

Arrhythmias in cardiac ischaemia and infarction

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Focus of lecture: VF

- VF is the most frequent cause of sudden cardiac death (SCD)
- SCD is often the first symptom of coronary artery disease (CAD) - with up to 50% of victims dying out of hospital

Present prophylaxis against VF is inadequate

Drug prophylaxis against SCD/VF by ion channel block has failed

Class I & III drugs are unsafe in high risk patients

- Flecainide (Class I) increased death (CAST)
- D-sotalol (Class III) increased death (SWORD)
- Amiodarone (Class III) many adverse effects (see next slide)

Class IV drugs (e.g., verapamil) are ineffective

....amiodarone-induced blue man syndrome

Enseleit, F. et al. *Circulation* 2006;113:e63

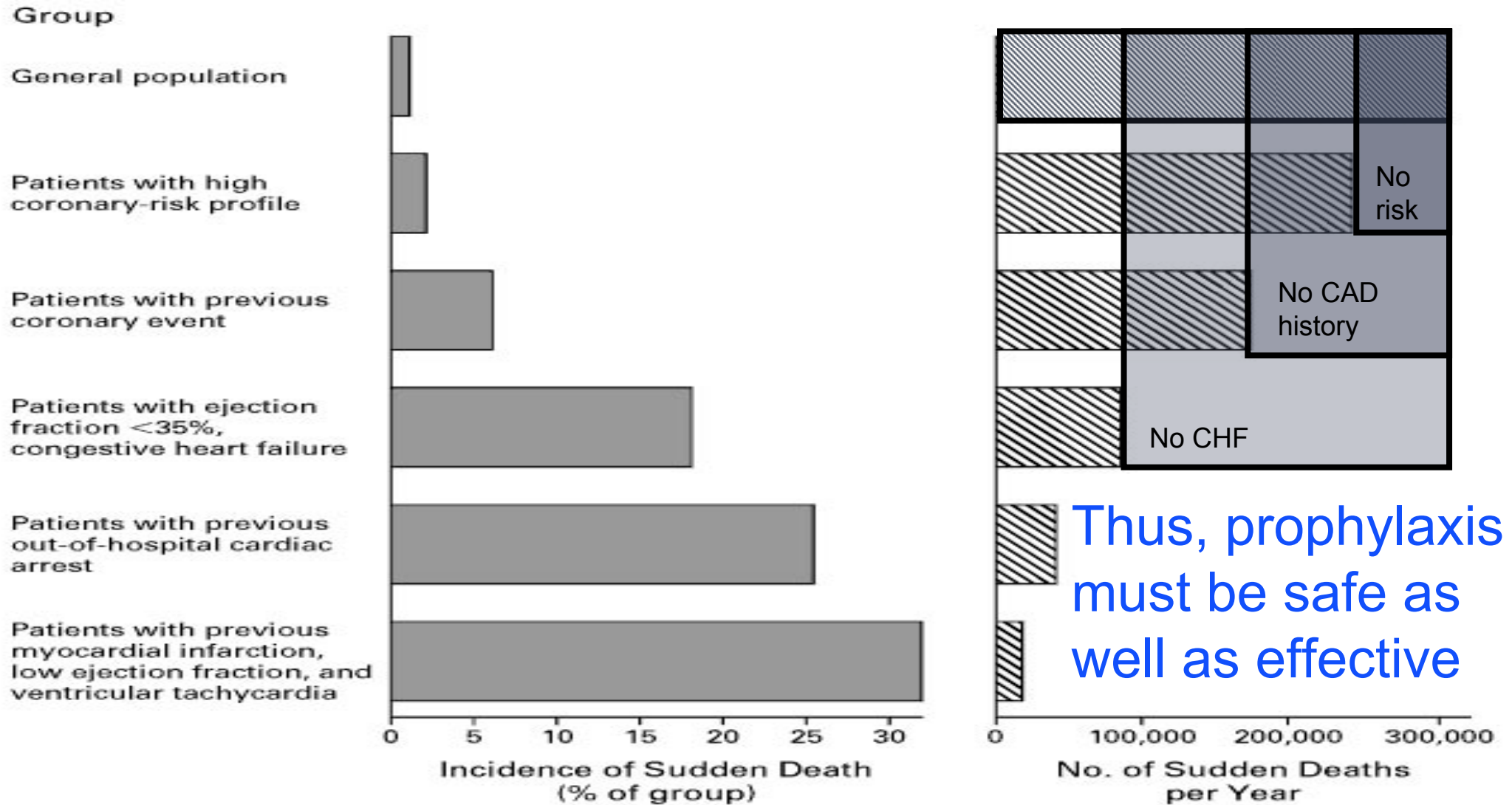


However, most SCD victims are in the lower risk populations

- It is here that effective VF prophylaxis would have the greatest impact on SCD
- But to be useful, any effective drug must be free of adverse effects

Risk-benefit ratio does not favour use of any of the anti-VF drugs presently available

75% of SCD victims no HF, 50% no prior CAD



We require new effective and safe
drugs for VF caused by ischaemia
and infarction

What do animal model studies tell us about VF in ischaemia and infarction?

Regional ischaemia: powerful VF trigger in all species studied (primate, pig, dog, rat) except mouse

- VF determined by size of ischaemic territory
- VF determined by collateral flow to the territory
- Risk modulated most strongly by blood K

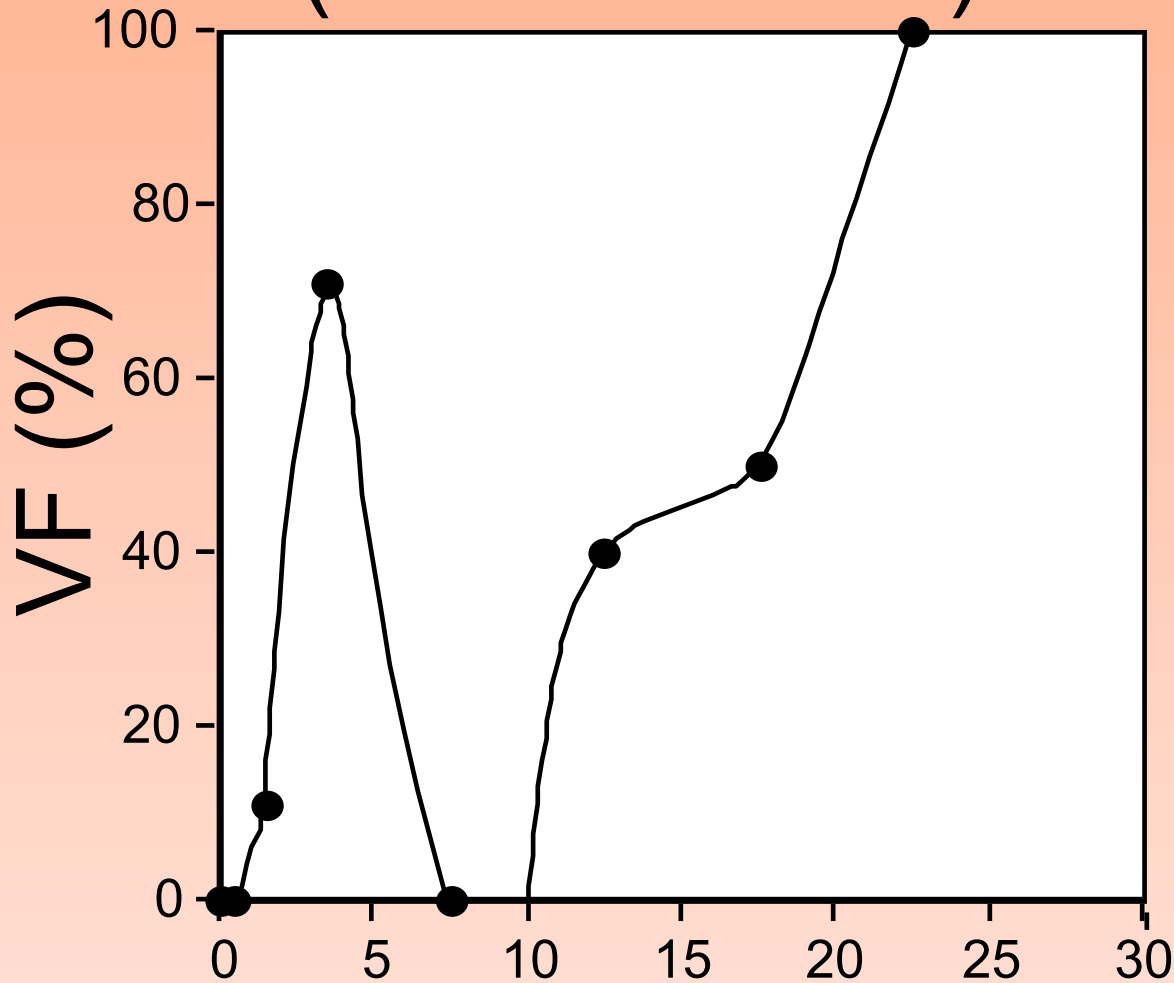
Importantly:

