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# The effects of carbon monoxide on the heart

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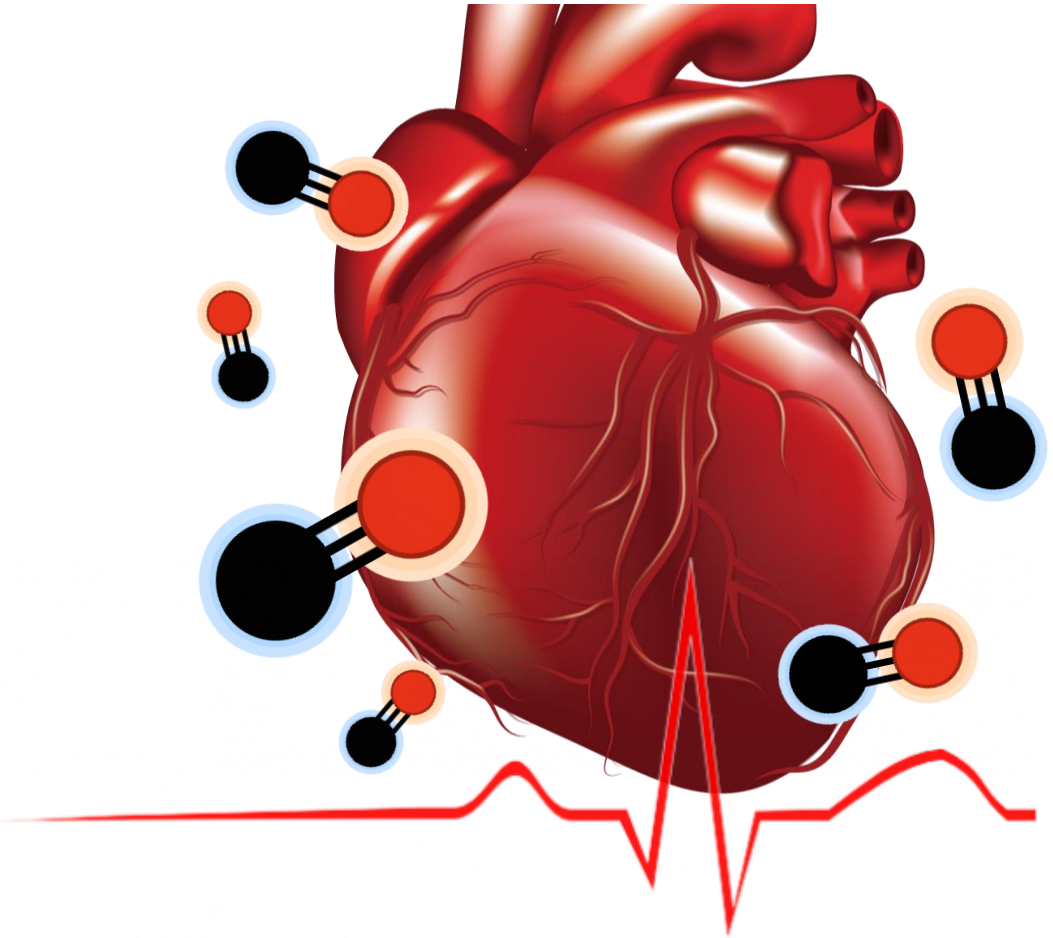
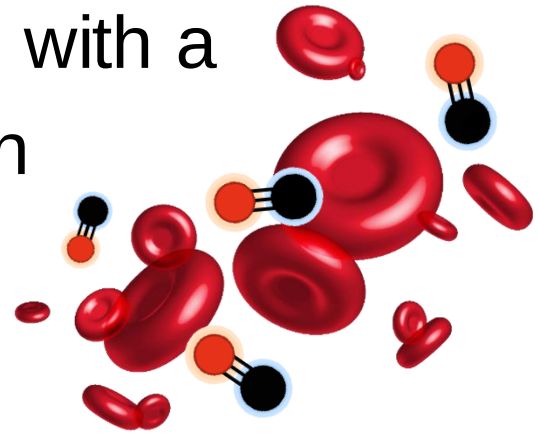


