Dexmedetomidine and Clonidine Inhibit Ventricular Tachyarrhythmias in a Rabbit Model of Acquired Long QT Syndrome

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Background: Agents with α-2 adrenoceptor (AR) agonistic action have reportedly suppressed tachyarrhythmias.

Methods and Results: We hypothesized that α-2 AR agonists would have an inhibitory effect on abnormal repolarization-related ventricular tachyarrhythmias (VTs). To test this hypothesis, the effects of 2 clinically available α-2 AR agonists (dexmedetomidine and clonidine) on the occurrence of VTs were assessed in a methoxamine-sensitized rabbit model of acquired long QT syndrome (Study 1: n=45). In control rabbits, administration of methoxamine and nifekalant almost invariably caused VTs (14/15). In contrast, incidence of VT significantly decreased during the treatment with dexmedetomidine (1 μg · kg⁻¹ · min⁻¹: 5/12 [P<0.01 vs. control]) or with clonidine (33.3 μg · kg⁻¹ · min⁻¹: 10/18 [P<0.01]). To verify that VTs in this animal model are triggered by early afterdepolarization (EAD), the monophasic action potential on the left ventricular surface was recorded in 28 open-chest rabbits (Study 2). EAD-like hump was less frequently detected during treatment with clonidine or dexmedetomidine (2/14) than in saline-treated rabbits (9/10, P<0.005). Presence of a hump was significantly related to the advent of VTs (P<0.05).

Conclusions: Agents with α-2 AR agonistic action have an inhibitory effect on VTs in a rabbit model of long QT syndrome. Alpha-2 AR agonists, especially dexmedetomidine, may be a therapeutic choice for abnormal repolarization-related VTs that are resistant to conventional treatment. (Circ J 2012; 76: 2343–2347)

Key Words: Clonidine; Dexmedetomidine; Early afterdepolarization; Methoxamine; Nifekalant

Dexmedetomidine, a highly selective α-2-adrenoceptor (AR) full agonist, is currently used in a variety of clinical settings as a sedative and analgesic agent with minimal effect on respiration. In addition to its well-known properties, dexmedetomidine has shown an inhibitory effect on supraventricular and ventricular arrhythmias.1 Dexmedetomidine also suppressed adrenaline-induced ventricular tachyarrhythmias (VTs) via enhanced vagal nerve activity in an experimental study.2

Alpha-2-AR stimulation alleviates cardiovascular and electrophysiological changes caused by α-1-stimulation and attenuates the L-type Ca²⁺ current.3 Because autonomic nervous activity is a determinant for the appearance of early afterdepolarization (EAD), α-2-AR agonists may play a possible therapeutic role for abnormal repolarization-related VTs.4

In the present study, we assessed the incidence of VT during treatment with dexmedetomidine or clonidine. partial α-2 AR agonists, using a methoxamine-sensitized rabbit model in combination with an Iᵥ blocking agent. The aims of this study were: (1) to explore the potential antiarrhythmic action of dexmedetomidine and (2) to ascertain if other α-2-AR agonists share this favorable effect, if it exists. In addition, to obtain an insight into the mechanism, we also measured the epicardial monophasic action potential (MAP).

Methods

Animal Preparation

This experiment was approved by the local institutional review board. All procedures were carried out in accordance with the guidelines of the Committee of Animal Care and Experiments of Teikyo University.

Seventy-three Japanese white rabbits (2.4–2.7 kg) were anesthetized with intravenous thiamylal sodium (25 mg/kg). Additional doses were given if necessary to maintain an appropriate level of anesthesia. Rabbits were ventilated with room air.
through an artificial respirator (model 6025, Ugo, Basile, Italy) via a tracheal cannula. Arterial blood pressure was monitored using a right femoral artery cannula attached to a Statham pressure transducer (Amplifier AP621G, Nihon Koden, Tokyo, Japan). Body temperature was maintained at approximately 37°C with an electrical blanket. Arterial blood gases and electrolytes were measured with a portable clinical analyzer (i-STAT 200A, i-STAT Corporation, Princeton, NJ, USA). Tidal volume and respiratory rate were adjusted to maintain arterial blood gases and pH within physiological ranges. Two surface electrocardiograms, lead I and II, were continuously monitored and the data were stored in a personal computer together with that for arterial blood pressure for subsequent analysis (PowerLab 8-channel System, ADInstruments Pty Ltd, Sydney, NSW, Australia).