Every (rat) heart will develop *early* (phase 1) VF if:

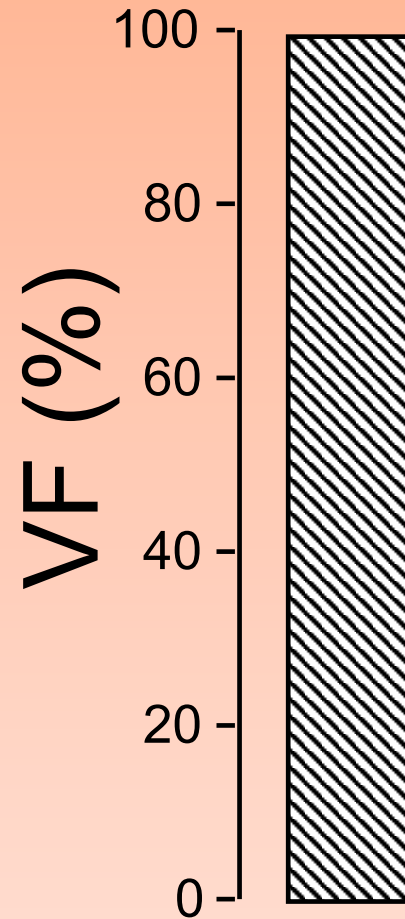
- ischaemic territory $> 35\%$ of LV, and
- collateral flow $< 5\%$ of normal flow, and
- blood $K^+ < 4$ mM

Anaesthetised dog (no collaterals)

Adapted from Meesman W. 1978
See Curtis MJ 1998



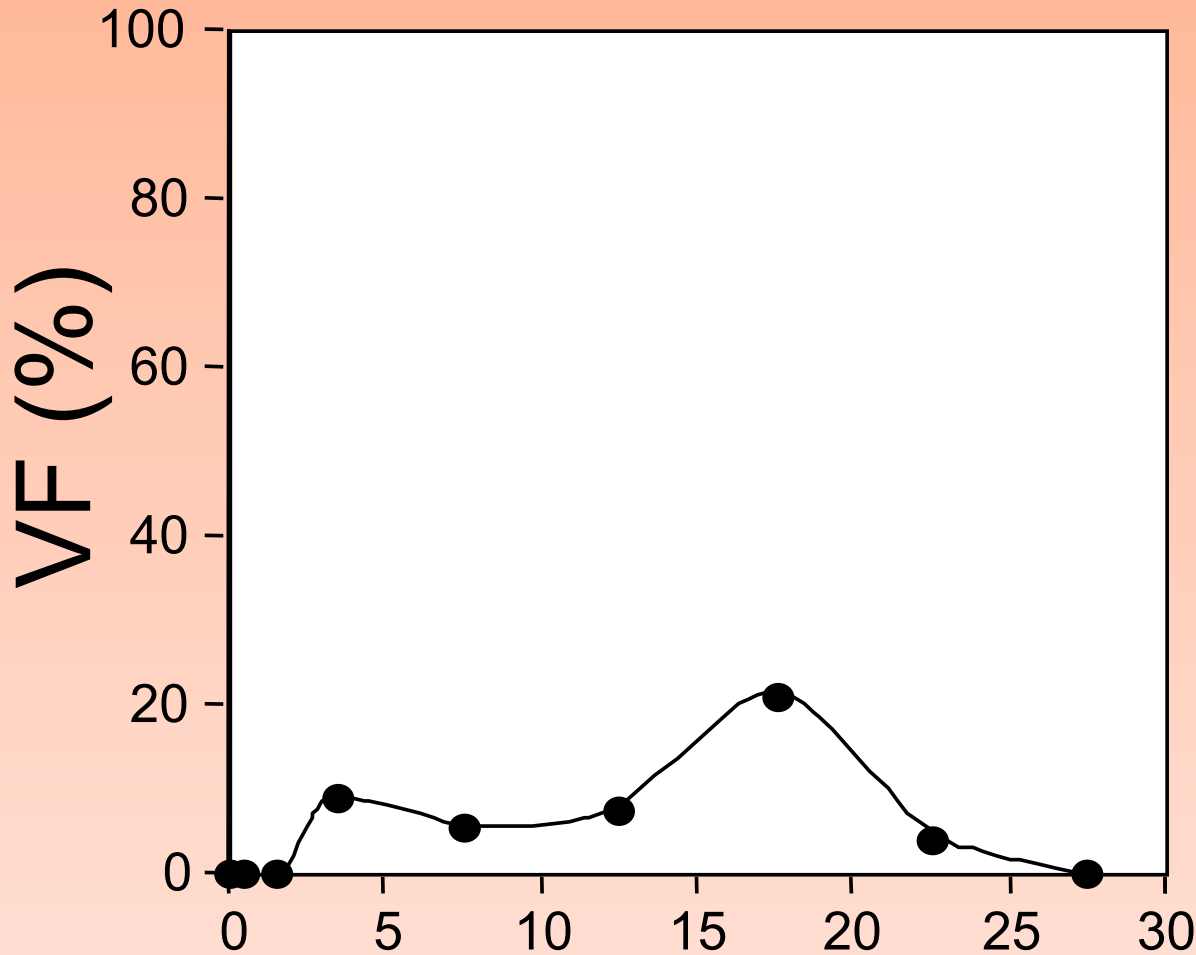
Time (min) after
ischaemia onset



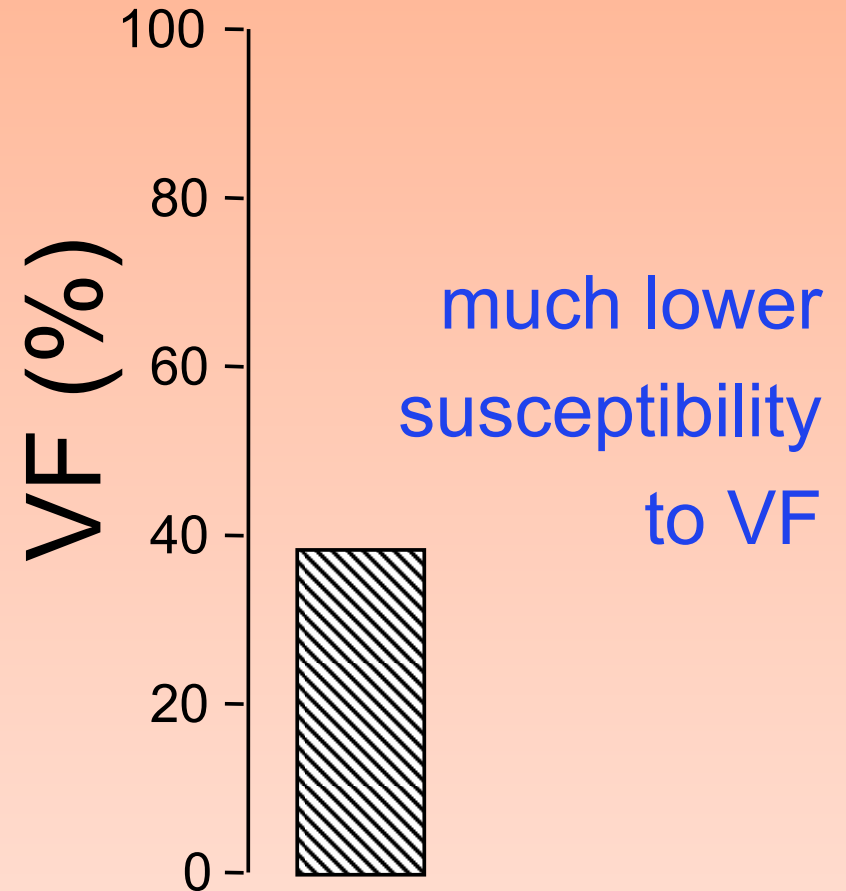
0-30 min
VF total

Anaesthetised dog (extensive collaterals)

