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Ventricular arrhythmias triggered by alerting stimuli in conscious rabbits pre-treated with dofetilide

Abstract  We tested whether normally benign alerting/arousing stimuli provoke cardiac arrhythmias in conscious rabbits with electrically unstable myocardium. Alerting stimuli (loud sound, tapping and moving the cage, pinprick, inhalation of formaldehyde vapour) were presented before and after administration of dofetilide to conscious unrestrained rabbits (New Zealand White). Dofetilide (0.28 – 3.0 mg/kg i.v.) caused prolongation of QT interval (from 131 ± 9 to 217 ± 11 ms; p < 0.01, n = 6) and Tpeak-Tend interval (from 34 ± 5 to 81 ± 9 ms; p < 0.01, n = 6), altered ventricular conductance, and caused appearance of spontaneous ventricular ectopic beats. Alerting stimuli elicited ventricular ectopic beats in 18/30 trials in all dofetilide-treated animals, with a short latency (3.1 ± 0.4 s). Formaldehyde vapour, in addition, elicited profound bradycardia, and precipitated non-sustained polymorphic ventricular tachycardia (torsades de points) lasting 0.6 – 8.5 s in 5/6 animals. These arrhythmias occurred also with a short latency (mean 8.7 ± 1.6 s). Beta-adrenergic blockade with propranolol (1.5 mg/kg i.v.) abolished spontaneous ventricular ectopy, suppressed torsades de points precipitated by formaldehyde, and significantly (p < 0.05) reduced the number of ventricular ectopic beats triggered by alerting stimuli. In predisposed hearts, alerting stimuli precipitate arrhythmias by producing transient increases in sympathetic discharge in the ventricular myocardium. Vagally induced bradycardia with concurrent ventricular beta-adrenoreceptor activation may underlie development of torsades de points in patients with long QT syndrome precipitated by swimming, diving or facial immersion.

Key words  Long QT syndrome – ventricular repolarization – sudden death – ECG, ventricular arrhythmia

Introduction

Malignant cardiac arrhythmias are more likely to be triggered by acute psychological stress when there is pre-existing myocardial electrical instability, and when there is a background of chronic psychological stress or depression [11, 21, 29, 30]. Holter monitors and implantable cardioverters/defibrillator studies have documented the relationship between acute psychological stress and ventricular arrhythmias in predisposed individuals, as exemplified by the cardiac events precipitated by the Marmara earthquake [18] and the World Trade Center terrorist attack [20]. In patients with long QT syndrome, sudden arousing stimuli may precipitate ventricular arrhythmias within seconds [8, 43], suggesting that they are neurally triggered.

The acute proarrhythmic effects of brain stimulation have been clearly demonstrated in anesthetized animals (see [28] for review). Perhaps surprisingly, there have...
been few studies in conscious animals of the acute cardiac arrhythmogenic effects of psychological stress. To the best of our knowledge, arrhythmogenic effects of acute stressors in conscious animals with normal hearts have not been demonstrated. In conscious animals with post-infarct myocardial damage, arrhythmias do occur when the animal is exposed to an unfamiliar environment, or in a conditioned-fear paradigm reexposing the animal to an environment in which it was previously stressed [14, 37].

Many drugs acting on the delayed rectifier potassium channels alter myocardial excitability, resulting in acquired long QT syndrome and predisposing the patient to cardiac arrhythmias [9]. In particular, sotalol is still a valuable antiarrhythmic agent even though in predisposed patients it can itself provoke arrhythmias [17, 19]. In the present study, we have examined the ECG effects of sudden, brief alerting stimuli in conscious rabbits before and after electrical destabilization of the myocardiun by intravenous administration of dofetilide, a D-sotalol derivative. Our alerting stimuli included nasopharyngeal stimulation by inhalation of formaldehyde vapour, a procedure that elicits a vigorous diving-type reflex in rabbits [42]. In humans cardiac arrhythmias are known to be precipitated by similar stimuli (see references in Discussion). We determined whether stimulus-elicited arrhythmias occurring in dofetilide-treated rabbits are sympathetically mediated by testing the effects of beta-adrenergic blockade.

Methods

Experiments were carried out on 12 New Zealand White rabbits weighing 2.5 – 3 kg. All procedures were approved by the Flinders University Animal Ethics Committee. In preliminary surgery under a combined Midazolam (0.3 mg/kg i.m.)/Hypnorm (2 mg/kg i.m.) anesthesia, ECG Grass silver electrodes were implanted subcutaneously, with wires connected to a headpiece fixed to the skull by stainless steel screws and dental cement.

Experimental protocol

Experiments were performed in an isolated laboratory room, and particular care was taken to reduce external noises that could alert animals. On the day of the experiment, the marginal ear vein was catheterized under local anesthesia, and the rabbit was placed in a small experimental cage, covered with a drape and remained undisturbed for 30 min.

In the experimental group (n = 7), standardized alerting stimuli were presented at 1-min intervals in the following sequence: loud sound (96 dB, 5 KHz, 0.5 s), cage tap (with a trigger-controlled spring), cage movement (drop of back side of the cage from 2-cm height), pin-prick (with syringe needle), and nasopharyngeal stimulation (saturated paraformaldehyde vapour was blown in front of the rabbit’s nares for about 1 s). Five minutes following alerting stimulation, slow infusion of dofetilide was started using a syringe pump (341B, Sage Instruments, MA, USA). Under visual monitoring of the ECG, dofetilide was infused at a constant rate of 0.28 mg·kg⁻¹·min⁻¹ to a total dose of 5 mg/kg or until the occurrence of the first ventricular ectopic beat, whichever happened first. At this point, the infusion pump was switched off, and alerting stimuli were presented once again. Subsequently, propranolol (1.5 mg/kg, Sigma, USA) was injected i.v., and alerting stimulation was repeated twice, starting seven and 25 min after propranolol. In preliminary experiments, performed with alerting stimuli as described above, we found that proarrhythmic effect of dofetilide is reduced or abolished during subsequent (2 – 4 days later) drug administration. This hampered utilization of a conventional two-step experimental protocol, with administration of either propranolol or vehicle to dofetilide-treated animals. Our criterion for inclusion of animals into the experiment was occurrence of ectopic beats after dofetilide. Dofetilide (a gift from Pfizer, Sandwich, UK) was dissolved in acidified 20% DMSO in Ringer solution.

In the control group (n = 6), two types of experiments were performed on each animal. Experiment 1 was designed in a way similar to described above, except that vehicle was infused instead of dofetilide, and propranolol was not injected. In Experiment 2, animals received four consecutive intravenous injections of isoproterenol (2 μg/kg) separated by 20-min intervals. Five minutes prior to the third injection, propranolol (1.5 mg/kg) was injected i.v. On different days, Experiment 2 was repeated, with vehicle injected instead of propranolol. Both drugs were from Sigma (USA) and were dissolved in saline prior to injection.

Data acquisition and analysis

The headpiece was connected to the cardiomonitor (SpaceLab, USA) via a flexible cable. Analogue ECG signals were digitized at 1 KHz with MacLab (ADInstruments, Australia), and stored on a G3 Macintosh computer. Signal-averaged ECG was computed for 60 s periods, just prior to each sequence of alerting stimuli, using Chart software (ADInstruments, Australia). The following ECG intervals were detected: R-R, P-Q (from the P-wave onset to the Q-wave onset), Q-T_peak (from the Q-wave onset to the maximum of the T-wave) and Q-T_end (from the Q-wave onset to the end of the T-wave); T_peak - T_end was calculated from the two latter intervals. Corrected QT intervals (Rtcorr) were computed according to