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Relationship between genetic variation in the α_{2A}-adrenergic receptor and the cardiovascular effects of dexmedetomidine in the Chinese Han population

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Abstract: There are differences in individual cardiovascular responses to the administration of dexmedetomidine, a highly selective α_{2A}-adrenergic receptor (ADRA2A) agonist. The aim of this study was to investigate *ADRA2A* gene polymorphisms in the Chinese Han population and their association with the cardiovascular response to intravenous dexmedetomidine infusion. Sixty elective surgery patients of Chinese Han nationality were administered 1 μg/kg dexmedetomidine intravenously over 10 min as a premedication. *ADRA2A* C-1291G and A1780G polymorphism status was determined in these patients, and their relationships to changes in blood pressure and heart rate after dexmedetomidine administration were analyzed. There were neither significant differences in systolic or diastolic blood pressure changes in individuals with different A1780G and C-1291G genotypes after dexmedetomidine administration, nor in heart rates among the different A1780G genotypes. However, there were significant differences in changes in heart rates in patients with different C-1291G genotypes. There were no significant differences in the sedative effects of dexmedetomidine among different A1780G and C-1291G genotypes. Logistic regression revealed that the C-1291G polymorphism was associated with differential decreases in heart rate after intravenous infusion of dexmedetomidine. These findings indicate that the *ADRA2A* C-1291G polymorphism can affect heart rate changes in patients after intravenous infusion of dexmedetomidine.

Key words: Dexmedetomidine; α_{2A}-Adrenergic receptor; Polymorphism; Blood pressure; Heart rate
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1 Introduction

Dexmedetomidine is a highly selective α_{2A}-adrenergic receptor (ADRA2A) agonist, which has analgesic, sedative, and sympathetic nervous system (SNS) inhibitory functions. It can reduce the required dosages of other anesthetics, improve hemodynamic stability during surgery, and reduce the incidence of myocardial ischemia; dexmedetomidine has accordingly become a commonly used drug in clinical anesthesia (Mantz et al., 2011; Neema, 2012). Dexmedetomidine administration can lead to hypotension and bradycardia due to its central SNS inhibition; however, it is also accompanied by an initial increase in blood pressure due to peripheral vasoconstriction (Talke et al., 2003; 2005). Hypotension and bradycardia are common in patients sedated with dexmedetomidine, causing hemodynamic instability (Ice et al., 2016). Obvious inter-individual variability in the effects of dexmedetomidine on intensive care unit (ICU) sedation has been observed (Kohli et al., 2012). A given dose of medication can lead to either inadequate sedation or an overdose, resulting in the abovementioned complications. Therefore,

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individualized dosing is necessary to avoid serious complications. To this end, examining the effects of *ADRA2A* gene polymorphisms can provide valuable information, enabling personalized clinical administration of dexmedetomidine and other *ADRA2A* agonists.

Studies have shown that the *ADRA2A* polymorphism can contribute to the different effects of dexmedetomidine, including its sedative effect and changes in blood pressure (Kurnik et al., 2011; Yağar et al., 2011). However, the minor frequencies of some *ADRA2A* polymorphisms differ between Asian and Caucasian populations (Small et al., 2006). The purpose of this study was to investigate *ADRA2A* gene polymorphisms in the Chinese Han population and their association with the cardiovascular responses of patients to dexmedetomidine administration.

2 Materials and methods

2.1 Ethics

This study was approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University (Hangzhou, China). Written informed consent was obtained from all patients. The study was registered in the Chinese Clinical Trial Registry (ChiCTR) on April 24, 2016, with the registry number ChiCTR-OPC-16008350.

2.2 Patients

Sixty adult patients of Chinese Han nationality who had undergone elective surgery, with American Society of Anesthesiologists physical status I–II and without hypertension, diabetes, or a history of any other major organ diseases, were enrolled in this study between May 1 and September 30, 2016. Exclusion criteria were major organ diseases, obesity (body mass index ≥30), hypertension, arrhythmia, and dexmedetomidine contraindications.