Adapted from Meesman W. 1978
See Curtis MJ 1998



Time (min) after
ischaemia onset



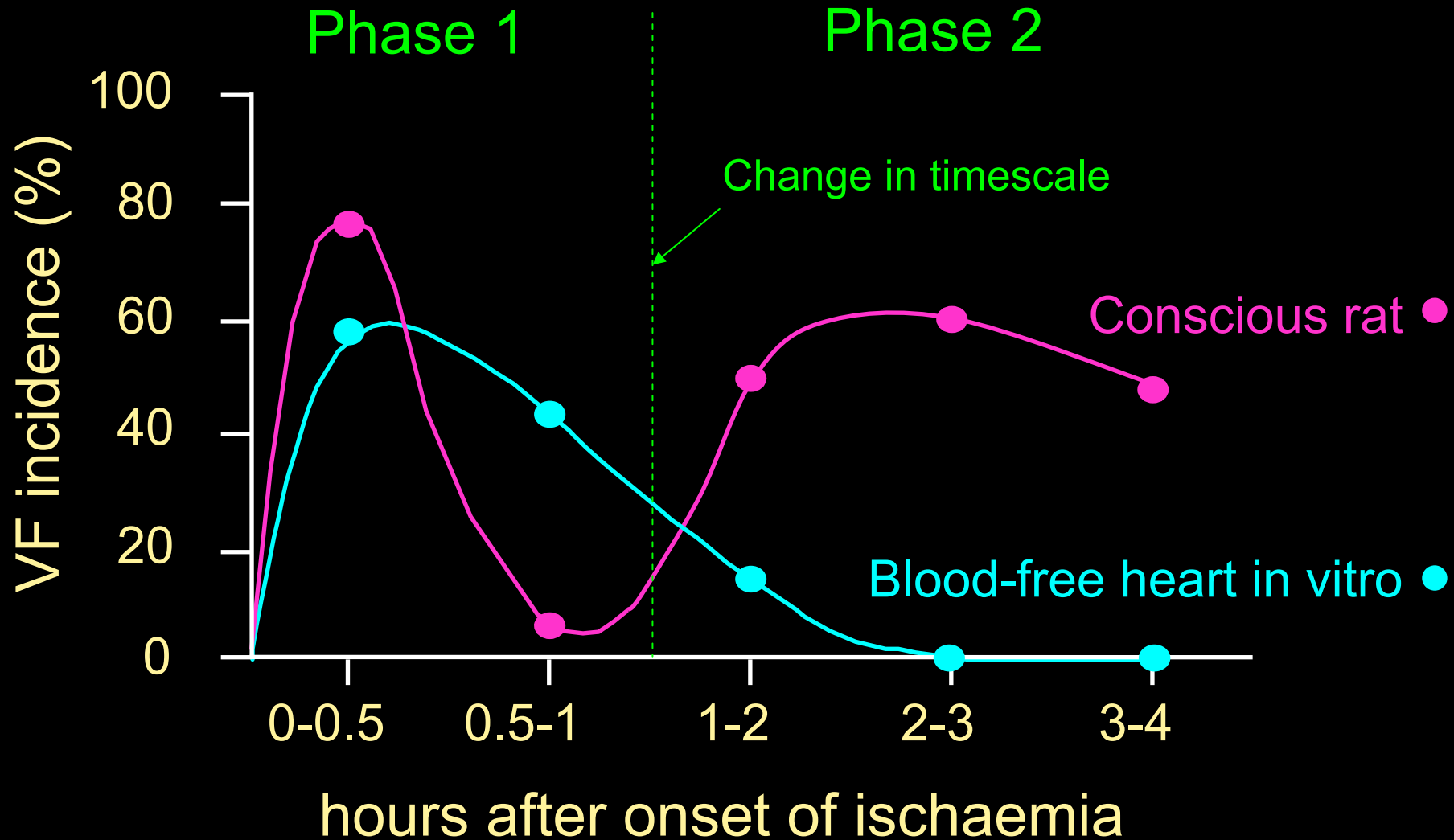
0-30 min
VF total

In animals resuscitated from phase 1 VF:

Survivors may get *late* (phase 2 VF)

- associated with appearance of infarct
- less well characterised
- dependent on blood and/or nerve effects

Phase 1 and 2 VF in rat models



Human ischaemia-induced VF may be more common than is appreciated

- VF most commonly occurs outside the realm of hospital medicine, bypassing the cardiologist

(First symptom  mortuary)

Ischaemia-induced VF/SCD may be under-appreciated as an unmet therapeutic target

What is the best approach to developing safe prophylaxis?

Selective targeting (effectiveness with safety)

- Disease selectivity
- Tissue selectivity

How may selective targeting be achieved?

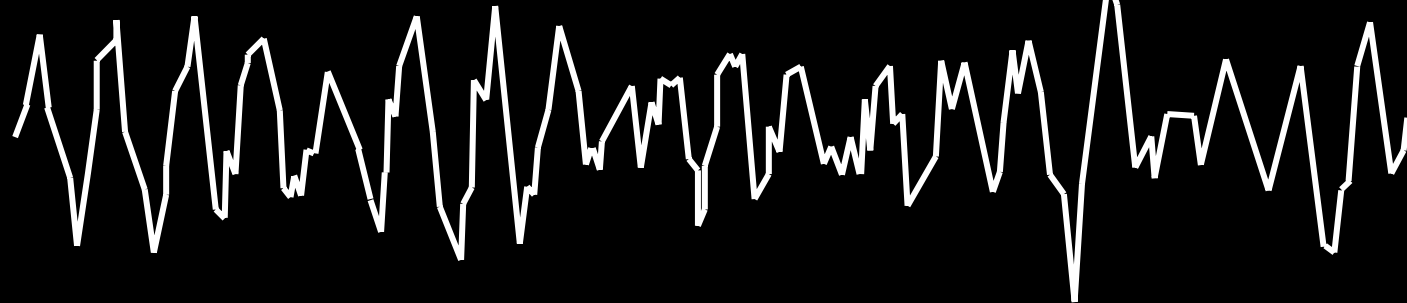
- VF is an electrophysiological event, but
- In ischaemia, change in local biochemistry is the main cause of changes in electrophysiology
- Change in the local biochemical milieu is therefore the 'substrate' for VF

Targeting the appropriate components of the milieu may provide effective and safe therapy