According to an in vivo animal model of torsades de pointes (TdP) established by Carlsson et al.\(^3\) we administered nifekalant chloride concomitantly with methoxamine, an α-1 stimulant.

**Experimental Protocol**

**Study 1: Effect of Treatment With Dexmedetomidine, Clonidine or Saline on Occurrence of VTs in Closed Chest Rabbits (n=45)**

The protocol of this part of the study is schematically shown in Figure 1. After a 10-min period of stabilization, methoxamine was intravenously administered at a rate of 70 nmol·kg\(^{-1}\)·min\(^{-1}\). A 10-min infusion of methoxamine was followed by administration of nifekalant chloride (0.2 mg·kg\(^{-1}\)·min\(^{-1}\)). Twelve rabbits were treated with intravenous infusion of dexmedetomidine (Maruishi Pharmaceutical, Osaka, Japan) at a rate of 1 μg·kg\(^{-1}\)·min\(^{-1}\), and 18 rabbits were treated with clonidine hydrochloride (33.3 μg·kg\(^{-1}\)·min\(^{-1}\), Sigma-Aldrich, St Louis, MO, USA). The remaining 15 rabbits were given 0.5 ml/min of saline solution (control group). Treatment with dexmedetomidine, clonidine, or saline started simultaneously with the administration of nifekalant.

The number of premature ventricular contractions (PVC), time elapsed from the onset of administration of the treatment drug to the onset of the first PVC and the provoked VT, if it existed, were measured.

**Study 2: Recording of MAP in Open-Chest Rabbits (n=28)**

This part of the study was designed to verify that VTs in this animal model were actually triggered by EAD. The heart was exposed through a midsternal incision, and suspended in a pericardial cradle. MAP was recorded on the left ventricular surface using a contact electrode with an interelectrode distance of 3 mm. MAP signals were amplified with frequency range of 0.1–10 KHz (AP-621G; Nihon Kohden, Tokyo, Japan), and were performed in the baseline state and during treatment with dexmedetomidine (n=9), clonidine (n=9), or saline (n=10) at the same dose as in Study 1. MAP was accepted when the amplitude was stable and >10 mV.

**Definitions and Measurement**

VT was defined as an episode of at least 6 coupled ventricular complexes. Heart rates and QT intervals were obtained from the measurements of 3 consecutive RR intervals or those of 3 beats in either lead with more prominent T waves, respectively. The QT interval was corrected by the Bazett formula (QTc). The measurements of variables in the baseline state were made prior to the administration of methoxamine. Measurements during the treatment with each agent were performed 5 min from the onset of administration of nifekalant. After this time, frequent PVCs or VTs interfered with the measurements of ECG variables in the control rabbits. We compared the number of PVC per minute in each rabbit that had VTs among 3 groups to quantify the antiarrhythmic action of clonidine and dexmedetomidine.

**Statistical Analysis**

All continuous data are expressed as the mean±SD. Comparisons of variables among the groups were done by analysis...
of variance. In the presence of a significant F value, further comparison between each pair of variables was done by the Bonferroni method. Intergroup difference in the incidence of VT in Study 1 and the association between EAD-like hump and the appearance of VT in Study 2 were tested using Fisher’s exact test. Probability values <0.05 were considered to indicate significance.

Results

Study 1

VT occurred in 14 of 15 control rabbits (93%). VT was less frequently seen in rabbits treated with dexmedetomidine (42%, P<0.01 vs. control) or clonidine (56%; P<0.01 vs. control), respectively (Figure 2). The proportion of rabbits that developed VT during treatment with dexmedetomidine did not significantly differ from that during treatment with clonidine (P=NS).

Widely fluctuating RR interval and blood pressure or inconspicuous T wave hampered the measurement of heart rate, systolic blood pressure (SBP), or QTc in 10 rabbits. Heart rates, SBPs, and QTc for the remaining 35 rabbits are shown in Table 1. Heart rate decreased in all 3 groups. SBP increased in the control group (P<0.001) and clonidine group (P<0.001), but not in the dexmedetomidine group. Although the QTc interval was prolonged in all groups, it was less remarkable in the dexmedetomidine- or clonidine-treated rabbits (P<0.001 vs. control).