2.3 Dexmedetomidine administration and determination of its effects

After patients entered the preparation room and were awaiting anesthesia and surgery, intravenous dexmedetomidine was administered as a premedication. An intravenous cannula was initially inserted for infusion, and a 5-mL blood sample was drawn in an ethylenediaminetetraacetic acid-coated vacuum tube for DNA extraction. The patients were monitored for electrocardiogram activity, pulse oxygen saturation, and blood pressure, and these parameters served as the baseline parameters (time 0). In addition to routine monitoring, the bispectral index (BIS) was used, which has been shown to correlate with loss of consciousness and increased sedation in patients under anesthesia. Paliwal et al. (2015) verified the clinical validity and reliability of BIS for monitoring sedation and investigated the correlation with Ramsay sedation score in ICU patients. A 4-μg/mL solution of dexmedetomidine was intravenously infused at a rate of 1 μg/kg over 10 min using a syringe pump (Graseby 3500 Anaesthesia Pump; Graseby Medical Ltd., Watford, Herts, UK). Systolic blood pressure, diastolic blood pressure, heart rate, and BIS were recorded every 5 min from the beginning of infusion until 30 min later. During this time, disturbance of the patient, including dialogue and medical checks, was avoided. We prepared atropine for treatment if the heart rate decreased to <40 beat per minute (bpm), ephedrine if systolic blood pressure decreased to <80 mmHg (1 mmHg=133.3 Pa), and urapidil if systolic blood pressure increased to >180 mmHg. If a patient was treated with one of these drugs, he were excluded from the analysis.

2.4 Detection of *ADRA2A* SNPs by PCR and DNA sequencing

ADRA2A C-1291G (rs1800544) and A1780G (rs553668) single-nucleotide polymorphisms (SNPs), located in the 5'-promoter region and the 3'-noncoding region, respectively, were examined. We chose these SNPs because genetic variations in rs1800544 were associated with the sedative effect of dexmedetomidine (Yağar et al., 2011), and variations in rs553668 were associated with cardiovascular diseases such as hypertension (Kurnik et al., 2006). Genomic DNA was extracted from 5 mL of anticoagulant blood using a standard salt precipitation method. Target fragments were amplified by polymerase chain reaction (PCR) using previously described primers (Lima et al., 2007): C-1291G forward, 5'-GGAGGTTACTTCCCTCG-3', reverse, 5'-GGTACCTTGAGCTAGAGAC-3'; A1780G forward, 5'-CAGAGCAGCACTGGACTAC-3', reverse, 5'-TGGAAGGCATCTCTCCCAAG-3'.

For genotyping, the PCR products were sequenced on an ABI 7500 sequence detector (Applied Biosystems, Foster City, CA, USA) using the forward primers.

2.5 Statistical analysis

Data are expressed as mean±standard deviation (SD). Analyses were performed using SPSS v.17.0 statistical software. Genotype distribution was assessed for deviation from Hardy-Weinberg equilibrium using a chi-square test. The relationship between *ADRA2A* gene polymorphisms and cardiovascular system responses to intravenous administration of dexmedetomidine was analyzed using one-way analysis of variance, followed by Student-Newman-Keuls post-hoc multiple comparison test to identify different pairs among groups (for A1780G, with three groups), or Student's *t*-test (for C-1291G, with two groups). When there were changes in blood pressure and/or heart rate at any time point between the different genotypes, the patients with the maximal changes of ≥20% and <20% compared to their baselines were considered different patient groups. Logistic regression was performed to reveal the reason for changes in cardiovascular parameters after dexmedetomidine infusion, by examining variables such as age, sex, weight, height, and genotypes of C-1291G and A1780G. *P*-values of <0.05 were considered statistically significant.

3 Results

All patients (28 men and 32 women) completed the study. The ages of these patients ranged from 27 to 60 years (mean (44.02±7.94) years). Their weights ranged from 43 to 82 kg (mean (62.15±9.29) kg), and their heights ranged from 151 to 183 cm (mean (164.58±7.03) cm).

After intravenous infusion of 1 μg/kg dexmedetomidine, there were no serious adverse cardiovascular reactions. Some patients experienced hypotension, hypertension, or bradycardia, but none required intervention. Two patients experienced short-term oxygen desaturation (88%–90%) but soon recovered.

The genotype of the A1780G SNP in the Chinese Han population was A/A in 11 patients (18.33%), A/G in 34 patients (56.67%), and G/G in 15 patients (25.00%). The genotype of the C-1291G SNP was C/C in 3 patients (5.00%), C/G in 31 patients (51.67%), and G/G in 26 patients (43.33%). All genotypes conformed to Hardy-Weinberg equilibrium (all $P>0.05$). Because of the low frequency of the C/C genotype of C-1291G, patients were grouped into a CC/CG group with the C/G patients (i.e., with a C allele) and compared to the G/G group (i.e., without a C allele).