Ischaemia → **Mediator**



Modulator → **X**



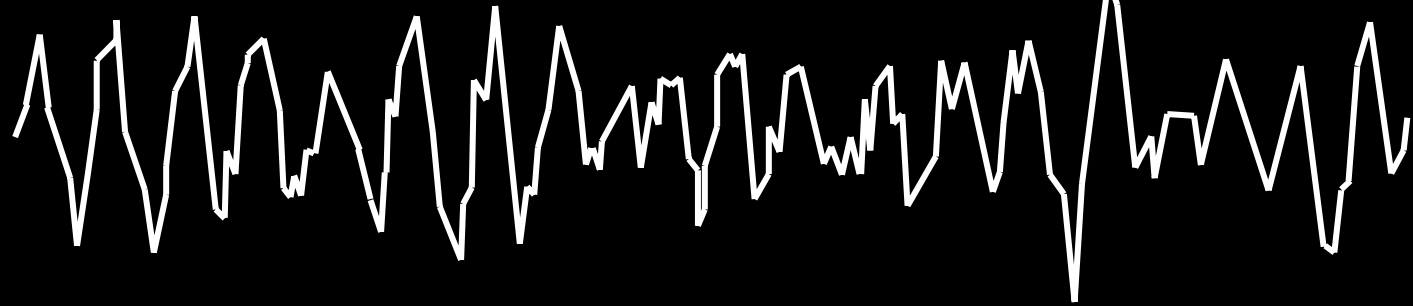
VF

Novel drug $\xrightarrow{\ominus}$ **Mediator**

\oplus ↓

Modulator → **X**

↓

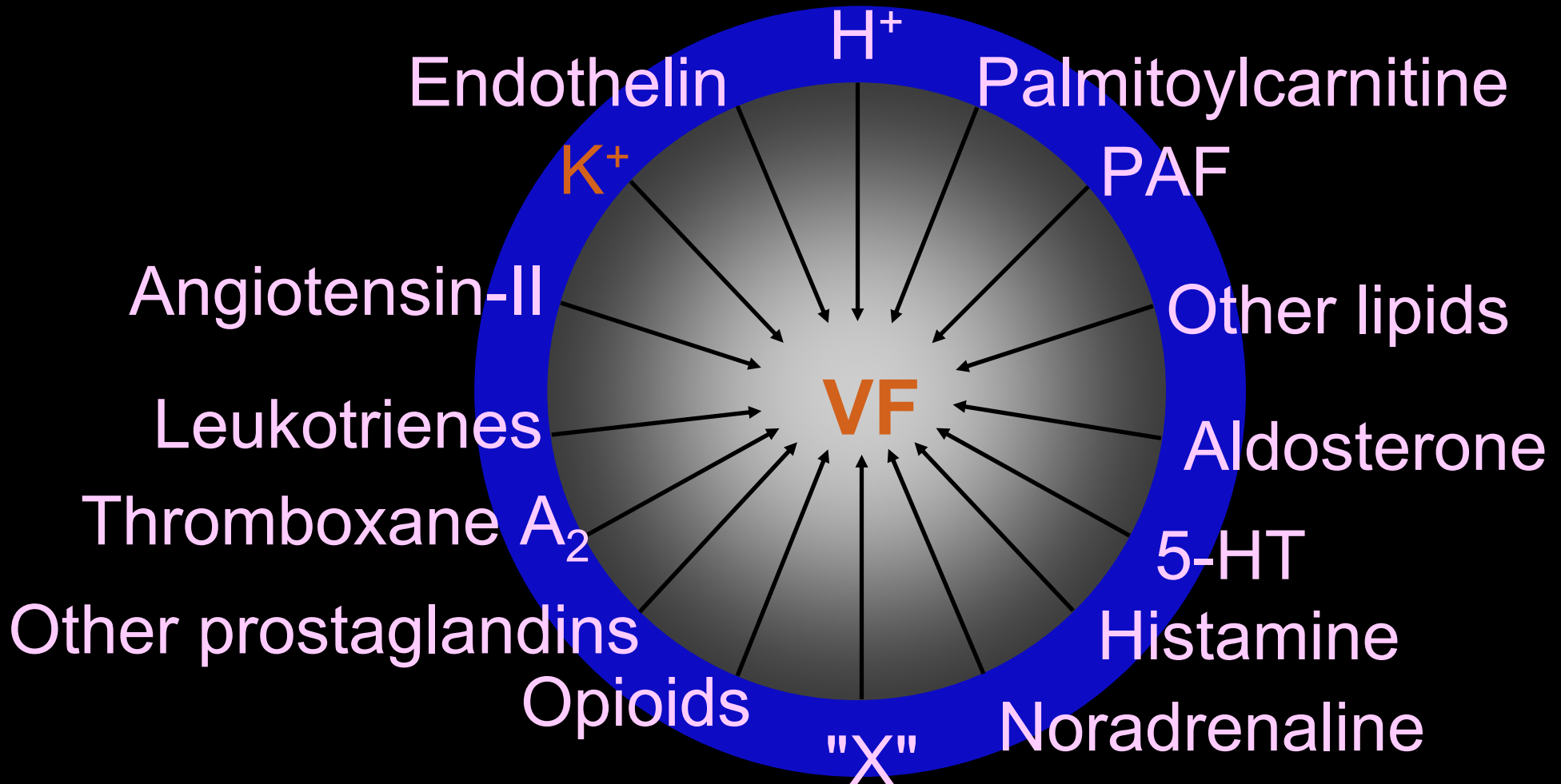


VF

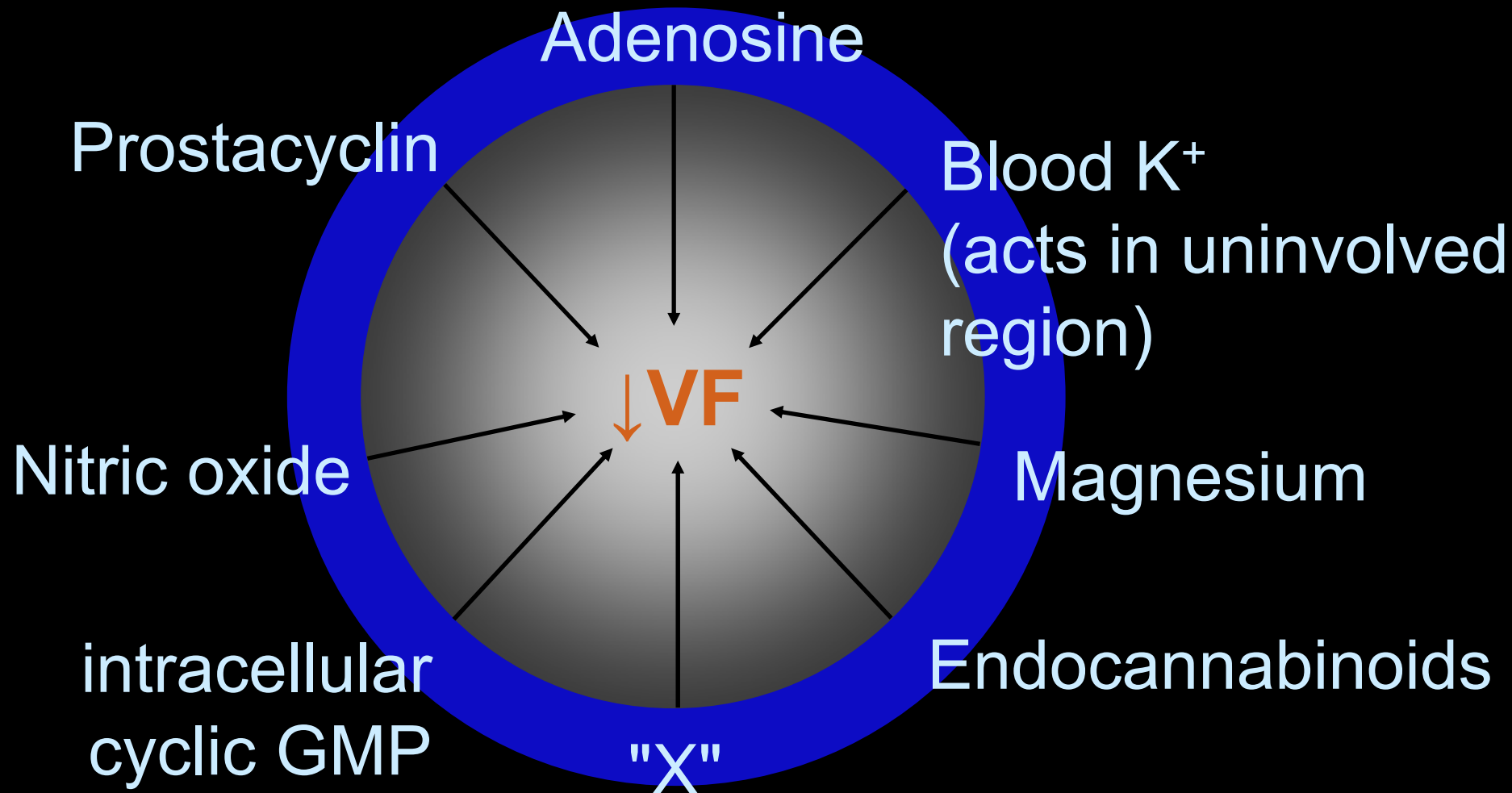
Which mediator/modulator should be targeted?

