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Chronotropic Effect of Isoproterenol is Reduced in the Female after Continuous Cervical Epidural Blockade Combined with Light General Anesthesia

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Abstract

The contribution of cardiac β-adrenoceptor sensitivity secondary to cervical epidural anesthesia induced cardiac sympathectomy has not been confirmed in humans. This study was designed to evaluate whether cardiac sympathectomy induced by continuous cervical epidural anesthesia could modify the sensitivity to the chronotropic effect of isoproterenol in lightly anesthetized female adult patients.

51, ASA physical 1 status and adult female patients who were scheduled for mastectomy under general anesthesia combined with cervical epidural blockade. 10 ml of 2% plain lidocaine was administered every hour through an indwelling epidural catheter placed at C6-C7. Anesthesia was maintained with 60% nitrous oxide in oxygen supplemented by diazepam 5 mg, every one hour.

We measured the dose of isoproterenol that increased heart rate by 25 bpm, chronotropic dose of 25, after each epidural injection. We also measured blood concentrations of lidocaine 15 min after each epidural lidocaine administration and plasma epinephrine and norepinephrine levels before the first epidural injection, 30 min after the start of surgery and 90 min after the end of surgery.

Chronotropic dose of 25 after the fourth epidural injection increased significantly from the first chronotropic dose of 25. Blood lidocaine concentrations after all epidural injections were not different. Plasma levels of norepinephrine and epinephrine measured 30 min after the start of surgery and 90 min after the end of surgery significantly decreased compared to those measured before 1st epidural administration.

In lightly anesthetized females, cardiac β-adrenoceptor sensitivity to isoproterenol was decreased after the fourth dose of cervical epidural lidocaine. This implies that β-adrenoceptor of the heart could modulate cardiovascular function after cervical epidural anesthesia in humans.

Key words : Pulse rate, Cervical epidural, Isoproterenol, β-adrenoceptor sensitivity

Introduction

Decreased heart rate, prolongation of atrioventricular nodal conduction time and refractoriness during thoracic epidural anesthesia have been attributed to blockade of cardiac sympathetic activity[1]. Similar electrophysiologic changes are seen after administration of β-adrenoceptor blocking drugs. In addition, induction of thoracic epidural anesthesia during β-adrenoceptor blockade may have additive effects on sinoatrial and atrioventricular nodal functions, as well as on left ventricular inotropy[2]. They reported that cardiac electrophysiological effects induced by

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thoracic epidural anesthesia are mainly caused by decreased β-adrenoceptor stimulation[2].

It is reasonable to assume that β-adrenoceptor activity could influence the cardiovascular dynamics after cervical epidural anesthesia. It is, however, uncertain whether cervical epidural anesthesia induced cardiac sympathectomy affects cardiac β-adrenoceptor sensitivity in humans. The CD_{25} (chronotropic dose 25) is defined as the dose of isoproterenol required to increase the heart rate by 25 bpm. It can be used is evaluate the degree of β-adrenoceptor blockade[3]. Accordingly, we designed an isoproterenol dose response study to determine whether cardiac sympathectomy induced by continuous cervical epidural anesthesia modified the chronotropic effect of isoproterenol during light general anesthesia in female patients. This technique could provide useful and detailed information concerning the physiological properties induced by cervical epidural anesthesia.

Materials and Methods

Fifty-one ASA physical status 1 or 2 female patients, who were scheduled to have cervical epidural blockade combined with general anesthesia for mastectomy, were enrolled. The study protocol was approved by the Institutional Clinical Research Committee. Informed consent was obtained from each patient. None of the patient selected had cardiopulmonary or neurologic disorders. Premedication consisted of intramuscular hydroxydine 100 mg and atropine 0.5 mg 60 min before induction of anesthesia. An intravenous cannula was placed for infusion of lactated Ringer's solution and for drug administration. A radial artery catheter was inserted to permit continuous recording of arterial pressure and heart rate was computed electronically using a R-wave triggered instantaneous rate meter. A 17-gauge Tuohy needle was inserted into the epidural space at the C6-C7 or C7-T1 intervertebral space using a hanging-drop technique and an epidural catheter was placed 3 cm in a cephalad direction. Ten ml of 2% lidocaine without epinephrine were injected into the epidural space through the epidural catheter. After determining the analgesic level using the pinprick method general anesthesia was induced with thiamylal 4 $mg \cdot kg^{-1}$ iv followed by succinylcholine 1 $mg \cdot kg^{-1}$ iv for tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen supplemented by diazepam 10 mg. During surgical procedure, 2 $ml \cdot kg^{-1} \cdot hr^{-1}$ of lactated Ringer's solution was administered. Pancuronium 0.04 $mg \cdot kg^{-1}$ for muscle relaxation and ephedrine 5 mg and rapid infusion of fluid to keep the blood pressure within 20% from the baseline value were administered as needed. Ventilation was controlled to maintain end-tidal carbon dioxide tension approximately 35 mmHg. Multilead ECG and Spo_2 were also monitored. Ten ml of 2% lidocaine were administered every hour depending on the duration of surgical procedure. Patients were allocated into four groups depending on the frequency of epidural injection: group 1; one epidural injection, group 2; two epidural injections, group 3; three epidural injections, and group 4; four epidural injections.