LEEDS MCRC

# Acute or chronic CO exposure is common

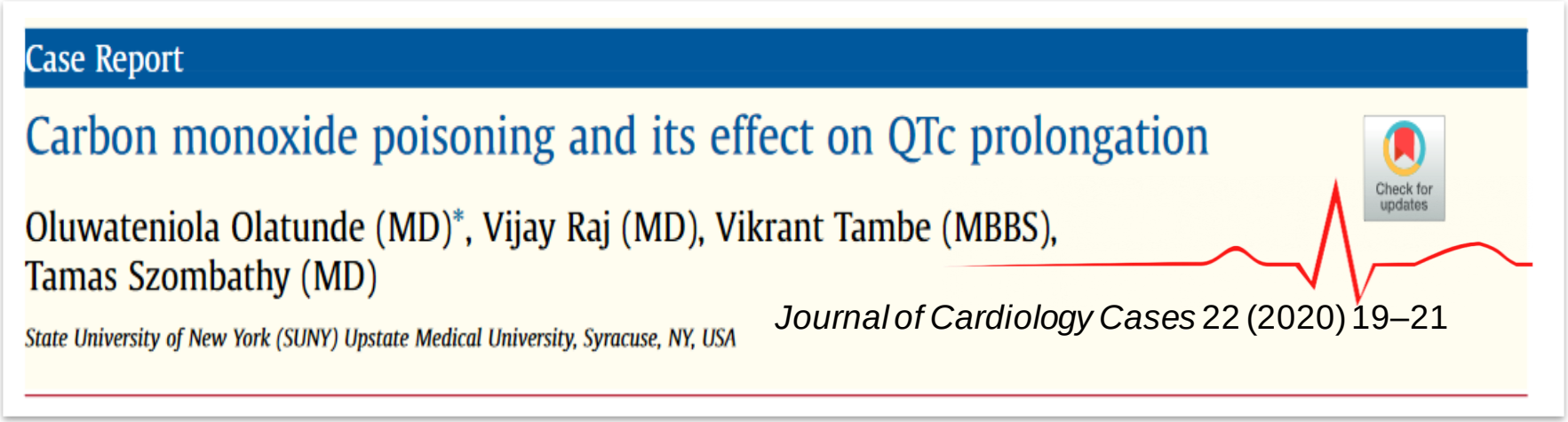
Toxic, odourless, colourless, tasteless gas with a higher affinity for haemoglobin than oxygen



- Faulty gas appliances
- Solid fuel appliances with inadequate ventilation
- Smokers
- Firefighters
- Workers in close proximity to traffic
- Pedestrians
- Those living in town or city centres

# CO exposure affects cardiac function

- Clinical reports have shown that CO exposure can cause in an irregular heart rhythm
- Prolongation of the ECG ‘QT’ interval is a commonly reported clinical outcome



