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AN INCREASE IN CO_2 LEVELS BY UPREGULATING LATE SODIUM CURRENT IS PROARRHYTHMIC IN THE HEART

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Increased CO_2 levels in general circulation and/or in the myocardium are common under pathological conditions. To test the hypothesis that an increase in CO_2 levels, but not just the subsequent extra- or intra-cellular acidosis, would augment late sodium current (INa,L) and contribute to arrhythmogenesis in hearts with reduced repolarization reserve. Monophasic action potential durations at 90% completion of repolarization (MAPD90) from isolated rabbit hearts, INa,L and extra- (pHo) and intra-cellular pH (pHi) values from cardiomyocytes using the whole-cell patch-clamp techniques and BCECF-AM respectively, were measured. Increasing CO_2 level from 5% to 10% and 20% and administration of 1 nM sea anemone toxin (ATX)-II increased INaL and prolonged both epi- and endo-MAPD90 (n=7 and 10) without causing arrhythmic activities. Compared to 5% CO_2, 10% and 20% CO_2 decreased pHo and pHi, in hearts treated with 1 nM ATX-II caused a greater prolongation of MAPD90 and elicited ventricular tachycardias. Increasing CO_2 levels from 5% to 10% and 20% with pHo remained at 7.4 produced smaller changes in pHi ($P < 0.05$) but similar increase in INa,L prolongation in MAPD90 and incidence of ventricular tachycardias (n=8). Inhibition of INa,L reversed the increase in INa,L suppressed MAPD90 prolongations and ventricular tachycardias induced by 20% CO_2. Increased phospho-CaMKIIδ and phospho-NaV1.5 protein levels in hearts treated with 20% CO_2 was attenuated by eleclazine. In conclusion, increased CO_2 levels enhance INa,L and are proarrhythmic factors in the heart with reduced repolarization reserve, possibly through mechanisms related to the phosphorylations of CaMKIIδ and NaV1.5.

BIOGRAPHY

Lin Wu received his MD Degree from Beijing Medical University, completed his Postdoctoral training at the University of Florida and worked as a Senior Research Scientist at CV Therapeutics and Gilead Sciences in California, USA. Now he is a full-time Professor and Chief Physician at Department of Cardiology, Peking University First Hospital, China. He has made important contributions to our understanding of the role of endogenous and enhanced late sodium current in ventricular and atrial arrhythmias. He has in-depth experience in cardiac electrophsiology, especially in late sodium current-associated cardiac arrhythmias and myocardial ischemia, evidenced by 36 world-circulated reputed journals and over 34 presentations at international scientific conferences.

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