- Need to know *strength of evidence* of substance's involvement as mediator/modulator
- For mediators (many have been proposed) need to know *which are sufficient and which are necessary* for the appearance of VF
- Need to consider *practicality* of targeting the mediator (or mimicking the modulator) with a drug

Putative mediators

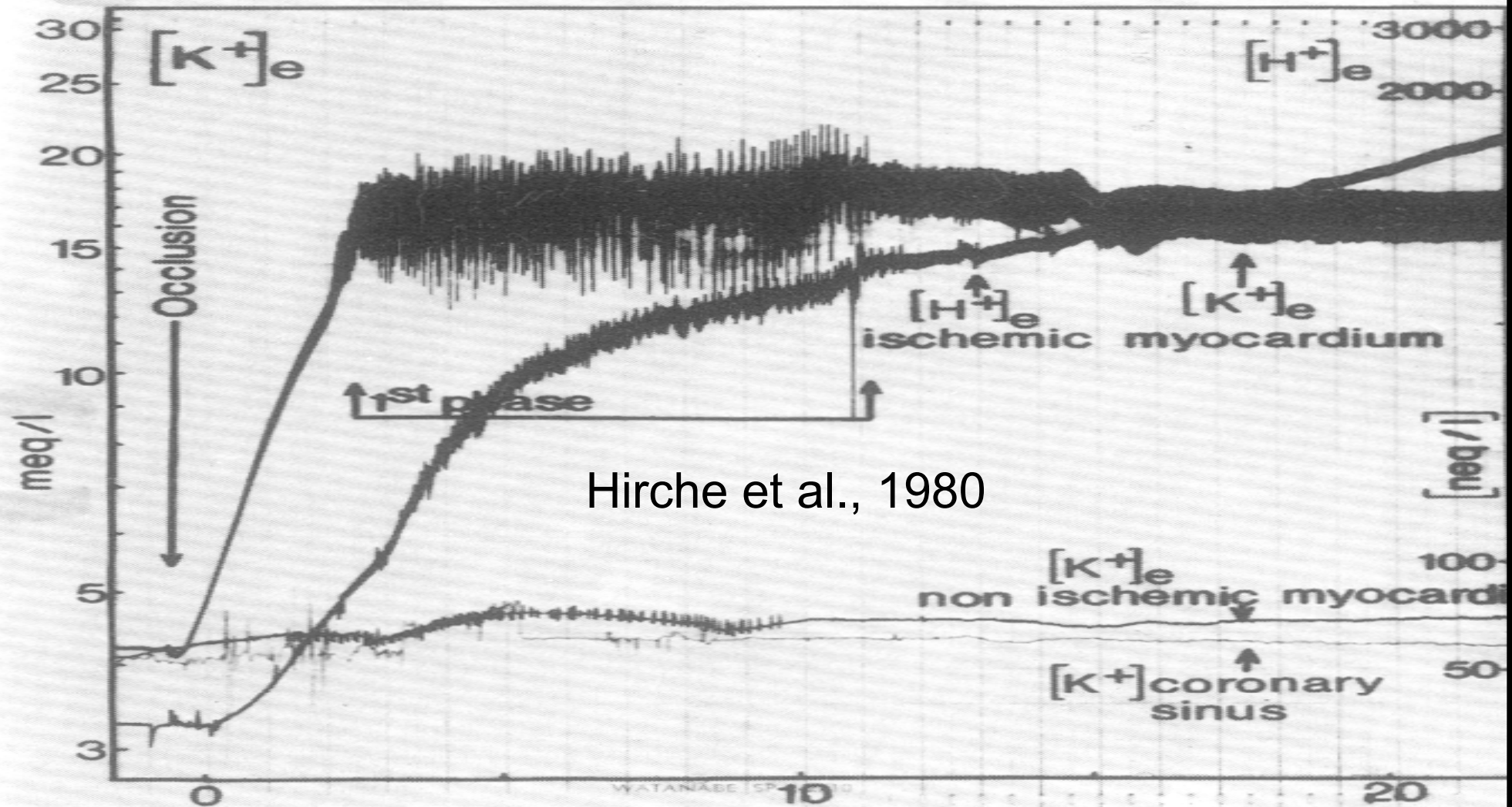


And some putative modulators



Evidence for mediator involvement: potassium

Very rapid local increase during ischaemia



Evidence for mediator involvement: potassium

Local (intracoronary) injection of potassium: arrhythmogenic

Harris et al., 1958

Arrhythmic and Antiarrhythmic Effects of Sodium, Potassium, and Calcium Salts and of Glucose Injected into Coronary Arteries of Infarcted and Normal Hearts

By A. SIDNEY HARRIS, PH.D., LOUIS A. TOTH, PH.D., AND TAN ENG HOEY, M.D.

With the technical assistance of Duncan D. Burford, A.B., Richard A. Liptak, B.S.,
and Anwar Djamadin, B.S.

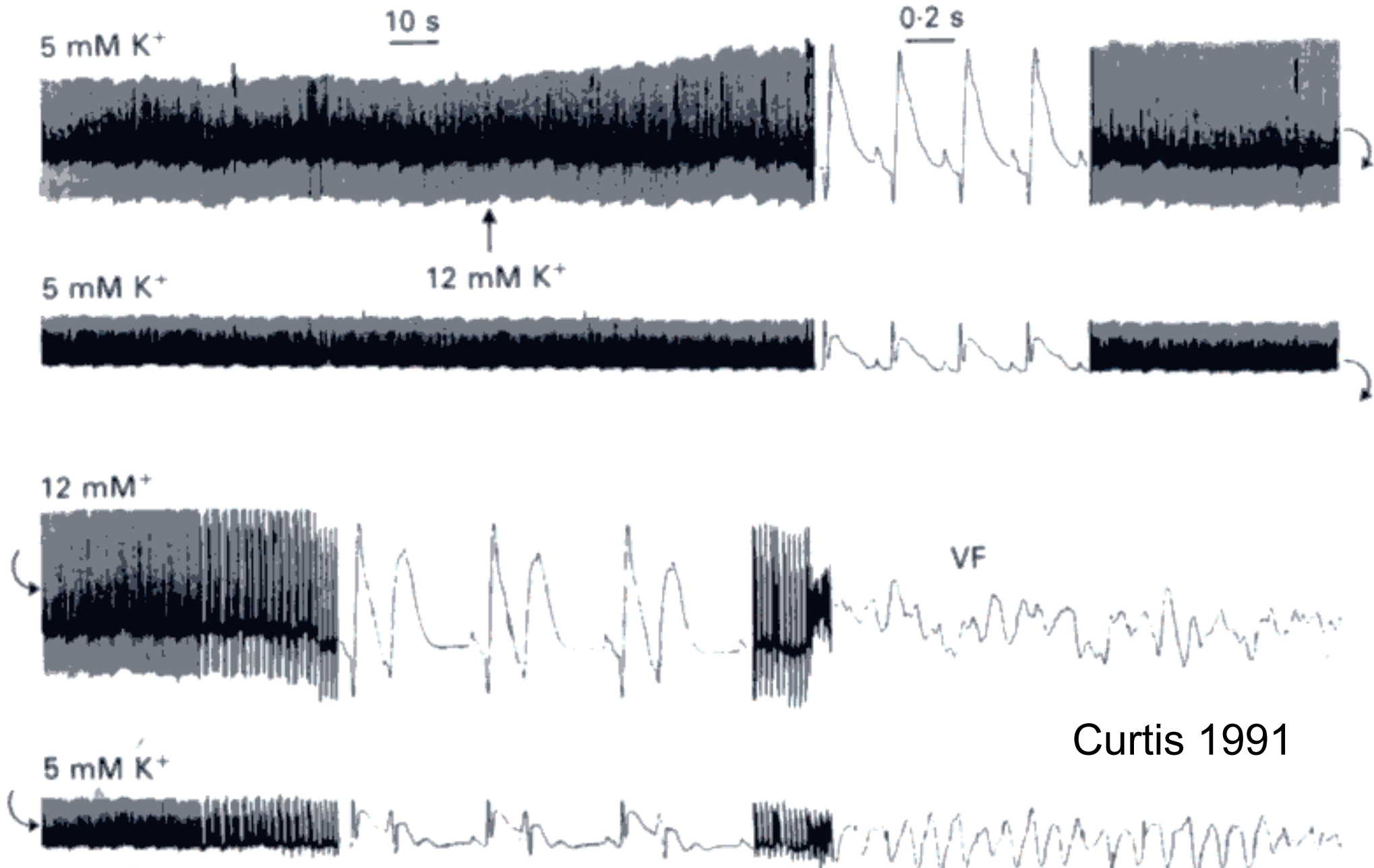
Substances that have not exhibited properties as excitants of ectopic activity by intracoronary injection into normal hearts often produce rapid ectopic activity and sometimes ventricular fibrillation upon slow injection through the vascular bed of an infarcted area, particularly upon the first one or two injections. Sodium lactate has reduced and stopped ectopic activity for brief periods. Excesses of both potassium and calcium have increased ectopic activity in infarction and produced it in normal hearts. No