Case Report

Carbon monoxide poisoning and its effect on QTc prolongation

Check for updates

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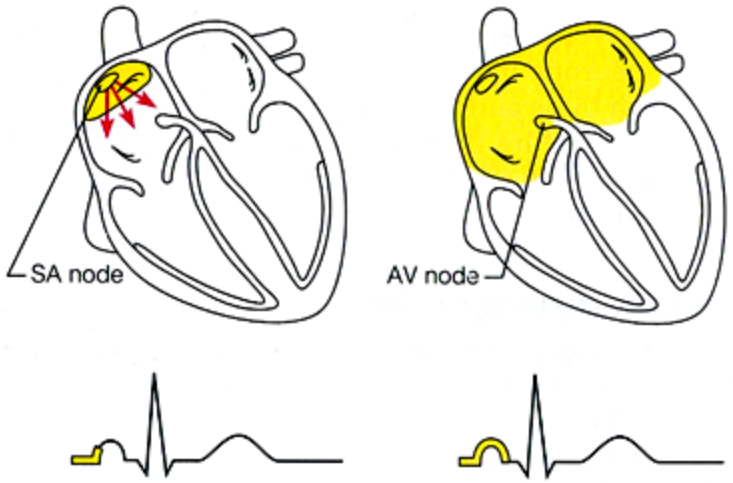
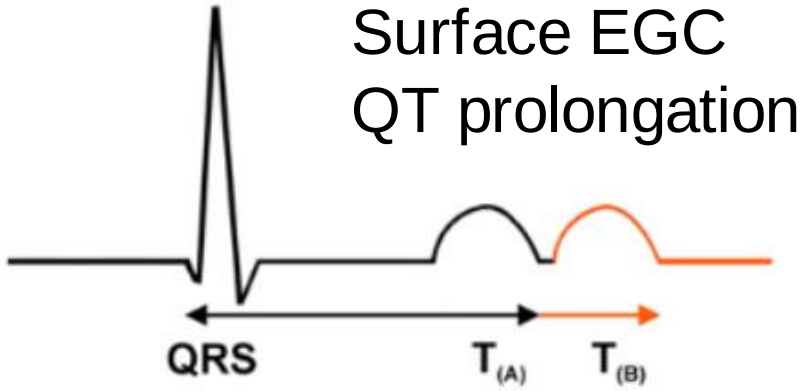
*Journal of Cardiology Cases* 22 (2020) 19–21

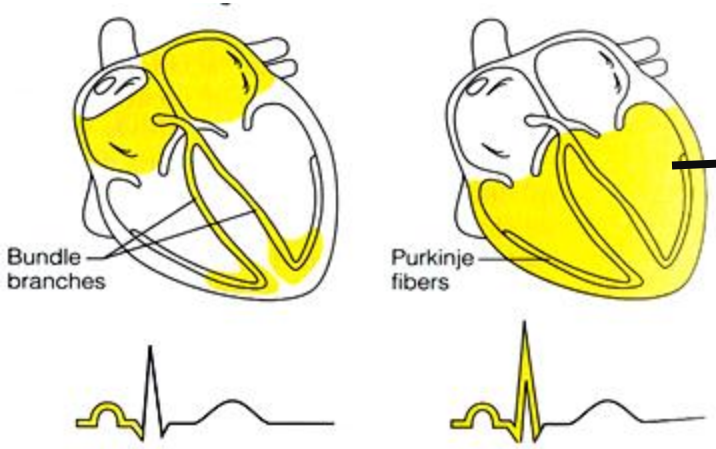
Normal QTc interval <440 ms, following CO exposure, QTc = 622 ms

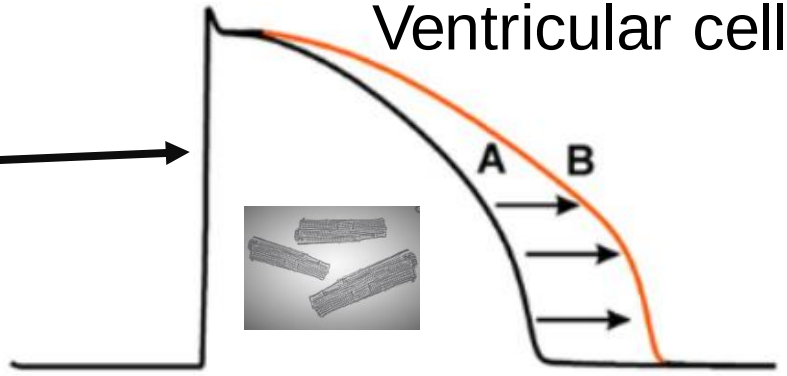
# Cardiac electrical activity and CO exposure