Time to the first PVC from the onset of the administration of nifekalant was longer in the dexmedetomidine and clonidine groups than in the control group (241±41 s in controls, 357±49 s in dexmedetomidine group, 453±24 s in clonidine group; P<0.01). The numbers of PVCs in rabbits with VT were similar among the 3 groups (1.0±0.9 in controls, 0.9±0.61 in dexmedetomidine group, 1.8±1.6 in clonidine group; P=NS).

Study 2

Figure 3A shows demonstrable ECG and MAP recordings obtained from a control rabbit, and those from a rabbit treated with dexmedetomidine are shown in Figure 3B. EAD-like hump was found in all 10 rabbits treated with saline, and VT occurred in 9 of them. EAD-like hump was less frequently detected during treatment with clonidine or dexmedetomidine (2/18, P<0.01 vs. control) than with saline. When observations of all the rabbits treated with saline, clonidine, or dexmedetomidine were collectively analyzed, VT occurred more frequently in rabbits with EAD-like hump than in rabbits without it (10/12 vs. 8/16, P<0.05).

Discussion

The major findings of the present study are: (1) both dexmedetomidine and clonidine reduced the incidence of VT in a rabbit model of acquired long QT syndrome; (2) SBP was preserved in the dexmedetomidine group, but not in the clonidine or control group; (3) prolongation of QTc and the frequency of PVCs were both alleviated in rabbits administered dexmedetomidine or clonidine; and (4) VTs in this animal model and their disappearance during treatment with an α2-AR agonist were associated, if not entirely, with the advent of EAD-like hump.

Abnormal repolarization has been confirmed to be involved in provoked VTs in this model. Spatial dispersion of ventricular repolarization, as well as triggered PVCs, may play a key role in long QT syndrome. Dexmedetomidine and clonidine might have suppressed both of these, based on the following findings. (1) The α2 agonists diminished not only the occurrence of induced VTs but also EAD-like hump on epicardial MAP recordings, as compared with the control group. The α2 agonists also attenuated prolongation of QT intervals (Table 1). These results are consistent with those from our previous reports using hANP or xyladine. (2) The PVC study revealed that dexmedetomidine and clonidine could suppress resultant triggered PVCs in affected rabbits but not in those that had VTs.

EAD-like hump on the MAP recordings did not always coincide with the appearance of VT, which occurred without a noticeable EAD-like hump in some rabbits, but did not occur in other rabbits that had the hump. Whether “EAD-related VT” and “EAD-unrelated VT” coexist remains uncertain. However, it is not too much to say that the association of appearance of a hump with the incidence of VT suggests that the majority of VTs may be, if not entirely, attributable to EAD.

Alpha-2 ARs distribute in the brain stem, peripheral vasculature, and presynaptic nervous terminal as an “auto-suppressive receptor”. The receptor suppresses its own adrenaline release from the terminal reticulum to the effector including brain system, vasculature, and the heart, achieving sedation, analgesia, decreased BP, and bradycardia. Receptors in the peripheral vasculature control vessel tone in a contradictory fashion: vasoconstriction, vasorelaxation, and modifying α2 agonists diminished not only the occurrence of induced VTs but also EAD-like hump on epicardial MAP recordings, as compared with the control group. The α2 agonists also attenuated prolongation of QT intervals (Table 1). These results are consistent with those from our previous reports using hANP or xyladine. (2) The PVC study revealed that dexmedetomidine and clonidine could suppress resultant triggered PVCs in affected rabbits but not in those that had VTs.