Is regional K elevation sufficient to mediate ischaemia-induced VF?

Concentration dependence studies

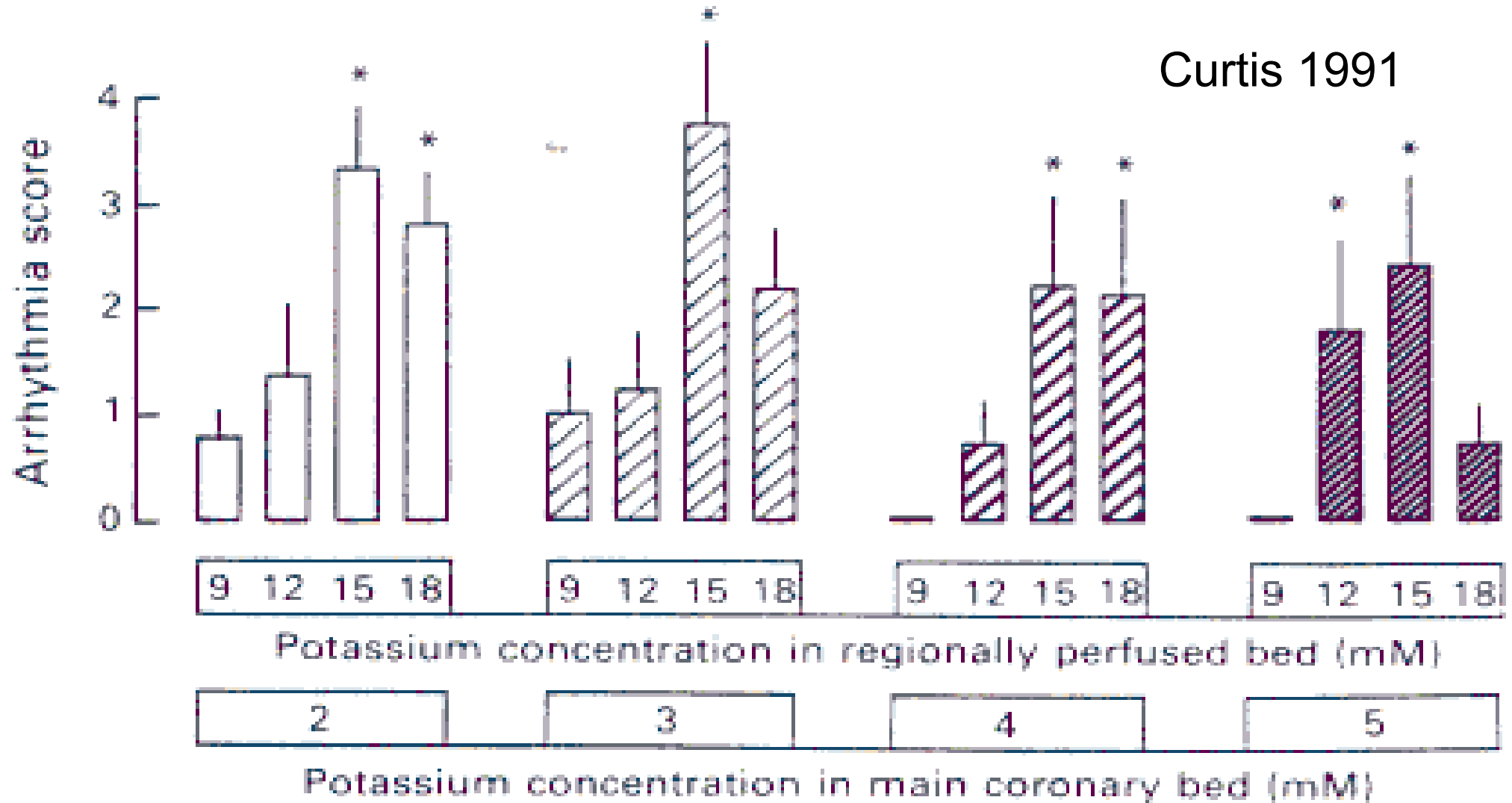
- Isolated rabbit heart (Langendorff perfusion)
- Epicardial cannulation of LAD
- Independent perfusion of LAD
- Local infusion of K-supplemented Krebs
- Electrogram recorded from LAD and RV territory

Regional K elevation (no ischaemia) can cause VF



Curtis 1991

Arrhythmias most severe with 15 mM K and reduced by small K increase in adjacent bed



What is the mechanism?

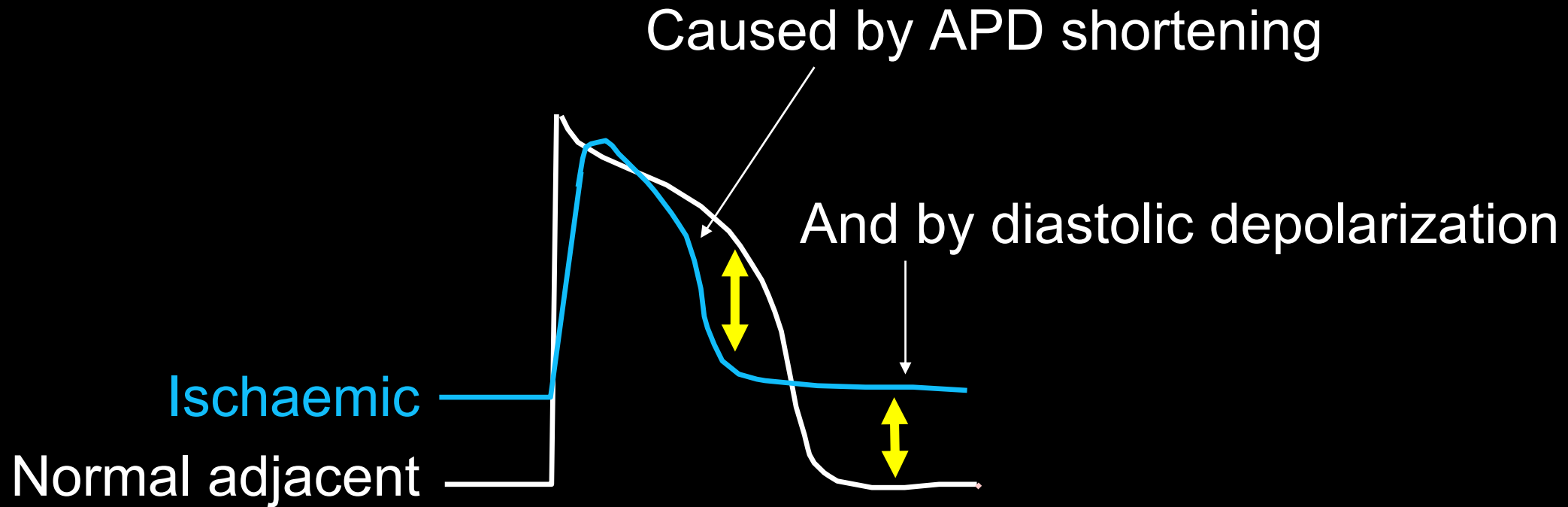
Regional hyperkalaemia has three important effects