Systolic blood pressure, diastolic blood pressure, and heart rate changes after dexmedetomidine administration and their relationships with *ADRA2A* gene polymorphisms are shown in Figs. 1–3, respectively. For almost all *ADRA2A* genotypes, systolic and diastolic blood pressures decreased significantly 20–30 min after dexmedetomidineadministration; however, there were no differences between individuals harboring different A1780G and C-1291G gene polymorphisms. The heart rate decreased significantly 5 min after administration and remained low until 30 min after administration in patients with all *ADRA2A* genotypes. However, although there were no significant differences among the A1780G genotypes, there was a significant difference between the CC/CG and G/G genotypes of the C-1291G polymorphism ($P<0.05$; Fig. 3).

The heart rates of patients with CC/CG genotypes in the C-1291G polymorphism were significantly slower than those of patients with the G/G genotype. However, we could not detect differences in sedative effects between patients with the CC/CG and G/G genotypes, because there were no significant differences in BIS values after dexmedetomidine administration (Fig. 4). Logistic regression showed that the different heart rate changes were significantly related to different C-1291G genotypes ($P<0.05$; Fig. 3a).

4 Discussion

We observed that dexmedetomidine administration caused a significant decrease in heart rates in all patient groups, and that the C-1291G polymorphism of the *ADRA2A* gene was associated with differential changes in heart rate. In contrast, the A1780G polymorphism had no significant effect on changes in heart rate or blood pressure. The observed minor

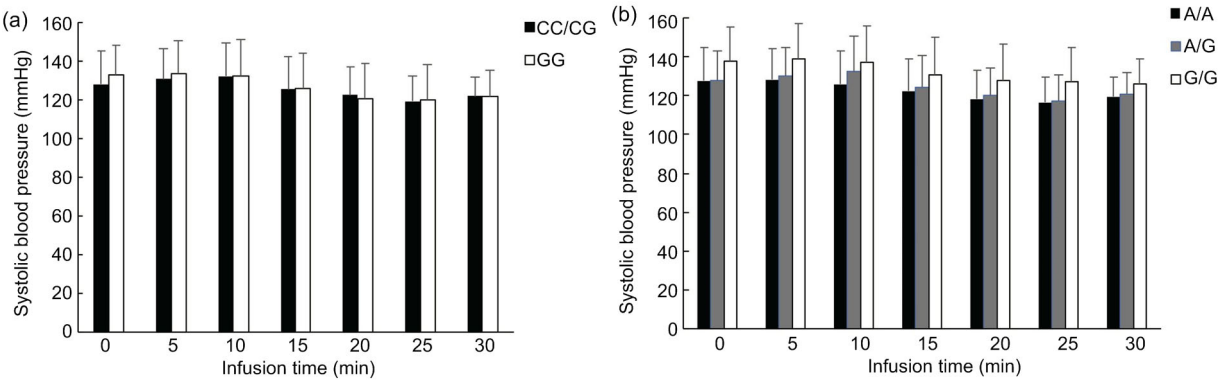

Fig. 1 Systolic blood pressure changes after intravenous infusion of dexmedetomidine to patients with different α_{2A}-adrenergic receptor (*ADRA2A*) C-1291G (a) and A1780G (b) polymorphism genotypes
Data are expressed as mean±standard deviation (n=60)

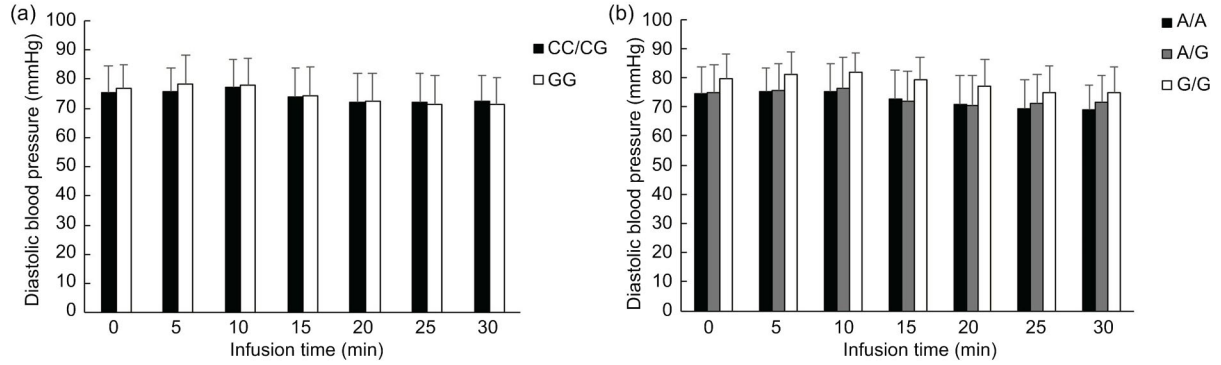

Fig. 2 Diastolic blood pressure changes after intravenous infusion of dexmedetomidine to patients with different α_{2A}-adrenergic receptor (*ADRA2A*) C-1291G (a) and A1780G (b) polymorphism genotypes
Data are expressed as mean±standard deviation (n=60)