Surface EGC
QT prolongation



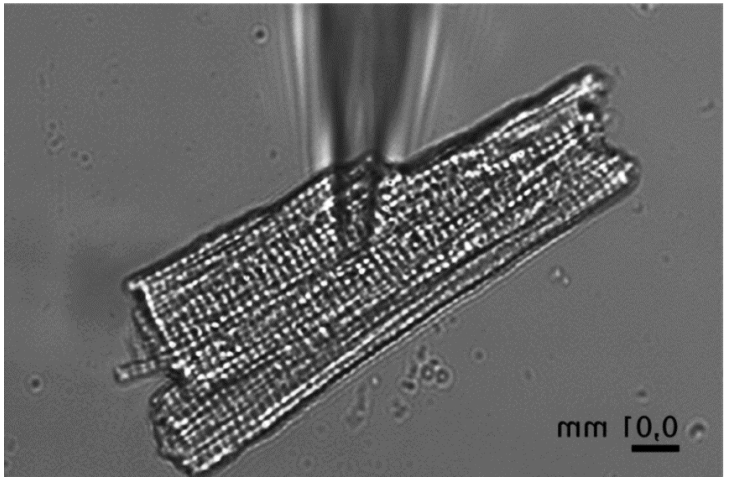




Ventricular cell AP

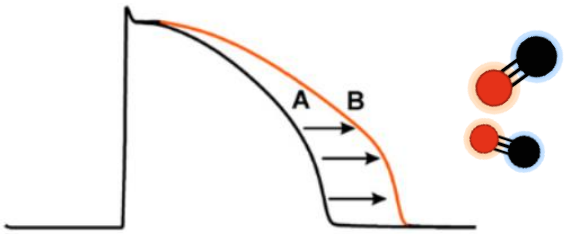
Hancox Pharmacology & Therapeutics 119 (2008)

# Studying effects of CO on isolated cardiac cells

- Patch clamp recording
- Solutions bubbled with CO or
- CO releasing molecules CORM-2 or CORM-3
- Effects of CO on action potentials in isolated cardiac (ventricular) cells
- Effects of the function of ion channels that underlie the shape of the action potential