- Regional depolarization
- Regional APD shortening
- Regional slowing of conduction velocity

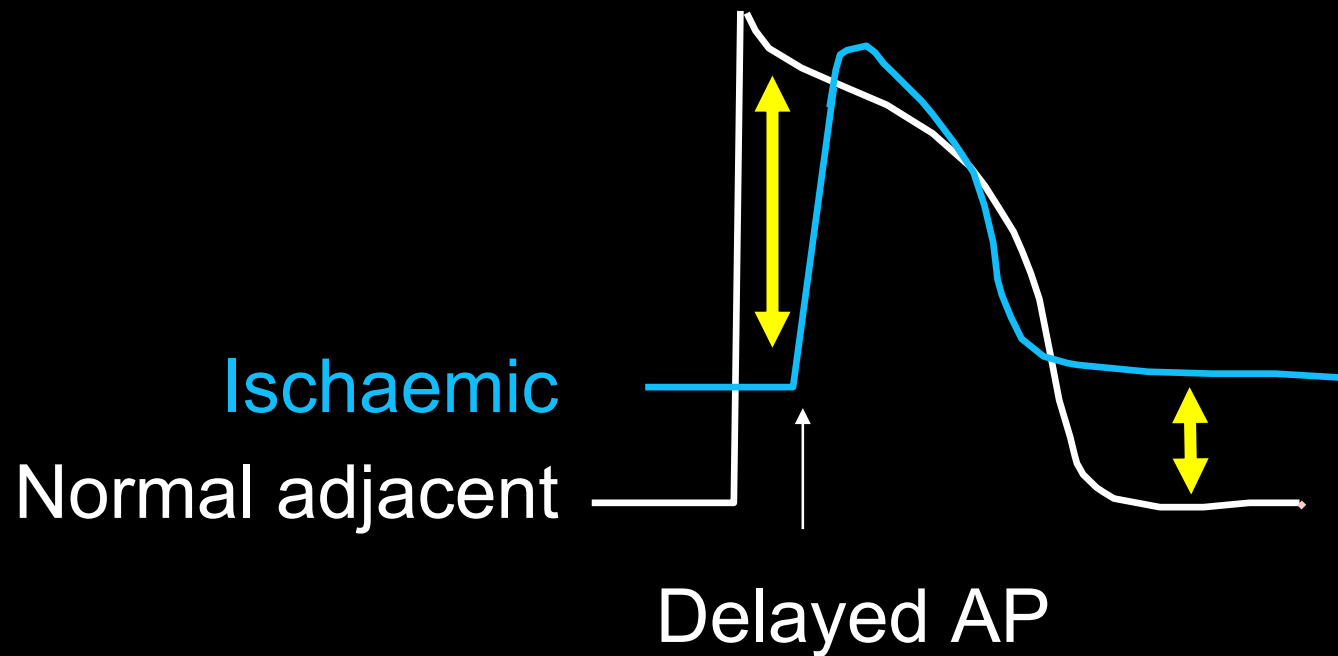
This facilitates flow of injury current

- This creates ventricular ectopic (VPB)
- The VPB propagates (re-entry) and fragments to VF

Flow of injury current \updownarrow



Altered by ischaemic conduction delay



Ischaemic AP also facilitates re-entry

Diastolic depolarisation
Due to partial I_{Na}
inactivation

AP upstroke
slowed

APD shortened
due to $\uparrow I_{K_{ATP}}$
and $\Delta I_{Na/Ca}$

θ slowed

RP reduced

Ischaemia

$$(\omega = \theta \times RP)$$

VPB more likely to initiate VF



But . . . there are numerous candidate VF mediators

- K^+ is just one of many
- How do we decide which are sufficient and which are necessary?

Criteria for establishing if mediator is sufficient

- Present in ischaemic milieu
- Mimics effects of ischaemia to cause VF
- Drugs that block its actions block VF
- Drugs that block its synthesis block VF
- Drugs that mimic its actions cause VF
- KO of its synthesis or its target must block VF
- Upregulation of its synthesis or target must facilitate VF

Necessary? It is difficult to prove the role of a putative mediator

No substance has yet been proven to be necessary for mediating VF

Moreover, the substance for which evidence is best (K^+) may not be amenable as a drug target

- Attempts to block K^+ accumulation by block of I_{KATP} failed to block ischaemia-induced VF in dogs and rats

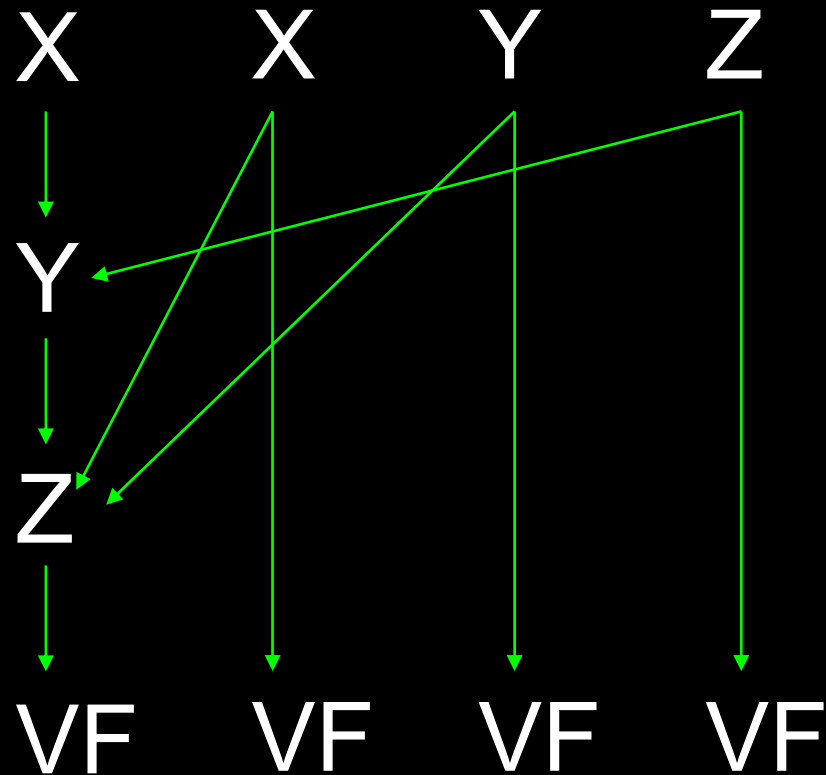
Problems with identification of mediators

- If several mediators are sufficient for VF, not all may be necessary
- Thus, selective block of one may have no effect on VF incidence
- This indicates “pathophysiological reserve”

