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'Undoing' of Electrical Remodeling by BAY Y 5959 Terminates Atrial Fibrillation in the Goat

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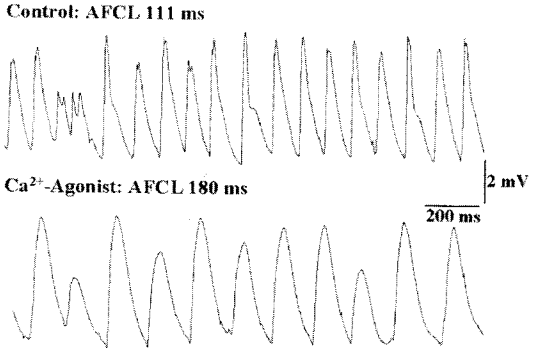
Background: Development of persistent atrial fibrillation (AF) is promoted by atrial electrical remodeling based on downregulation of the L-type Ca^{2+} current. We tested the hypothesis that a Ca^{2+}-channel agonist can partly 'undo' the effects of electrical remodeling in fibrillating atria. Methods: In 4 goats with pacing induced AF(5-21days) the Ca^{2+}agonist BAY Y5959 was infused (50μg/kg/min). Endocardial monophasic action potentials (MAP) were recorded from the right atrium. AF cycle length (AFCL) and MAP duration were measured. Results: In all goats AF cardioverted to sinus rhythm shortly after infusion of BAY (4-11 min). AFCL increased from 116$\pm$7 to 155$\pm$12ms ($p<0.05$) prior to cardioversion. This increase in AFCL was due to prolongation of the MAP duration (see figure). Reinitiation of AF by burst pacing only induced paroxysms of short duration (21-480 sec). Conclusions: Intravenous administration of a Ca^{2+}-agonist in electrically remodeled atria markedly prolongs the action potentials during AF. This causes prolongation of AFCL and termination of atrial fibrillation. This observation warrants further exploration of a possible role of Ca^{2+}-agonists in pharmacological cardioversion of AF.



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Alterations of Both Conduction and Automaticity Can Explain the Irregular Ventricular Response during Supraventricular Tachycardias: Direct Recordings from the AV Junction

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There has been controversy regarding whether the mechanism to explain the irregular ventricular response during atrial tachycardia (AT) or atrial fibrillation (AF) was due to conduction or automaticity. METHODS. We studied 12 Langendorff preparations perfused with Tyrodes solution containing 5-10mM diacetyl monoxime. The latter mitigated contraction allowing the use of intracellular action potential (AP) recordings. The right atrial free wall was excised along with the sinus node in order to expose the AV junction. Pin electrodes in the bath were used to record standard ECG leads from the volume conductor. In addition, an octapolar catheter (2mm rings, 2mm spacing) was secured along the tricuspid annulus from the apex to the base of the triangle of Koch to record both His bundle (Hb) and AV nodal potentials (AVNP). All extracellular recordings were filtered between 0.1-250 Hz. RESULTS. During 16 spontaneous junctional rhythms a low amplitude (average, av: 107$\pm$54μV) long duration (av: 92$\pm$25 msec) AVNP consistently preceded Hb activation (av: 92$\pm$25 msec) in 12 with 4 showing the Hb potential as the earliest deflection. Validation was obtained with AP recordings from the AV node and Hb cells. AT or AF induced by rapid atrial pacing showed a variety of irregular ventricular responses: 1) repetitive concealed conduction leading to irregular ventricular responses each of which were preceded by AVNPs and Hb waveforms with fixed intervals to the QRS. The QRS was unchanged from that seen with 1:1 AV conduction 2) repetitive concealed conduction inducing complete AV block with a slow Hb escape rhythm not preceded by AVNPs. 3) fascicular escape rhythm inducing fusion beats. 4) Hb escapes during 2:1 and higher grade AV block. CONCLUSION. Extracellular and intracellular recordings from the AV node and Hb indicate that both repetitive concealed conduction or electrotonic inhibition and enhanced automaticity can play a role in the irregular ventricular response seen during AT or AF.

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The Effect of Electrical Restitution on the Stability of Scroll Reentry in Anatomically Realistic Simulated Rabbit Ventricles

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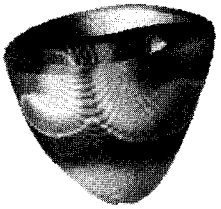
Numerical simulation studies have demonstrated that restitution of action potential duration (APD) plays a crucial role in the stability of spiral and scroll wave reentry in both homogenous and heterogeneous cardiac tissue slabs. Whether this holds true for an anatomically-realistic model of the ventricles has not yet been demonstrated. In simulated homogeneous 3D tissue, four different phenotypes of scroll waves (stable, meandering, hyper-meandering and breakup) were generated by reducing the maximum conductance of the Ca current to alter the slope of APD restitution in the Luo-Rudy action potential model. We examined whether the same scroll wave phenotype was retained when reentry was initiated in a model of the rabbit ventricles which incorporates realistic anatomical features including anisotropic fiber rotation. We find that: 1) With a flat APD restitution curve, an initiated single or double scroll wave remains stationary or meanders weakly, depending on the initiation protocol. 2) As APD restitution becomes steeper, the initiated scroll wave displays chaotic meandering or breakup, which sometimes terminated due to small tissue size. 3) Anisotropic fiber rotation in the ventricular model reduces the threshold of APD restitution steepness required to induce breakup. In conclusion, in an anatomically-realistic model of the rabbit ventricles, APD restitution steepness remains an important determinant of scroll wave stability, suggesting that reducing the dynamic instability of cardiac cells by interventions which flatten APD restitution steepness may have merit as an antifibrillatory strategy.



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Defibrillation Model of Langendorf Perfused Rabbit Heart Exhibits No Transmural Reentry

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Although optical mapping has advanced understanding of defibrillation and shock-induced arrhythmogenesis, due to experimental limitations it is not yet possible to examine the role of transmural activations . We use a realistic bidomain model of a Langendorff perfused rabbit heart to *provide for the first time information regarding post-shock electrical activity in the transmural direction and to ascertain if post-shock transmural reentry occurs in such a preparation*. Methods: We have developed a 3D active bidomain finite element model of anatomically accurate rabbit ventricles that incorporates fiber architecture. Tachyarrhythmia is induced by rapid epicardial pacing, and after several seconds of self-sustained activity, a strong monophasic shock is delivered between base and apex. Results: The figure illustrates shock-induced virtual electrode polarization on the epicardial surface (left) and in a transmural direction (right) for a shock strength of 109 mA. Transmural electrical activity is present immediately following the shock; break wavefronts induced as a result of tissue-blood interface polarization on the endocardium propagate transmurally. However, following failed shocks, no post-shock transmural reentry and no isoelectric window is observed; the reentrant circuits are confined to the epi- and endocardial surfaces. Conclusions: This study provides for the first time information regarding post-shock transmural activity in the Langendorff-perfused rabbit heart.