The extent of β-adrenoceptor blockade was quantified using the isoproterenol sensitivity test. To achieve a stable hemodynamic baseline condition we waited for at least 20 min after tracheal intubation before the study began. An initial isoproterenol dose after the first epidural injection was 1 μg and the dose was gradually increased until the heart rate had increased by 25 bpm. If the heart rate had increased 25 bpm after 1 μg, the dose was then decreased. The same dose that increased the heart rate 25 bpm in the previous measurement was administered as the initial dose in the following test. Individual dose-response curves were constructed, and the dose of isoproterenol required to increase the heart rate by 25 bpm (chronotropic dose of 25: CD_{25}), was determined by interpolation. In addition, we avoid to use both ephedrine and pancuronium from 20 minutes before till the end of CD_{25} measurement.

Blood concentrations of lidocaine obtained 15 min after each epidural injection were measured by fluorescent polarization immunoassay. In addition, blood levels of epinephrine and norepinephrine were measured before the first epidural injection, 30 min after the start of surgery and 90 min after the surgical procedure. These were measured by high performance

liquid chromatography. Data are expressed as mean± SEM. ANOVA and Fisher PLSD were used for statistical analysis and P value less the 0.05 was considered significant.

Results

Mean age, weight and height of the patients were 46.7 yr (range: 34-66 yr), 53.7 kg, (range: 41-65 kg) and 153.7 cm (range: 143-167 cm), respectively. The mean analgesic levels obtained after the first epidural administration of lidocaine were between C4-T7. No patient required blood or other blood substitutes infusion because of slight blood loss. There was no significant difference in either baseline systolic or diastolic pressure in patients just before each isoproterenol sensitivity test. The values of arterial blood gas analyses measured in all subjects during anesthesia course were within normal limits. Baseline heart rates before the 3rd and 4th sensitivity tests were significantly decreased from the first one (Table 1). Patients whose surgical procedures were finished within two, three or four hours, had one, two and three isoproterenol sensitivity tests, respectively. The other 10 patients had four sensitivity tests after each epidural injection.

CD25 values after the first, second, third and fourth epidural injections were 1.3 μg, 1.4 μg 1.5 μg and 1.9 μg, respectively. CD25 after the fourth injection was significantly different from the first one (Figure 1). Blood concentrations of lidocaine 15 min after each epidural administration were not different (Figure 2). Blood levels of epinephrine and norepinephrine showed the same trend. Both levels measured after 30 min after start of surgery and 90 min after the end of surgery were significantly lower than those obtained before the first epidural administration (Figure 3). At postoperative visit, no patient complained of intraoperative awareness.

Table 1 Hemodynamic variables measured just before each assessment of CD_{25}

	SAP	DAP	HR	N
1st	106.2±5.3	61.4±4.3	69.2±3.9	51
2nd	100.8±4.3	59.1±3.2	64.7±2.7	49
3rd	104.7±2.5	62.4±3.0	60.9±1.6*	35
4th	99.8±2.2	58.2±1.9	60.9±2.5*	11

SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; CD_{25}=chronotropic dose of 25. Data are expressed as mean±SEM. #P<0.05 vs 1st assessment.

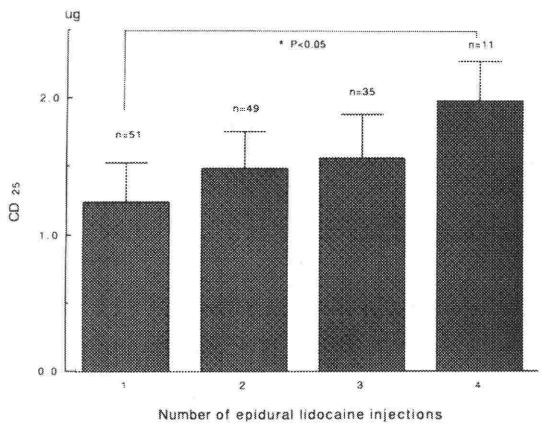

Fig. 1 Change in mean dose of isoproterenol that produced an increase in heart rate of 25 bpm. n=number of patients. Data are expressed as mean±SEM. CD_{25}=Chronotropic dose of 25. *denotes significant (p<0.05) difference between 1st and 4th measurement.

