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904-4 Cardiogenic Shock Complicating Acute Myocardial Infarction in California: Effect of Invasive Procedures on Mortality

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Background: Cardiogenic shock is an infrequent complication of acute myocardial infarction (AMI) that is associated with a very poor prognosis. Recent studies suggest an aggressive invasive approach reduces mortality.

Methods: We analyzed data from the 1994 California discharge data base to determine the resource utilization and outcome in a non-selected patient population with cardiogenic shock complicating AMI.

Results: Cardiogenic shock was diagnosed in 1122 patients as a complication of AMI. Mean age was 70.4 years, 54.7% were male, 20.3% were diabetics, and AMI was most commonly anterior (40.0%). Thrombolytic therapy was administered in 17.2% of patients. Pulmonary artery catheterization was utilized in 26.9% of patients, while 28.1% underwent placement of an intra-aortic balloon pump. Coronary angiography was performed in 40%, with 24.2% and 16.5% of patients eventually undergoing either coronary angioplasty or coronary artery bypass surgery (CABG). The overall in-hospital mortality was 50.1%. Significant reductions in mortality were noted in patients undergoing either angioplasty or CABG by multivariate analysis. The use of angioplasty was associated with a reduction in mortality from 62.8% to 32.9% ($p = 0.0001$), while those undergoing CABG had a decrease in mortality from 60.1% to 23.4% ($p = 0.0001$). There were non-significant trends in reduction of mortality with the use of intra-aortic balloon pumps and pulmonary artery catheters.

Conclusion: This study supports data documenting improvements in outcome with the invasive management of cardiogenic shock, and suggests that these procedures may be underutilized in this population.

905 Molecular Electrophysiology

Wednesday, April 1, 1998, 4:00 p.m.–5:00 p.m.
Georgia World Congress Center, Room 254W

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905-1 Molecular Localization of a Titratable Histidine Residue in the Intracellular pH Modulation of Human Kv1.4 N-type Inactivation Kinetics

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Inactivation of A-type K^+ currents is modulated by electrostatic interactions between the channel ball domain and its receptor. Since the charge of proteins is tightly regulated by pH, we examined the effect of pH on the inactivation kinetics of the human Kv1.4 channel (HK1) expressed in *Xenopus* oocytes using patch-clamp techniques on inside-out patches. We found that both HK1 current inactivation rate (τ) and peak current amplitude (I_{peak}) were tightly regulated by intracellular (pH_i) but not by extracellular pH. There was a four-fold change in τ and I_{peak} when pH_i changed from 6.0 to 8.0. HK1 τ increased from 30.5 ± 5.1 ms to 73.5 ± 19.2 ms ($n = 7$, $p = 0.002$) with a pH$_i$ change from 7.2 to 8.0 while τ decreased from 39.2 ± 3.2 ms to 18.4 ± 2.2 ms ($n = 4$, $p = 0.002$) with a pH$_i$ change from 7.2 to 6.0. The H^+ titration curve of inactivation τ showed a pK of 7.59 and that for I_{peak} was 7.50. The pH$_i$ effects on HK1 were not dependent on membrane voltages (−40 to +60 mV). The pH$_i$ effects were completely abolished when the HK1 N-terminus was deleted (Δ2-145) indicating that these effects were mediated through modulation of N-type inactivation. The H16S mutation eliminated H^+ titratability in the physiological pH range and altered the pK of τ changes to 6.60 and the pK of I_{peak} changes to 6.81 ($n = 14$). These results suggest that N-type inactivation in HK1 is regulated by pH$_i$ in the physiologic range through ionization of specific amino acid residues in the ball domain of the channel protein.

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905-2 Cell Swelling Increases L-type Ca^{2+} Channel Current and the Amplitude of Ca^{2+} Shortening in Ventricular Myocytes

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Background: It has been suggested that mechanical stretch may enhance the L-type Ca^{2+} channel current (I_{Ca}) in atrial cells. This can consistently explain the Frank-Starling mechanism if it also operates in ventricular cells. Thus, we studied the effects of cell swelling on I_{Ca}, intracellular free Ca^{2+} ($[Ca^{2+}]_i$), and cell shortening (CS).

Methods: We simultaneously measured I_{Ca} (whole cell patch clamp), $[Ca^{2+}]_i$ (indo-1) and CS (video motion detector) in isolated guinea pig ventricular myocytes. Cell volume was estimated by tracing cell area on video. To obtain cell swelling, cells were superfused with isotonic solution including 150 mM mannitol for 2 min and subsequently with hypotonic solution without mannitol.

