**Background and Purpose**

Since autonomic nervous modulation affects an appearance of early afterdepolarization (EAD), α-2 adrenoceptor (AR) agonists were expected to be therapeutic for abnormal repolarization-related ventricular tachyarrhythmia (VT). We tested whether two clinically available α-2 agonists, dexmedetomidine and clonidine, have an antiarrhythmic effect in a rabbit model of long QT syndrome. In addition, to obtain an insight into the mechanism, if exists, we also recorded the epicardial monophasic action potential (MAP).

**Materials and Methods**

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

Japanese white rabbits (2.4–2.7 kg, n=45) were anesthetized with intravenous thiamylal sodium (25mg/kg), and were assigned to:
- Twelve for dexmedetomidine (1ug/kg/min);
- Eighteen for clonidine hydrochloride (33.3 μg/kg/min);
- Fifteen for saline solution (0.5 ml/min, control group).

Incidence of VT, hemodynamic parameters, QTc, and number of premature ventricular contraction (PVC) were obtained.

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

The heart was exposed through a midsternal incision, and was investigated by recording the epicardial monophasic action potential (MAP).

**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.

Heart rate decreased in all 3 groups. Systolic blood pressure (SBP) increased in the control group (P<0.001) and clonidine group (P<0.001), but not in the dexmedetomidine group. Although the QTc was prolonged in all groups, it was less remarkable in the dexmedetomidine or clonidine treated rabbits (P<0.001 vs. control).

**Study 2**

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 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).

**Discussions**

We found that dexmedetomidine and clonidine inhibit VTs in a rabbit model of long QT syndrome. The α-2 AR agonists diminished not only occurrence of VT but also EAD-like hump on epicardial MAP recordings, as compared with the control group.

In this model, abnormal repolarization has been confirmed as a primary cause for provoked VTs. Therefore, the pathophysiology consists of spiral dispersion of ventricular repolarization and triggered PVCs. Dexmedetomidine and clonidine are supposed to inhibit VT via both of them, because:

1. The α-2 agonists attenuated prolongation of QT intervals.
2. They may 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, considering an appearance of hump was associated with the incidence of VT, it is not too much to say that the majority of VTs may be, if not entirely, attributable to EAD.

The present result supports the concept that dexmedetomidine is a sedative for patients with recurrent EAD-related VT, in addition to conventional therapy, anticipating a possible antiarrhythmic action.

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 α-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.

**Conclusion**

Both dexmedetomidine and clonidine favorably affected the inducibility of VTs in a rabbit model of long QT syndrome. The results suggest that α-2 agonists have a possible therapeutic role for EAD-related VTs.

**Disclosure of interest:**

None.