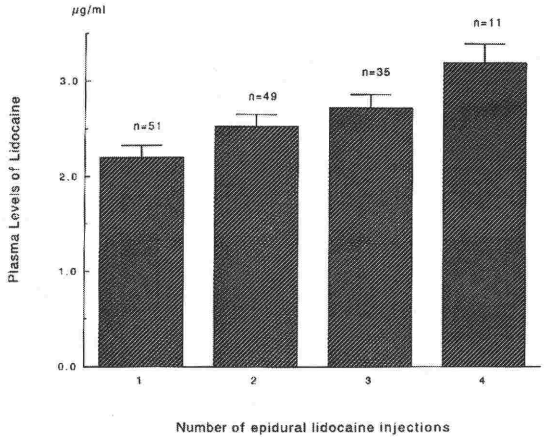

Fig. 2 Changes in blood concentration of lidocaine 20 min after each epidural lidocaine administration. No significant differences were noted. n=number of patients. Data are expressed as mean±SEM.

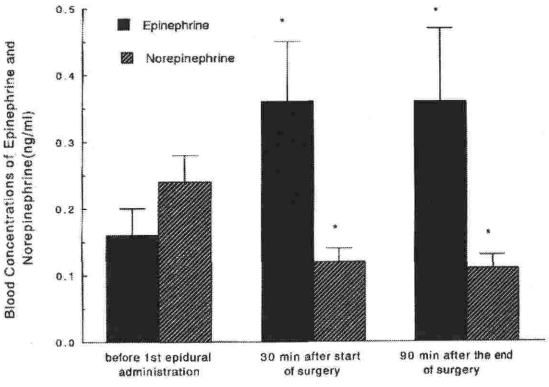

Fig. 3 Plasma levels of epinephrine and norepinephrine measured before the Ist epidural administration of lidocaine, 30 min after the start of surgery and 90 min after the end of surgery. * denotes significant difference vs the value before Ist epidural administration of lidocaine. n=number of patients. Data are expressed as mean±SEM.

Discussion

This is the first study evaluating the relation between cervical epidural blockade and cardiac β-adrenoceptor sensitivity in premedicated and lightly anesthetized healthy female patients. We demonstrated that cervical epidural anesthesia-induced cardiac sympathectomy decreased the chronotropic effect of isoproterenol in a time dependent manner. CD_{25} in anesthetized elderly patients increased significantly from 4.4 μg to 27 μg, 39 μg, and 95 μg in the patients treated with cardio-selective β-adrenoceptor antagonists, nonselective β-adrenoceptor antagonists, and an infusion of labetanol, respectively[4]. During isoflurane-nitrous oxide anesthesia, CD_{25} also increased from 3.8 μg in the control to 24.5 μg in patients receiving β-adrenoceptor blocking drugs[5]. Compared to these values, CD_{25} of 1.9 μg after the fourth epidural injection was lower than expected despite a significant increase from control values.

CD_{25} determined using an isoproterenol sensitivity test has been considered the only suitable mean to evaluate cardiac β-adrenoceptor activity during anesthesia[4]. Many factors can modify the heart rate response to isoproterenol resulting in variation of CD_{25}[6~8]. We enrolled ASA physical status 1 female patients without medication including β-adrenoceptor antagonist. In addition, no epinephrine was added to our local anesthetic solution and patients were kept normocarbia to avoid any other factors that could affect the CD_{25}. Intramuscular atropine 0.5 mg given 60 min before anesthetic induction might affect our results. But larger doses of atropine is necessary for cardiac effects[9], so can we neglect the effect of intramuscular atropine given almost 3 hours before CD_{25} measurement.

Although cervical or thoracic epidural anesthesia-induced cardiac sympathectomy can grossly reduce the left ventricular contractility, the intimate interplay between sympathetic and parasympathetic tone plays an important role in maintaining overall cardiovascular function. The principal interaction observed in cervical or high thoracic epidural blockade is that the inhibitory effects of vagal activity on the left ventricular inotropic state is not accentuated as the level of sympathetic activity is reduced[10,11]. In our study, decreased sensitivity to isoproterenol was observed within four hours after epidural-induced cardiac sympathectomy. Isoproterenol bolus dosing causes a baroreceptor-mediated decrease in parasympathetic nervous system activation, thus heart rate and blood pressure response to isoproterenol boluses are mediated not only by β-adrenoceptor stimulation but parasympathetic withdrawal[3]. The same author also stated that the changes in heart rate recorded after atropine and isoprenaline may be compared with the changes obtained before atropine. Also, increased vagal efferent activity after cervical epidural anesthesia that counteract this isoproterenol induced parasympathetic withdrawal could justify the usefulness of CD_{25} as a index of β-adrenoceptor sensitivity in this study.