Results: Exposure to hypotonic solution significantly increased I_{Ca} (by 42 ± 4%, $P < 0.01$), the amplitude of CS (by 28 ± 9%, $P < 0.01$) and cell area (by 5.1 ± 1.5%) within 3 min ($n = 6$) when pipette solution not including EGTA. We also confirmed increases in $[Ca^{2+}]_i$ and the amplitude of CS in the indo-1 loaded cells. When 10 mM EGTA included in the pipettes, swelling-induced increase in I_{Ca} was even larger (+68 ± 8%, $n = 19$) without changes in inactivation time, indicating that cell swelling does enhance I_{Ca}. Moreover, 10 μM bumetanide, which inhibits hypotonic swelling by blocking $Na^+/K^+/2Cl^-$ cotransport, attenuated this increase in I_{Ca}.

Conclusion: Cell swelling by exposure to hypotonic solution increased I_{Ca} and the amplitude of CS, suggesting that cell stretch may increase the contractility of ventricular cells by increasing I_{Ca}.

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905-3 Role of External Potassium in the Block of the Delayed Rectifier Potassium Current by Dofetilide

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Myocardial infarction is often accompanied by an increase in the extracellular K^+ concentration ($[K^+]_o$), while hypokalemia has been related to torsades de pointes tachyarrhythmias. The aim of this work, was to determine whether changes in $[K^+]_o$ would affect the block of the delayed rectifier K^+ current (I_K) by dofetilide (DOF). Whole cell patch-clamp experiments were performed in isolated guinea pig cardiomyocytes. Depolarizing pulses of 200, 500 and 2000 ms were applied to assess possible differential effects on the rapid (I_{Kr}) and the slow (I_{Ks}) components of I_K. Elevating $[K^+]_o$ from 3.5 to 10 mM decreased the tail current ($I_{K\,tail}$) by 29 ± 5%, 46 ± 3% and 54 ± 2% at 200, 500 and 2000 ms, respectively ($p < 0.05$). reducing $[K^+]_o$ from 3.5 to 1 mM increased $I_{K\,tail}$ by 29 ± 6%, 48 ± 7% and 55 ± 7% at 200, 500 and 2000 ms, respectively ($p < 0.05$). In both cases changes were larger at 2000 than at 200 ms, suggesting that I_{Ks} was the component of I_K most strongly affected by $[K^+]_o$. At 10 mM $[K^+]_o$, 10^{-7} M DOF decreased $I_{K\,tail}$ to a lesser extent than at physiological $[K^+]_o$ (−23 ± 7% vs −41 ± 7% at 200 ms, respectively, $p < 0.05$), although the relative contribution of I_{Kr} to total I_K was increased. At 1 mM $[K^+]_o$, 10^{-7} M DOF blocked $I_{K\,tail}$ to a similar extent compared to physiological $[K^+]_o$ (−41 ± 5% vs −41 ± 7% at 200 ms, respectively). Since the relative contribution of I_{Kr} to total I_K was decreased in hypokalemia, enhancement of I_{Kr} block by DOF at low $[K^+]_o$ is suggested.

Conclusions: 1) At high $[K^+]_o$, I_{Kr} block by DOF is reduced; this may imply a loss of efficacy during ischemia. 2) Block of I_{Kr} by DOF may be enhanced by hypokalemia, thus favoring proarrhythmic events.

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905-4 Differences Between the Delayed Rectifier K^+ Currents in Myocytes From Rabbit Sinoatrial and Atrioventricular Nodes

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Background: Recent experimental work has suggested that the delayed rectifier K^+ currents (I_K) in rabbit sinoatrial node (SAN) and atrioventricular node (AVN) are different. We have studied the electrophysiological differences of I_K in SAN and AVN cells by using Ibutilide, a recently developed antiarrhythmic agent which may function as a blocker of the rapid delayed rectifier K^+ current, $I_{K,R}$.

Methods: Rabbit SAN and AVN cells were isolated using collagenase and protease. Spontaneous action potentials and membrane currents were recorded using conventional membrane-ruptured or nystatin-permeabilized patch method.

Results: Superfusion with 100 nM Ibutilide caused decreases in the spontaneous firing frequency, maximal diastolic potential and prolongation of the action potential duration in both SAN and AVN cells. In the whole cell voltage clamp experiments, 100 nM Ibutilide blocked I_K, Ca^{2+} current and hyperpolarization-activated inward current of SA node cells by 40%, 10% and 11%, respectively ($n = 6$) and also reduced these currents in AVN cells by 68%, 13% and 10%, respectively ($n = 6$). 1 μM Ibutilide decreased $I_{K\,tail}$ in SAN cells by 67 ± 8%, whereas it blocked $I_{K\,tail}$ almost completely in AVN cells.