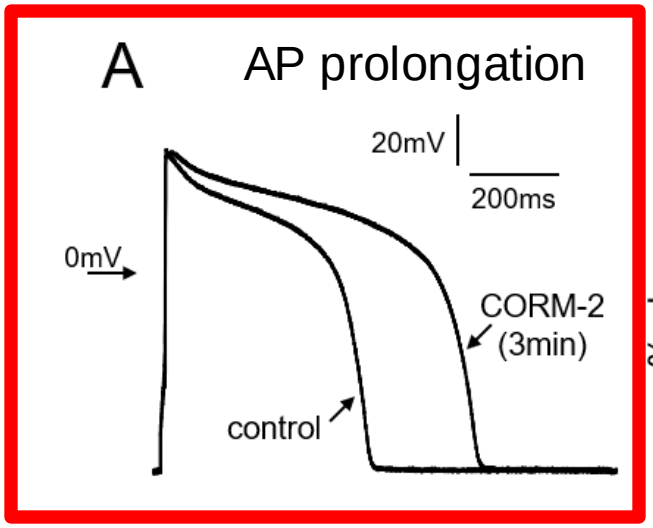


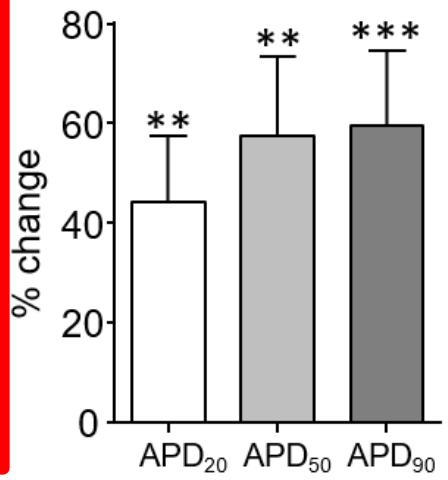

Patch clamp recording of single cell electrical activity

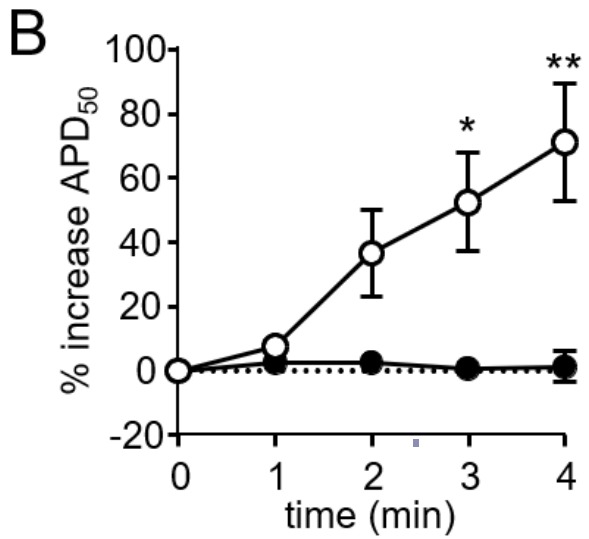


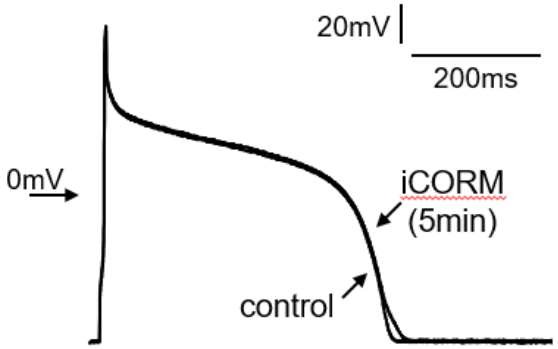

Hancox, Pharmacology & Therapeutics 119 (2008)

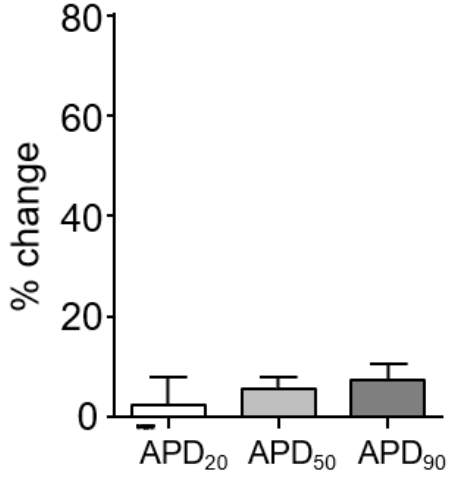
# Effects of CO on guinea pig cardiac cells

