The role of depolarising and repolarising currents in the induction of early afterdepolarisations during acute hypoxia in ventricular myocytes

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Ventricular arrhythmia is a major cause of death in patients suffering from myocardial infarction. Arrhythmias typically occur as a result of re-entrant excitation or increased automaticity in and around the infarct zone. Early afterdepolarisations (EADs), thought to be responsible for re-entry like activity, are depolarisations of the membrane during phase 2 or 3 of the cardiac action potential and require an inward current large enough to increase total inward membrane current. Acute hypoxia (decreasing PO_2 from 150 mmHg to 17 mmHg) is not energy limiting but can alter the function of a number of ion channels. Acute hypoxia decreases the transient Na^+-current ($I_{Na\text{-}T}$) but increases the persistent Na^+-current ($I_{Na\text{-}P}$) (Ju *et al*. 1996). Acute hypoxia also decreases the basal current through the L-type Ca^{2+} channel ($I_{Ca\text{-}L}$) (Hool, 2000) and decreases the slow component of the delayed rectifier K^+ channel (I_{Ks}) but not the rapid component (I_{Kr}) (Hool, 2004). Coronary occlusion is also associated with an increase in circulating and tissue catecholamines. Acute hypoxia increases the sensitivity of $I_{Ca\text{-}L}$ to β-adrenergic receptor stimulation (Hool, 2000). However, hypoxia also increases the sensitivity of I_{Ks} to β-adrenergic receptor stimulation, without altering I_{Kr} (Hool, 2004) which may counteract the effects of hypoxia on $I_{Ca\text{-}L}$. The net effects of acute hypoxia in the absence and presence of β-adrenergic receptor stimulation on the cardiac action potential are not known.

We incorporated all the published data reporting the effects of acute hypoxia on cardiac ion channels into the Luo-Rudy model. We then compared the results obtained from the model to experimental data obtained from ventricular myocytes isolated from anaesthetised adult guinea pigs using the current clamp configuration of the patch clamp technique. Our modelled data predicts that acute hypoxia has little effect on resting membrane potential (RMP, −88 mV *vs* −88 mV), action potential peak (APP, 47 mV *vs* 45 mV) and action potential duration (APD, 225 mV *vs* 219 mV). Furthermore, hypoxia alone could not trigger EADs. We then kept the values of all other channels at normoxic levels and only modified $I_{Ca\text{-}L}$ to hypoxic conditions. In the presence of the β-adrenergic receptor agonist isoproterenol (Iso) at a concentration of 0.6 nmol/L, (sub-threshold concentration during normoxia), hypoxia significantly prolonged APD to 450 ms and induced EADs. When this was repeated for I_{Ks} alone, there was no substantial change in APD and no EAD generation. Modelling the effects of hypoxia on $I_{Ca\text{-}L}$ and I_{Ks} together also prolonged APD and induced EADs indicating that any anti-arrhythmic effect of I_{Ks} is only small and that the effects of hypoxia and β-adrenergic receptor stimulation on $I_{Ca\text{-}L}$ predominate.

Our experimental data corresponded well with our modelled data. Acute hypoxia (PO_2 of 17mmHg) had little effect on RMP (−67 ± 3 mV *vs* −68 ± 2 mV), APP (56 ± 2 mV *vs* 56 ± 2mV), APD (227 ± 19 ms *vs* 221 ± 18 ms, $n = 9$). In the presence of 1 or 3 nmol/L Iso and hypoxia there was no change in RMP or APP but a significant increase in APD by 10% ($n = 5$, $p = 0.036$) and 20% ($n = 7$, $p = 0.022$) respectively were recorded. Three of the seven cells exposed to 3nmol/L Iso and hypoxia developed EADs and spontaneous tachycardia. This is in contrast to normoxic conditions where 3nmol/L Iso did not alter any action potential parameters ($n = 4$, all $p > 0.5$). We conclude that during acute hypoxia, EADs are induced predominantly as a result of an increase in the sensitivity of the L-type Ca^{2+} channel to β-adrenergic receptor stimulation.

Hool LC. (2000) *Circulation Research*, **87:** 1164-71.
Hool LC. (2004) *Journal of Physiology*, **554:**743-54.
Ju YK, Saint DA & Gage PW. (1996) *Journal of Physiology*, **497:** 337-47.