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AMILORIDE-QUINIDINE INTERACTION IN VITRO

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Quinidine (Qd) alters currents affecting both cardiac depolarization and repolarization. Amiloride (Amil) acidifies intracellular pH and such a pH change could modulate effects of Qd. Maximum rate of rise of phase 0 of action potential (Vmax), action potential duration at 95% repolarization (APD_{95}) and resting membrane potential (RMP) were measured in guinea pig papillary muscle at baseline, after pretreatment with Amil (1μM) or placebo (Plac) for 2 hours, followed by treatment with either Qd (2.5 or 10 μM), Amil, or Qd + Amil in combination for another 90 mins. Treatments were randomly assigned. Results: ($\bar{x}\pm SD$; Δ=changes from baseline; *=p<0.05 from Qd)

	ΔAPD(msec)	Δ RMP(mV)	Δ Vmax(V/s)
Amil (1μM) (n=6)	10.0 ± 6.0	1.0 ± 2.0	-3.0 ± 2.0
Qd (2.5μM)	13.8 ± 8.7	0.4 ± 0.5	-12.6 ± 3.5
Qd + Amil (n=10)	25.8 ± 6.7*	-0.4 ± 1.3	-21.6 ± 9.9
Qd (10μM)	11.0 ± 12.0	2.0 ± 3.0	-31.0 ± 23.0
Qd + Amil (n=22)	22.0 ± 5.0	1.0 ± 3.0	-82.0 ± 40.0*

Amil additively prolongs APD when combined with Qd. Amil alone does not decrease Vmax, however the decrease in Vmax with Qd+Amil is significantly greater than with Qd alone. In conclusion, amiloride causes a synergistic depression of Vmax when combined with quinidine.

A CELLULAR MECHANISM OF CYCLE LENGTH DEPENDENT AV NODAL "FACILITATION"

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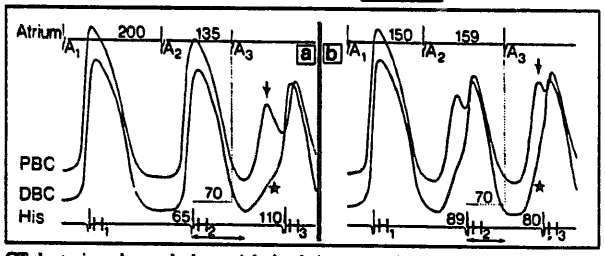
If a test atrial stimuli A_3 is applied at a fixed His-atrial (H_2A_3) coupling interval after a shorter preceding A_1A_2 interval, the resulting AV nodal conduction time (CT) A_3H_3 shortens (see figures). To study the mechanism of this paradoxical response, action potentials (AP) from different AV nodal cells were recorded using the above stimulation protocol in 10 superfused AV nodal rabbit preparations. A cycle-length dependent refractory barrier was identified between the N and NH regions. Typical responses of the proximal (PBC) and distal (DBC) barrier cells are compared below at A_1A_2 = 200 ms (panel a) and 150 ms (panel b) followed by a fixed H_2A_3 = 70 ms. The shorter A_1A_2 was associated with: 1. An obligatory longer A_2A_3 (159 ms vs 135 ms) due to the longer A_3H_3 (89 ms vs 65 ms). This led to a higher AP amplitude of PBC in response to the test beat A_3 (arrows). 2. A shorter AP (↔, measured after H_3) of the DBC which, at the fixed H_2A_3, led to a longer diastolic recovery of DBC. 3. A shorter A_3H_3 (80 ms vs 110 ms) which was related to a shorter step-delay (★) of DBC due to the combined action of 1. and 2. Conclusion: The AV nodal



CT shortening, observed when atrial stimulation protocols with fixed HA intervals are utilized, results from a complex mechanism. It includes a prolongation of the PBC coupling interval (a trivial, stimulation protocol dependent component) as well as possible enhancement of DBC excitability ("facilitation"). Evaluation of the differential role of these two components cannot be achieved with atrial stimulation.