Diazepam has the potential to affect CD_{25}, but there was no difference in the total dose of diazepam used among the groups, so it is unlikely that diazepam significantly influenced the CD_{25}. Blood levels of lidocaine following continuous administration were elevated in a time-dependent manner and could potentially affect our results[12]. In spite of a slight

increase in plasma concentration after additional injections, we could not find any significant difference among the groups. We think that thoracic epidural anesthesia itself could be the only causative factor affecting cardiac β-adrenoceptor activity.

Reasons for the slight decrease of β-adrenoceptor sensitivity after cervical epidural blockade we observed are speculative. In dogs pretreated with β-adrenoceptor antagonists, thoracic epidural anesthesia had additional and depressional effect on the sinoatrial and AV nodal function within 30 min after administration of epidural bupivacaine[2]. This decrease in β-adrenoceptor activity is not accord with our results. It is important to recognize that baseline contractility and responsiveness to sympathetic activation and sympathetic amines can be altered profoundly by general anesthesia and recent surgery. The surgical stress or anesthetic methods could significantly modify the β-adrenoceptor sensitivity[11]. Barbiturates, the most common anesthetic agents used in animal experiments, depress most aspects of autonomic reflex control, reduce myocardial contractility, and increase the baseline heart rates. In acute animal preparations, increased sympathetic tone in response to the stress can be superimposed on the effects of barbiturates[13]. Accordingly, the effects of β-adrenoceptor antagonist and epidural anesthesia-induced cardiac sympathectomy could de disturbed significantly.

In the dog experiments performed under pentobarbital anesthesia, bupivacaine was administered through an epidural catheter after completion of surgical preparation. In contrast, surgical intervention in our study was performed under complete blockade by epidural anesthesia. The significant difference of the baseline activity of sympathetic nervous system between our study and dog experiments could be the causative factor explaining the disparity in CD25.

Many mechanisms could potentially alter the inotropic or chronotropic responsiveness of the cardiac β-adrenergic receptor. For example, the density or affinity of the β-receptors may be altered, access of hormone to the β-adrenergic receptor complex may be changed, or the intracellular efficiency of the β-adrenergic receptor complex may be altered[11]. Though these are not always indicative of the cathecolamine concentration at the β-adrenergic receptor complex, plasma cathecolamine concentrations, especially norepinephrine, have been used widely as an indicator of sympathetic neural activity. Plasma concentrations of norepinephrine and epinephrine to evaluate surgical stress in our study demonstrated complete block of this stress. Compared to other anesthetic methods, epidural blockade could suppress surgical stress more completely as shown in our results[14]. This suppression of cathecolamines, especially norepinephrine responses, might be one reason for the decrease in β-adrenoceptor sensitivity associated with cervical epidural anesthesia. Although cardiac sympathectomy induced by cervical epidural anesthesia is enough to suppress the sympathomimetic effect of a drug such as ketamine[15] or stimulation due to manipulation of the airway[16], it is well documented that this type of sympathectomy does not cause any remarkable cardiovascular perturbation.

Though we don't have enough data to explain why continuous cervical epidural blockade under general anesthesia produced a decrease in β-adrenoceptor sensitivity, one possible mechanism might be the attenuation of norepinephrine release or uptake at the receptor site due to cervical epidural blockade. In the clinical settings, the long-term use of cervical epidural anesthesia, especially when combined with volatile anesthetics, could suppress β-adrenoceptor activity. If prolonged analgesia is required using cervical epidural analgesia, the decrease of β-adrenoceptor sensitivity may provoke cardiovascular disturbances in the late stage of surgery. In this situation, β-1-receptor agonists will be one choice to maintain cardiovascular dynamics[17]. A further study should be performed in patients with already compromised β-adrenoceptor activity, because more pronounced cardiovascular perturbation can be anticipated after cardiac sympathectomy induced by epidural anesthesia. Also addition of epinephrine to local anesthetics ensures a more complete sympathetic blockade and could enhance the depression of β-adrenoceptor sensitivity.

The authors conclude that continuous cervical epidural blockade under light general anesthesia dimin-

ishes sensitivity to the isoproterenol with no change in the blood levels of lidocaine.

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