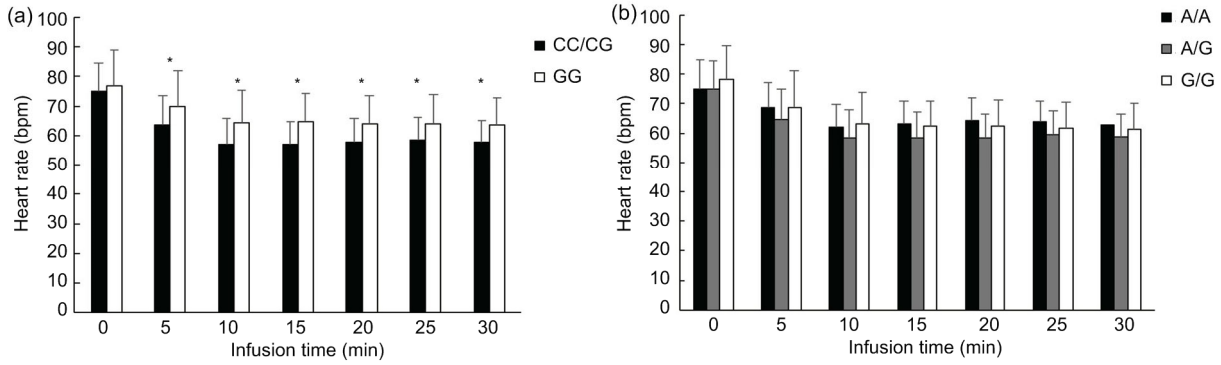

Fig. 3 Heart rate changes after intravenous infusion of dexmedetomidine to patients with different α_{2A}-adrenergic receptor (*ADRA2A*) C-1291G (a) and A1780G (b) polymorphism genotypes
Data are expressed as mean±standard deviation (n=60). * P<0.05, comparison between genotype groups

allele frequencies of the *ADRA2A* polymorphisms were similar to those reported for Asian (Small et al., 2006) and Chinese populations (Li et al., 2012; Yin et al., 2016), but were different from those reported for a Caucasian population (Small et al., 2006).

In addition to the effects of physiological factors such as age, sex, and pathological state, genome polymorphisms can contribute to individual responses to drugs. Polymorphisms of metabolic enzymes, for example, can lead to differences in pharmacokinetics,

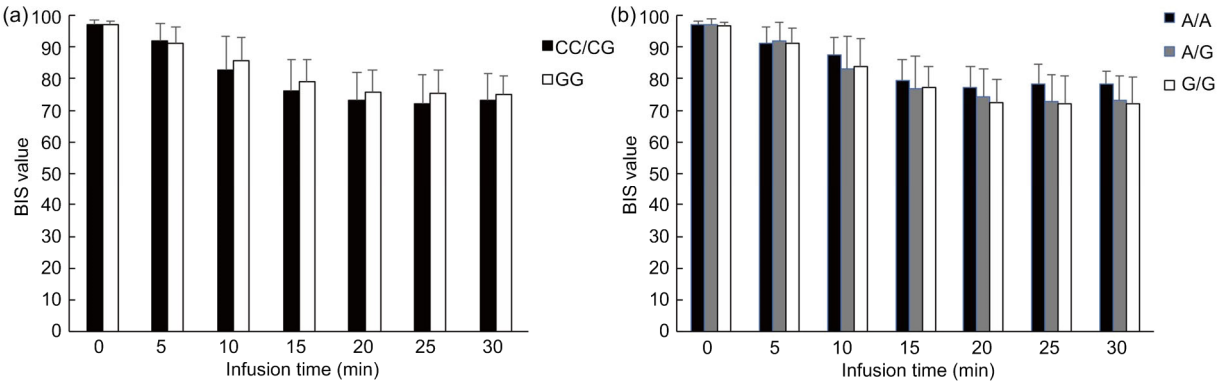

Fig. 4 Bispectral index (BIS) changes after intravenous infusion of dexmedetomidine to patients with different α_{2A}-adrenergic receptor (*ADRA2A*) C-1291G (a) and A1780G (b) polymorphism genotypes
Data are expressed as mean±standard deviation (n=60)

whereas drug receptor polymorphisms can lead to differences in pharmacodynamics (Galley et al., 2005). ADRA2A is widely distributed in the central nervous system and peripheral tissues. By inhibiting neuronal excitability and the secretion of norepinephrine and other neurotransmitters, ADRA2A mediates a series of important physiological responses and pharmacological effects (Madsen et al., 2002). In humans and other mammals, the receptor can be expressed as three subtypes, namely, α_{2A}, α_{2B}, and α_{2C}, with its main function performed by ADRA2A. Polymorphisms at the *ADRA2A* locus can lead to differences in a variety of physiological and pharmacological effects. *ADRA2A* polymorphisms can affect its expression level (Kurnik et al., 2011) and its binding affinity for ligands and drugs.