MULTIPLEXING STUDY OF THE EFFECTS OF RAPID ATRIAL PACING ON THE DEVELOPMENT OF FUNCTIONAL AREAS OF SLOW CONDUCTION-COMPARISON OF A PERICARDITIS MODEL WITH NORMAL ATRIA

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Development of an area of slow conduction in the right atrial free wall is critical for the initiation and maintenance of atrial flutter (AFl) due to reentry in the canine sterile pericarditis (P) model. To test the hypothesis that an area of slow conduction induced during rapid atrial pacing (RP) depends on both the RP rate and the RP site, we analyzed isochronous maps during RP in 20 dogs, 10 P and 10 normal (N) dogs. Electrograms were recorded simultaneously from 190 right atrial electrodes (converted in software to 95 bipolar pairs) during both sinus rhythm and RP from the right atrial appendage (RAA) and the posterior left atrium (PLA). RP was performed at increasing rates until AFl or atrial fibrillation was induced. RP induced stable AFl in 9 P dogs, but only transient (<30 sec) atrial fibrillation in 10 N dogs. During RP at a 250 ms cycle length (CL), no area of slow conduction appeared. During RP at a 150 ms CL, areas of slow conduction appeared in 10 P dogs but no N dogs. In 8 N dogs, a small area of slow conduction was produced by RP at a CL ≤ 130 ms. In 3 P dogs, an area of slow conduction was produced by RP only from the PLA, in 2 N dogs only from the RAA, and in 7 P dogs and 6 N dogs from the RAA and PLA. The location of the area of slow conduction produced from the same RP site varied from dog to dog, but always occurred where the wave front crossed perpendicular to the longitudinal orientation of the atrial muscle fibers. CONCLUSIONS: 1) The ability of RP to induce AFl in P but not N dogs is related to the production of large areas of slow conduction in P but not N dogs; 2) the RP rate, direction of the activation wave front, and presence of P are important factors for producing areas of slow conduction with RP; and 3) areas of slow conduction are associated with apparent anisotropic conduction in P and N dogs.

UNIDIRECTIONAL CONDUCTION BLOCK CAUSED BY VARIATIONS IN PATHWAY GEOMETRY: A NEW MECHANISM FOR REENTRY

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Reentrant arrhythmias are common in diseased myocardium where regions of normal tissue are interspersed with inexcitable tissue. We hypothesized that reentry may occur due to unidirectional block caused solely by variations in path width (PW) through diseased myocardium. To determine the exclusive role of pathway geometry a 16,000 cell grid (128x128) was modeled using the modified FitzHugh-Nagumo equations on a massively parallel computer (Connection Machine). Corridors of isotropic and uniformly excitable normal tissue of varying PW's surrounded by inexcitable tissue were created and conduction velocity (CV) measured following a single stimulus. CV increased with PW reaching a plateau speed where further increases in PW had no effect on CV (Fig. 1). Below a critical PW, decremental conduction was observed with impulses eventually dying out. This phenomenon was explained by the CV dependence on wave front curvature. During repetitive stimulation the critical PW for propagation also depended on the magnitude of the residual outward current. In paths with "funnel" shaped geometries (decreasing PW), unidirectional block was observed: impulses entering from the narrow end of the funnel propagated, while impulses entering from the wide end died out. Appropriate stimuli can induce reentry around one or multiple funnel shaped structures (Fig. 2). We conclude that reentry may occur in diseased myocardium due solely to variations in PW.

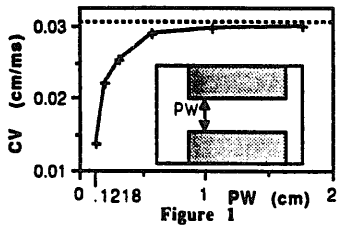

Figure 1

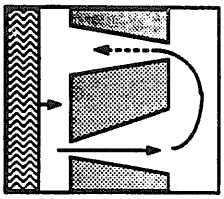

Figure 2