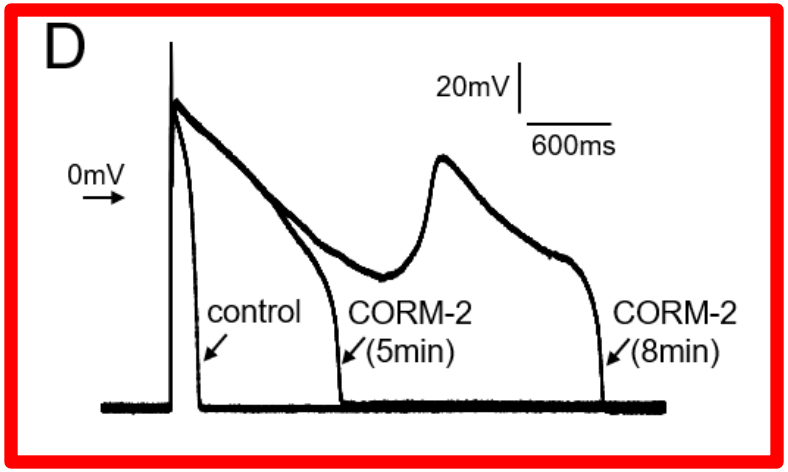


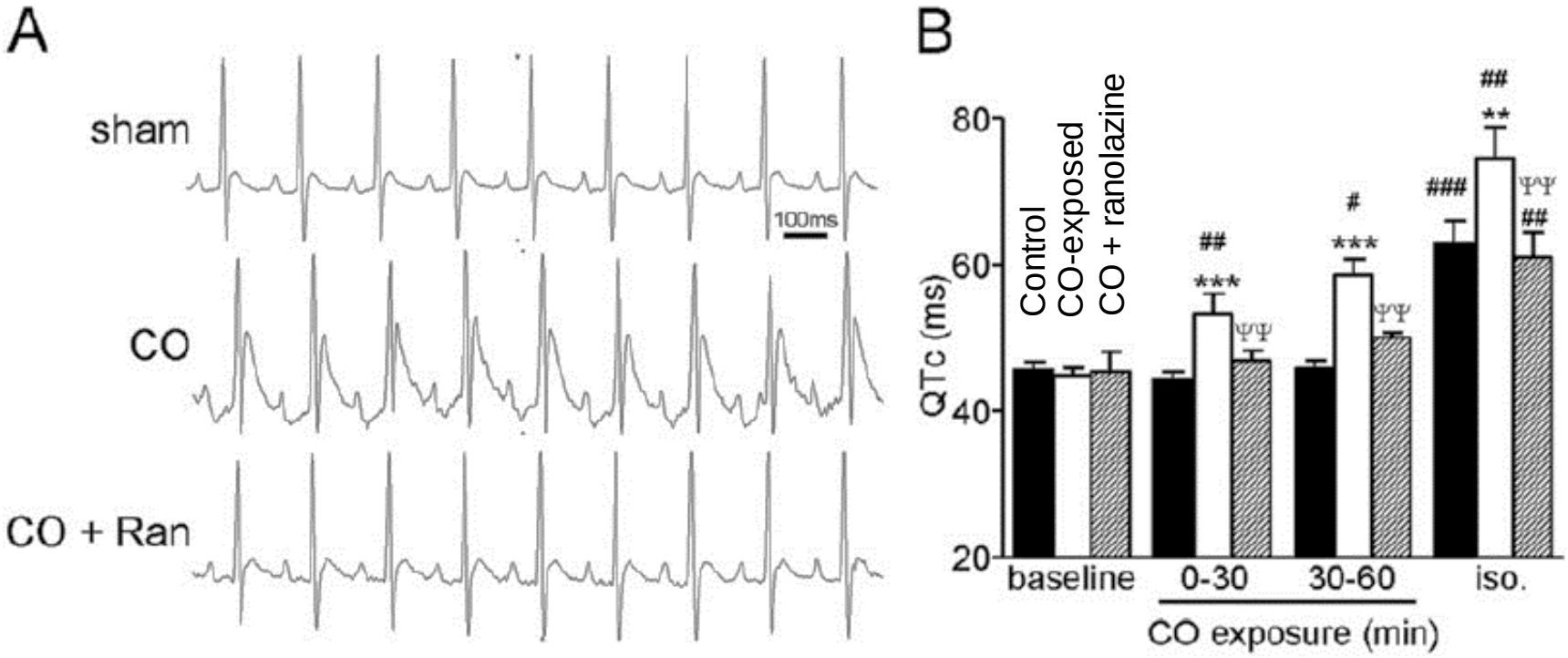




Arrhythmic activity (EADs)

Al-Owais *at al*., *FASEB J* 2017 31:4845-4854.

