Title : EFFECTS OF DANTROLENE ON EXCITATION-CONTRACTION COUPLING IN ISOLATED HEART MUSCLE

Authors : N. Roewer, M.D., E. Rumberger, M.D., J. Schulte am Esch, M.D.

Affiliation : Departments of Anaesthesiology and Physiology, University Hospital Eppendorf, Hamburg, West Germany

Introduction. Clinical observations indicate that intravenous dantrolene (D) can suppress cardiac arrhythmias associated with malignant hyperthermia (MH). It is not known whether this beneficial effect is due to the ability of D to relieve MH crisis in general or to a primary antiarrhythmic effect of D. Recent results about D obtained in isolated cardiac muscles have indicated, in contrast to the findings on skeletal muscle, that a sarcolemmal site of action may be of primary importance in cardiac muscle. Electrophysiologic studies upon Purkinje fibers[1] and ventricular muscles[2] suggest effects similar to those of Ca-channel blockers, such as verapamil. The purpose of this study was to elucidate the inotropic and electrophysiological effects of D on isolated ventricular myocardium.

Methods. Guinea pigs (300 – 400 g) were killed by cervical dislocation. Right ventricular papillary muscles were dissected from the freshly excised hearts in oxygenated tyrode solution and mounted in a recording chamber (volume: 0.8 ml), which was continuously perfused with tyrode solution (composition in mmol: NaCl 140, KCl 4.7, $CaCl_2$ 3.2, $MgCl_2$ 1.0, glucose 6.0, $NaHCO_3$ 11.4, NaH_2PO_4 0.38; pH 7.4) saturated with 97% O_2 and 3% CO_2. The temperature was maintained at 35 ± 0.5 °C and the flow rate through the chamber was 8 ml/min. The tendinous end of the muscle was connected to the arm of a mechano-electric transducer (type SS 201, Collins Corp., USA) for isometric tension measurements. The transducer was mounted on a micromanipulator which allowed carefully controlled stretching of the preparations to a length at which developed tension was maximal. The muscles were driven at 1 Hz by rectangular voltage pulses 4 ms in duration and about 10 % above threshold voltage through one concentric bipolar platinum electrode close to the base of the muscle. Glass microelectrodes filled with 3 mol KCl were used to impale muscle fibers and to monitor the transmembrane potential. Analog differentiation of the action potential (AP) was obtained with an electronic differentiator. AP, tension developement and upstroke velocity ($\dot{V}_{max}$) were monitored simultaneously on an oscilloscope (Tektronix, D 13) and converted to digital form (Tektronix, 5D10 waveform digitizer) for the final evaluation. A drug-free equilibration period of 60 min preceded each experiment. Then the muscles were exposed to D (100 µmol/l) over 90 min. Only measurements from continuous microelectrode impalements of one cell per preparation are reported. Stimulus intensity was increased to 8-fold threshold and frequency lowered to 0.5 Hz to elicit Ca-dependent slow AP in K-rich solution (24 mmol/l). Data are presented as mean values ± SD. Statistical analysis was performed by linear regression analysis or by unpaired t-test.

Results. D caused a 43.4 ± 4.9 % (n = 6, p < 0.0001) reduction of contractility. The duration of contraction was shortened (figure 1). The latent period between the upstroke of the AP and the onset of contraction did not change. D induced a significant prolongation of AP duration (APD) measured at the 90 % and 50 % repolarisation level, while APD_{20} was shortened like a plateau flattening. APD_{90} increased to 11.4 ± 1.6 % (p<0.01) of control value during 90 min D superfusion. The effects of D on APD_{90} and APD_{50} were significantly (p < 0.0001) dependent upon the frequency (0.25 – 2.0 Hz) of stimulation (figure 3). Resting potential, $\dot{V}_{max}$ and overshoot of normal (figure 1) and Ca-dependent slow AP (figure 2) were unaffected. Superfusion with drug-free solution for 4 hrs yielded only a partial wash-out of D effects, whereas a doubling of the extracellular Ca-concentration reversed D induced changes.

Discussion. The skeletal muscle relaxant dantrolene has a direct negative inotropic effect on ventricular myocardium. The decrease of contractility is not accompanied by a transmembrane influence such as an inhibition of fast Na- or slow Ca-channels. We observed no verapamil-like effect on the ventricular muscle. The only evidence of a direct transmembrane effect might be the increase of APD, possibly by a reduction of K-permeability. Alternatively, the effect could be explained by a secondary or indirect effect, such as a result of a reduced intracellular Ca-release, in line with the concept that intracellular Ca modulates the K-permeability in the heart muscle. The marked frequency-dependent prolongation of APD suggest antiarrhythmic properties of D.

References.

1. Salata J, Jalife J: Effects of dantrolene sodium on the electrophysiological properties of canine cardiac Purkinje fibers. J Pharmacol Exp Ther 220:157, 1982
2. Mészáros J, Kecskeméti V, Szegi J: Effect of dantrolene sodium on the mechanical and electrical properties of guinea pig ventricular myocardium. Arch Int Pharmacodyn 255 : 256, 1982

Figure 1

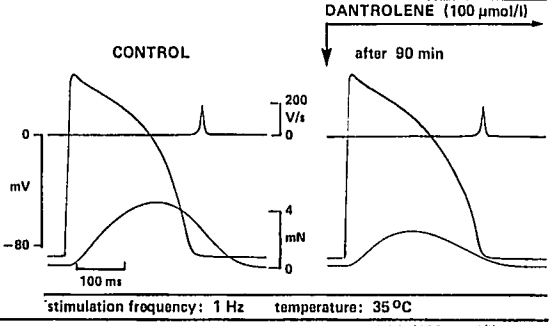

Figure 2

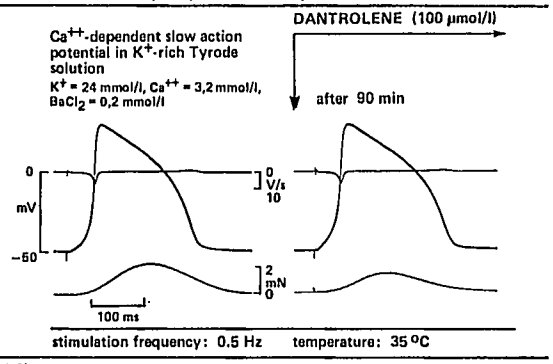

Figure 3