810 ± 15.529	.6417
12 h	98.5 ± 10.078	84.286 ± 14.742	.0017
24 h	95.333 ± 7.071	77.714 ± 9.419	<.0001

*Data are presented as the mean ± SD. *P* values <.05 are statistically significant.

In this study, continuous sedation with intravenous dexmedetomidine at clinically effective doses did not interfere with the normal course of ventilator weaning and extubation because it did not depress respiratory drive or decrease arterial oxygen saturation.

Herr and colleagues [2003] compared a dexmedetomidine-based sedation regimen with a variety of propofol-based sedation protocols. In that study, there were no significant differences between the groups in the median times to weaning or extubation [Herr 2003]. In the present study, we found a shorter time to extubation in the dexmedetomidine group than in the controls (55.389 ± 3.958 hours versus 46.619 ± 6.960 hours). Herr and colleagues found no significant differences between groups with respect to respiratory rates, oxygen saturation after extubation as measured by pulse oximetry (SpO_2), or blood gases immediately or 6 hours after extubation [Herr 2003]. We found significantly different heart rates between the groups at 12 and 24 hours, a result that may be due to inhibited sympathetic activity causing a decrease in heart rate. PO_2 values were higher at 12 and 24 hours in group D, but the difference disappeared by the time of weaning. Oxygenation was improved, and the PCO_2 was in the clinically normal range. Considering the preexisting cardiac problems of the patients, we did not use bolus dosing regimens or administer an initial dose in <10 minutes. Therefore, we did not observe any hemodynamic side effects. Omitting the loading dose avoided undesirable hemodynamic effects without compromising sedation and analgesia [Ickeringill 2004]. In this study, half of the hypotension episodes in the dexmedetomidine patients were resolved in response to dose titration or the addition of fluids.

Delirium in the context of postoperative cardiac surgery patients has been referred to as postcardiotomy delirium since as early as 1964 [Sockalingam 2005]. van der Mast and colleagues [2000] studied the interrelationships between plasma levels of amino acids, physical condition, and postoperative delirium in 296 patients who underwent elective cardiac surgery. They concluded that the resulting decreased serotonergic function and the normal or increased dopaminergic and noradrenergic function might be contributing pathogenetic factors in delirium after cardiac surgery [van der Mast 2000].

A 1990 review of instruments used for screening cognitive and mental status in older adults does not list any tools for the assessment of delirium. Since then, a few tools, such as the Delirium Rating Scale, the CAM, and the Cognitive Test for Delirium, have been developed. Neither the Delirium Rating Scale nor the CAM was designed for use in ICU patients, who are usually unable to speak because they are intubated and receiving mechanical ventilation. The first delirium assessment tool designed specifically for ICU patients, the CAM-ICU (Figure 2), has been validated. The CAM-ICU was adapted from the original CAM for use with nonverbal ICU patients. It is a well-validated, commonly used, and easy-to-administer scale for the assessment of delirium [Truman 2003]. In this study, we observed that the results obtained with this test were correlated with the evaluation results of the psychiatrist. Serial measurements of sedation obtained by using the RASS or other validated sedation scales and the Glasgow Coma Scale are helpful in detecting fluctuations from baseline. All symptoms of delirium disappeared 6 hours after dexmedetomidine administration in group D; group M required the use of other drugs, such as benzodiazepines, haloperidol, or atypical antipsychotics.

The Society of Critical Care Medicine recommends haloperidol for the treatment of delirium. Haloperidol, a dopamine receptor antagonist, inhibits dopamine neurotransmission. It is used to treat positive symptoms (for example, hallucinations and unstructured thought patterns) and often produces a sedative effect (that may lead to hypoactive delirium) [Truman 2003]. Haloperidol is associated with significant side effects, such as extrapyramidal symptoms, which are more frequent in the elderly and seriously ill patients, who are most vulnerable to delirium [Sockalingam 2005]. We usually avoid using this drug in the postoperative cardiac ICU because of its adverse effects, such as QT prolongation, arrhythmias, and extrapyramidal effects. We did not use this drug in group D after the initiation of dexmedetomidine infusion, but we needed to use it in group M, along with other atypical antipsychotics, such as olanzapine and risperidone.

In a pilot study, Siobal et al evaluated the use of dexmedetomidine for facilitating extubation in patients who had failed previous weaning attempts [Siobal 2006]. Their study population consisted of surgical patients under intensive care, and the sample size was small. Nevertheless, that study was the first to evaluate dexmedetomidine use for this particular purpose. In recent years, some studies have demonstrated a reduction in the incidence of delirium among cardiac surgery patients in association with dexmedetomidine use and have shown the benefits of this treatment in facilitating extubation in the ICU [Maldonado 2003; Arpino 2008].

Riker et al [2009] randomized 375 mechanically ventilated ICU patients from 68 medical centers in 5 countries between March 2005 and August 2007 to receive either dexmedetomidine or midazolam. Doses were adjusted to achieve light sedation and a RASS score between –2 and +1. They reported

a statistically significant difference in the number of days on mechanical ventilation, with dexmedetomidine demonstrating a reduction in the time to extubation of almost 2 full days. The prevalence of delirium during treatment was lower with dexmedetomidine-treated patients than with patients treated with midazolam [Riker 2009].

Dexmedetomidine has been used for many years in the postoperative cardiac ICU for the purpose of sedation; however, there remain few studies of its benefits in facilitating the extubation of cardiac patients. The delirium symptoms disappeared in our patients who received dexmedetomidine, and this treatment led to shorter times to extubation without any hemodynamic disturbance. These benefits may be due to the stimulation of α_2-adrenoreceptors in the central nervous system (specifically in the locus coeruleus). Thus, sympathetic activity is reduced, and norepinephrine release is inhibited.

The ICU environment predisposes patients to develop agitation and delirium due to noradrenergic hyperfunction. A reduction in sedation can provoke a stress response, catecholamine release, and agitation, which can lead to tachypnea, tachycardia, and hypertension. The sympatholytic property of dexmedetomidine reduces plasma epinephrine and norepinephrine levels and attenuates the hyperdynamic physiological response to stress. Siobal et al explained why their patients could be extubated during dexmedetomidine infusion despite having failed previous attempts [Siobal 2006]. We observed the same clinical effects in our patients. Because α_2-receptor stimulation does not cause respiratory depression, sedation with dexmedetomidine may facilitate the transition to unassisted breathing in agitated patients. Dexmedetomidine may inhibit the hemodynamic stress response during weaning from mechanical ventilation and may help to eliminate the emergence of agitation when sedation is being tapered. It therefore may help to facilitate earlier extubation in some patients.

Sedation with dexmedetomidine may also reduce or eliminate the need for continuous intravenous sedation with opiates and benzodiazepines in some patients. Continuous intravenous sedation with these drugs is associated with prolonged mechanical ventilation [Siobal 2006].

CONCLUSION

In this study, dexmedetomidine administration in our patients caused the disappearance of delirium symptoms and led to shorter times to extubation, without any hemodynamic disturbance. In conclusion, dexmedetomidine can be a good choice for the management of the delirium state associated with prolonged mechanical ventilation after cardiac surgery. Initiation of dexmedetomidine treatment when the first signs of delirium appear in patients who could not be switched to CPAP after cardiac surgery may help to eliminate the emergence of agitation during sedation tapering and therefore may help to facilitate earlier extubation.

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