# *In vivo* ECG changes in rats exposed to CO

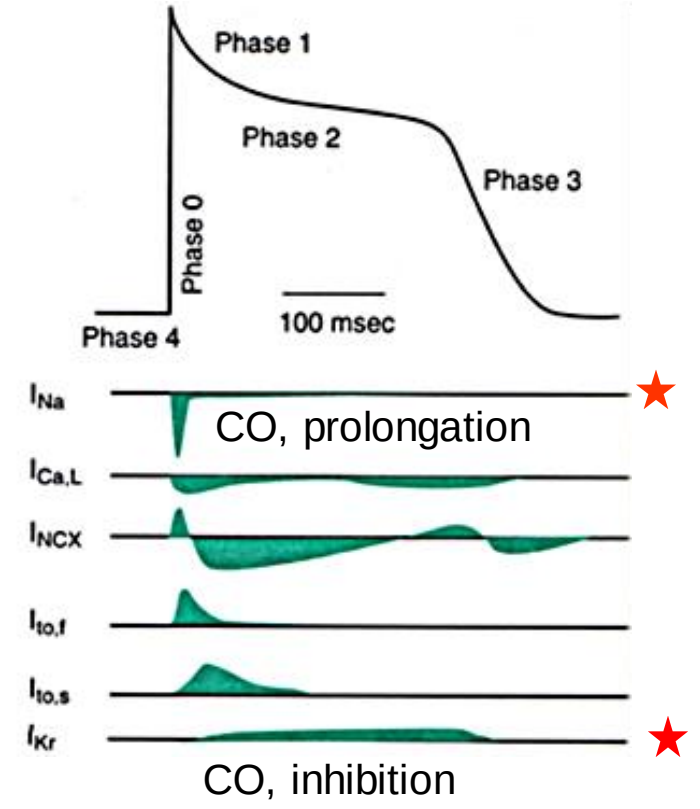


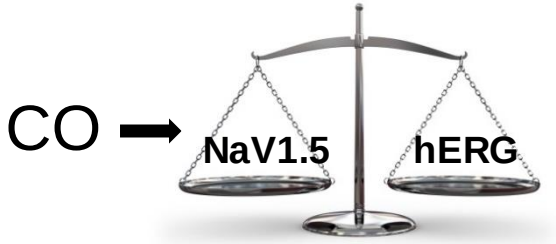

- In CO exposed rats, QT prolongation can be "switched off" by the drug ranolazine

Dallas *et al*., *Am J Respir Crit Care Med* 2012 **186**:648-56.

# Mechanism, relevance to man and possible treatment

- In man, we know that CO causes action potential (and QTc interval) prolongation and arrhythmias
- Our work on animal heart cells has identified the $Na^+$ channel (Nav1.5) and the (h)ERG $K^+$ channel (Kv11.1) as sites of action for CO
- In man, the relative effect of CO on **Nav1.5** and **hERG** will determine the primary proarrhythmic mechanism **AND** the choice of drug therapy

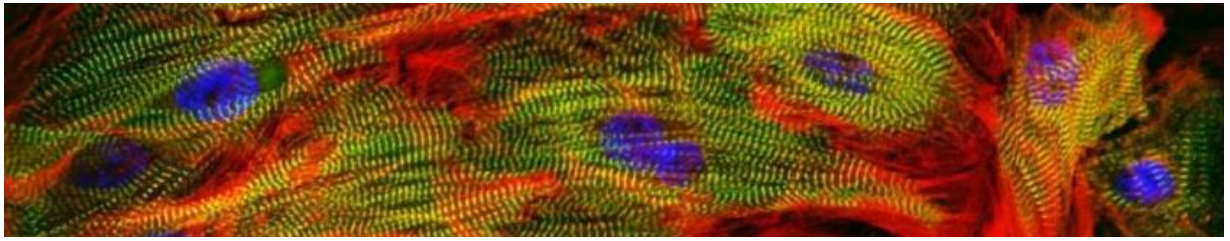



Arrhythmia mechanism

# Future directions and recently funded CORT study

- In a project funded by CORT, our aim is now is to identify a drug therapy that can “switch off” CO-induced arrhythmias in man
- Healthy human cardiac cells cannot be produced routinely from clinical samples of heart tissue
- ‘Human induced pluripotent stem cell cardiomyocytes’ (hiPSC-CMs) are increasingly used for cardiac toxicity studies
- hiPSCs have been shown to predict accurately the effects of drugs and toxic agents in humans, including proarrhythmic actions mediated via hERG and Nav1.5



Fujifilm/Cellular Dynamics ICell$^2$ hiPSC-CMs

# Acknowledgements

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