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Alpha-2 ARs distribute in the brain stem, peripheral vasculature, and presynaptic nervous terminal as an “auto-suppressive receptor”. The receptor suppresses its own adrenaline release from the terminal reticulum to the effector including brain system, vasculature, and the heart, achieving sedation, analgesia, decreased BP, and bradycardia. Receptors in the peripheral vasculature control vessel tone in a contradictory fashion: vasoconstriction, vasorelaxation, and modifying each other. Shimizu et al reported that medetomidine, a selective α2 AR agonist, modifies the cardiac autonomic state not only by suppressing cardiac noradrenaline release but also

<table>
<thead>
<tr>
<th>Table 1. Heart Rate, SBP, and QTc in Study 1</th>
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<tr>
<td>Treatment</td>
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<tr>
<td>Saline (n=10)</td>
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<td>Clonidine (n=15)</td>
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<td>Dexmedetomidine (n=10)</td>
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*P<0.01 vs. saline. Differences between the baseline and treatment values were significant except for SBP in the dexmedetomidine group. SBP, systolic blood pressure.
Figure 3. Illustrative electrocardiograms (ECGs) and epicardial monophasic action potentials (MAPs) in the control group (A) and dexmedetomidine group (B). MAP duration at 90% repolarization (MAPD90) was noted beneath the MAP electrogram. In the saline group, early afterdepolarization-like hump as indicated by arrows was observed on MAP recordings during administration of methoxamine and nifekalant. A ventricular ectopic beat could then trigger ventricular tachyarrhythmia (VT). In contrast, VT did not occur in the dexmedetomidine-treated rabbit.

<table>
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<tr>
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<th>Hump(+)/VT(+)</th>
<th>Hump(+)/VT(−)</th>
<th>Hump(−)/VT(+)</th>
<th>Hump(−)/VT(−)</th>
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<tbody>
<tr>
<td>Saline (n=10)</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clonidine (n=8)</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Dexmedetomidine (n=10)</td>
<td>1</td>
<td>1</td>
<td>4</td>
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<td>Total no.</td>
<td>10</td>
<td>2</td>
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EAD, early afterdepolarization; MAP, monophasic action potential; VT, ventricular tachyarrhythmia.
by activating vagal acetylcholine release.\textsuperscript{13}

In the present study, an increase in BP was attenuated by dexmedetomidine but not by clonidine (Table 1). The difference between them in agonist-binding mode is that dexmedetomidine is almost a full agonist and clonidine is a partial agonist, which may explain the variability in the hemodynamic response. Another possible explanation is that the experimental protocol subjected the rabbits to a large amount of the \(\alpha\)-2-agonist that almost saturated the \(\alpha\)-2 AR, unexpectedly stimulating the \(\alpha\)-1 AR. The finding by Masuki et al that clonidine has less \(\alpha\)-1/\(\alpha\)-2 selectivity than dexmedetomidine seems consistent with this concept.\textsuperscript{14}

The acute hemodynamic effect of \(\alpha\)-2 AR agonists may raise safety concerns. High doses (>0.7 \(\mu g \cdot kg^{-1} \cdot min^{-1}\)) of dexmedetomidine have caused bradycardia requiring intervention.\textsuperscript{15} Moreover, bradycardia enhances cardiac susceptibility to TdP. In the present study, even though a marked decrease in heart rate occurred with high doses of both dexmedetomidine and clonidine, VT appeared less frequently than in controls. Lowered BP during the infusion of dexmedetomidine did not seemingly abolish its favorable effect on VTs. These observations indicate that neither chronotropic nor hemodynamic alteration caused by \(\alpha\)-2 agonists affects their antiarrhythmic action.

**Study Limitations**

As Parent et al noted,\textsuperscript{2} dexmedetomidine would be a choice for sedation for patients with recurrent VTs, in addition to conventional therapy, anticipating a possible antiarrhythmic action. The results of the present study give dexmedetomidine a possible role as an antiarrhythmic agent in the treatment of VT. Caution needs to be taken with the drug’s tendency to reduce heart rate and BP, although no life-threatening adverse effect was observed in this experiment. Given the dose of the \(\alpha\)-2 agonists in this study was much greater than the usual clinical dose, extrapolation of the present results to the clinical setting requires further investigation.

Care should be taken in interpreting the result of an electrophysiological study using either clonidine or dexmedetomidine as sedative in both the experimental and clinical situation with regard to the electrophysiological effect observed in this study. Because the presence or absence of EAD-like hump was subjectively judged by the observer, the result of Study 2 was not free from bias.

**Conclusions**

Both dexmedetomidine and clonidine favorably affected the inducibility of VTs in a rabbit model of long QT syndrome. The present study results support the view that \(\alpha\)-2 agonists have a possible therapeutic role for EAD-related VTs.

**References**