Kurnik et al. (2006, 2008, 2011) and Kohli et al. (2010) investigated *ADRA2A* polymorphisms in an American population (including individuals of African-descent and those of European-descent) and examined their effects on blood pressure and the pharmacological effects of dexmedetomidine. Yağar et al. (2011) studied the association between *ADRA2A* C-1291G gene polymorphisms and the clinical effects of dexmedetomidine and demonstrated that the C-1291G polymorphism was associated with differences in the sedative effect of dexmedetomidine, although no differential effects were observed on the cardiovascular system.

We could not determine whether the differential changes in heart rate after dexmedetomidine administration were related to its sedative effect. We chose intravenous infusion of 1 μg/kg dexmedetomidine, because this dosage caused sedation with minimal side effects. BIS values were typically 70–80 after infusion of dexmedetomidine for 10–30 min. Decreases in heart rate likely occurred as a result of both the infusion of dexmedetomidine and sedation itself.

Although our study shows a clear relationship between *ADRA2A* gene polymorphisms and the response to dexmedetomidine administration, it has certain limitations. First, we detected only two SNPs in *ADRA2A*, and whether SNPs at other sites affect the cardiovascular response to dexmedetomidine will require further study. Second, we did not administer dexmedetomidine in combination with other anesthetics. Third, the statistical analyses were challenging because of the relatively small sample size. Future studies are needed to track the changes in pharmacokinetics. Dexmedetomidine significantly inhibits central SNS release, and has peripheral vasoconstriction effects, and if combined with other anesthetics, these effects can become pronounced (Talke et al., 2003). Accordingly, the cardiovascular response, including changes in blood pressure and heart rate, may be different. In addition, our patients were anxious, as they were awaiting surgery, and their heart rates were frequently increased. Therefore, the degree of heart rate reduction was also related to the baseline heart rate. We also found that "younger patients" were more likely to slow their heart rate after dexmedetomidine infusion than "older patients" ((41.74±7.51) years vs. (47.95±7.19) years), possibly because the younger patients were more anxious, and their heart rates were faster before medication.

Intravenous infusion of dexmedetomidine generally leads to bradycardia during clinical application.

Our results suggest that it is important to consider, prior to the administration of dexmedetomidine, that some patients might be genetically prone to bradycardia.

5 Conclusions

We found that the *ADRA2A* C-1291G polymorphism could affect changes in the heart rates of patients in Chinese Han population after intravenous infusion of dexmedetomidine.

Contributors

Shao-jun ZHU performed the experimental research and data analysis, wrote and edited the manuscript. Xiong-xin ZHANG collected the data and performed the sequencing experiments. Sheng-mei ZHU and Kui-rong WANG contributed to the study design, data analysis, and editing of the manuscript. All authors read and approved the final manuscript.

Compliance with ethics guidelines

Shao-jun ZHU, Kui-rong WANG, Xiong-xin ZHANG, and Sheng-mei ZHU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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中文概要

题　目：中国汉族人群中肾上腺素 α_{2A} 受体基因多态性与右美托咪定心血管效应的相关性研究

目　的：通过对右美托咪定静脉输注的临床研究，评价中国汉族人群中肾上腺素 α_{2A} 受体基因多态性与右美托咪定心血管效应的相关性。

创新点：探索右美托咪定的心血管系统反应与肾上腺素 α_{2A} 受体基因多态性的关系，期望为临床个体化应用右美托咪定及其他 α_2 受体激动剂提供重要的依据。

方　法：本研究取得单位伦理委员会的批准，所有受试者告知受试内容并签署知情同意书。60 例美国麻醉医师协会 I–II 行择期手术汉族患者根据标准入选本研究。通过静脉输注右美托咪定，记录收缩压、舒张压、心率等心血管效应数据，并用聚合酶链式反应（PCR）法检测 *ADRA2A* 基因单核苷酸多态性。

结　论：中国汉族人群中肾上腺素 α_{2A} 受体 C-1291G 基因多态性与应用右美托咪定后心率变化有相关性。

关键词：右美托咪定；肾上腺素 α_{2A} 受体；多态性；血压；心率