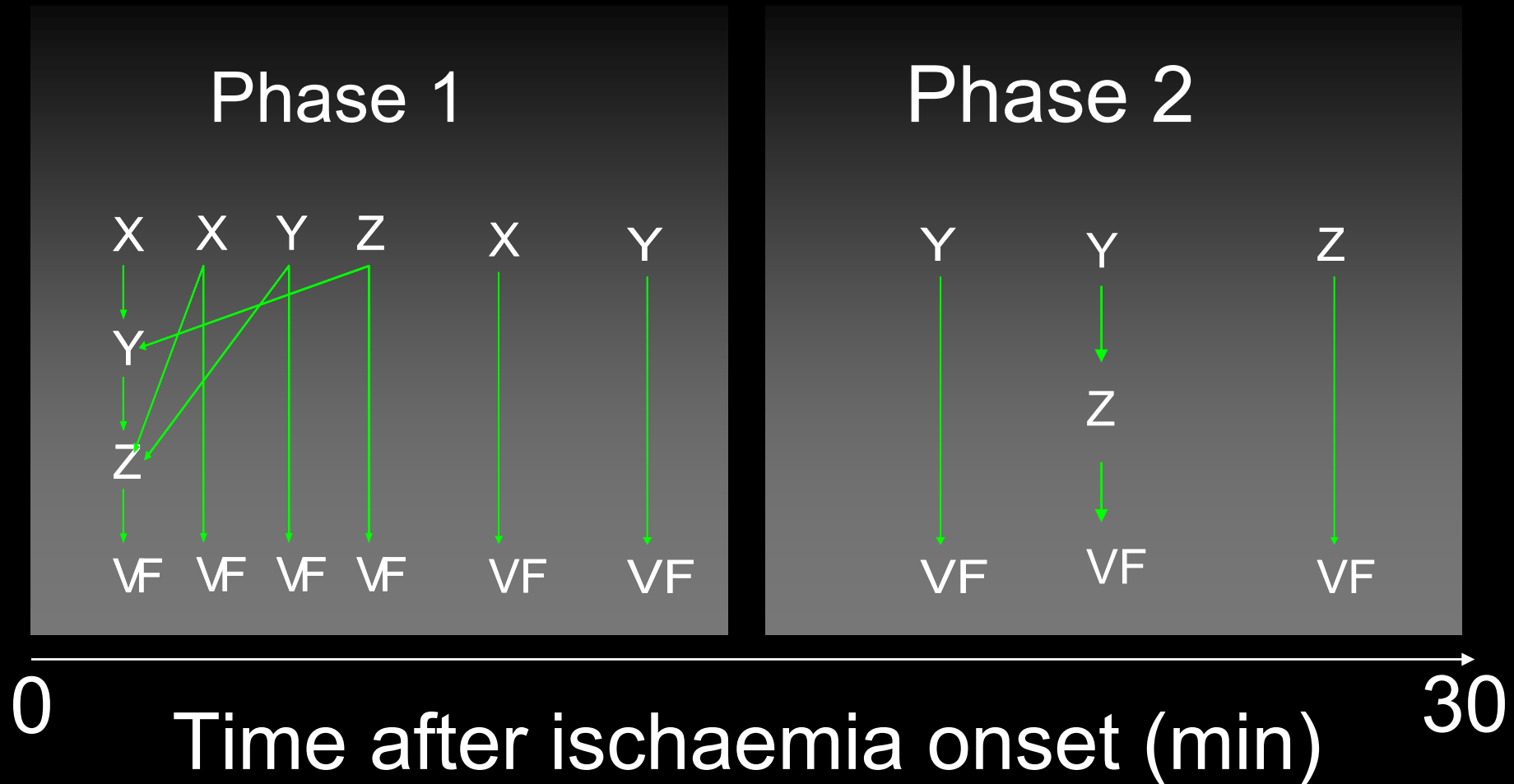
Further problems with identification of mediators

- Mediators may operate in parallel and in series, facilitating or blocking one another's actions
- Block of one may have unpredictable effects on actions of others
- The role of a mediator may vary with time (during progression of ischaemia)

Mediators may act in series, and in parallel, and may interact



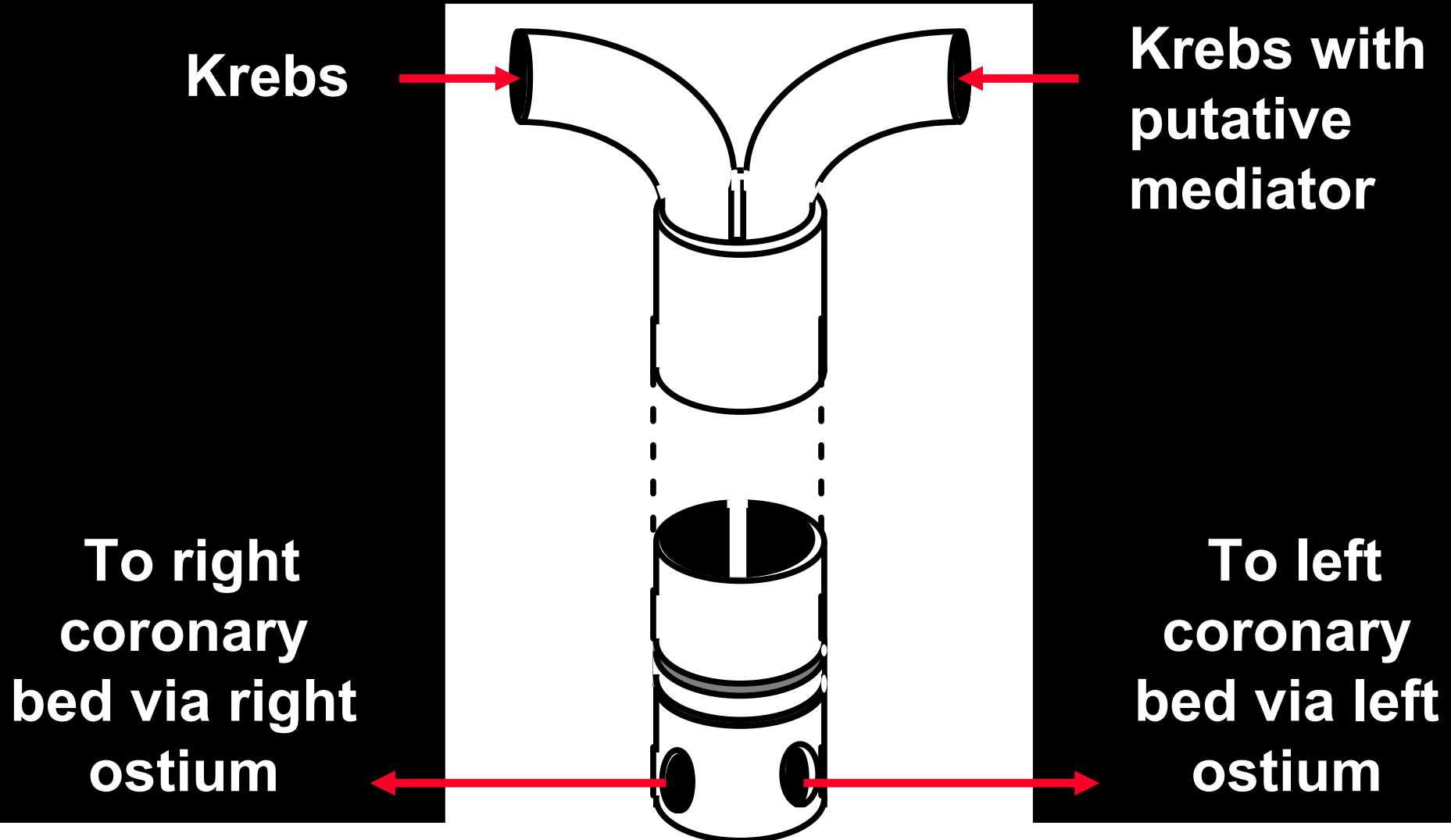
And the role of a mediator may change as ischaemia progresses to infarction



To test if a putative mediator is sufficient to cause VF requires a small heart bioassay

- Allows precise concentration-response assessment

Small (rat) heart bioassay became possible with the 'dual perfusion' cannula



Dual perfusion studies revealed evidence of species variation in mediator actions

- Neither K^+ nor noradrenaline evoked VF in the rat, although the combination did

Baker & Curtis, Br J Pharmacol **142**: 352-366, 2004

- Contrasts with earlier rabbit data - K^+ alone caused VF

Curtis et al., Cardiovasc Res **27**: 703-719 1993

Dual perfusion further revealed evidence of complex mediator interactions

- Left coronary perfusion with platelet activating factor (PAF) alone evoked VF in the rat
- However K^+ antagonised the ability of PAF to evoke VF in the same species

Baker & Curtis, Br J Pharmacol **142**: 352-366, 2004

- Thus one proarrhythmic mediator can antagonise the proarrhythmic actions of a second mediator

There are lots of other examples of quirky findings

Mediation and modulation of infarct-induced VF?

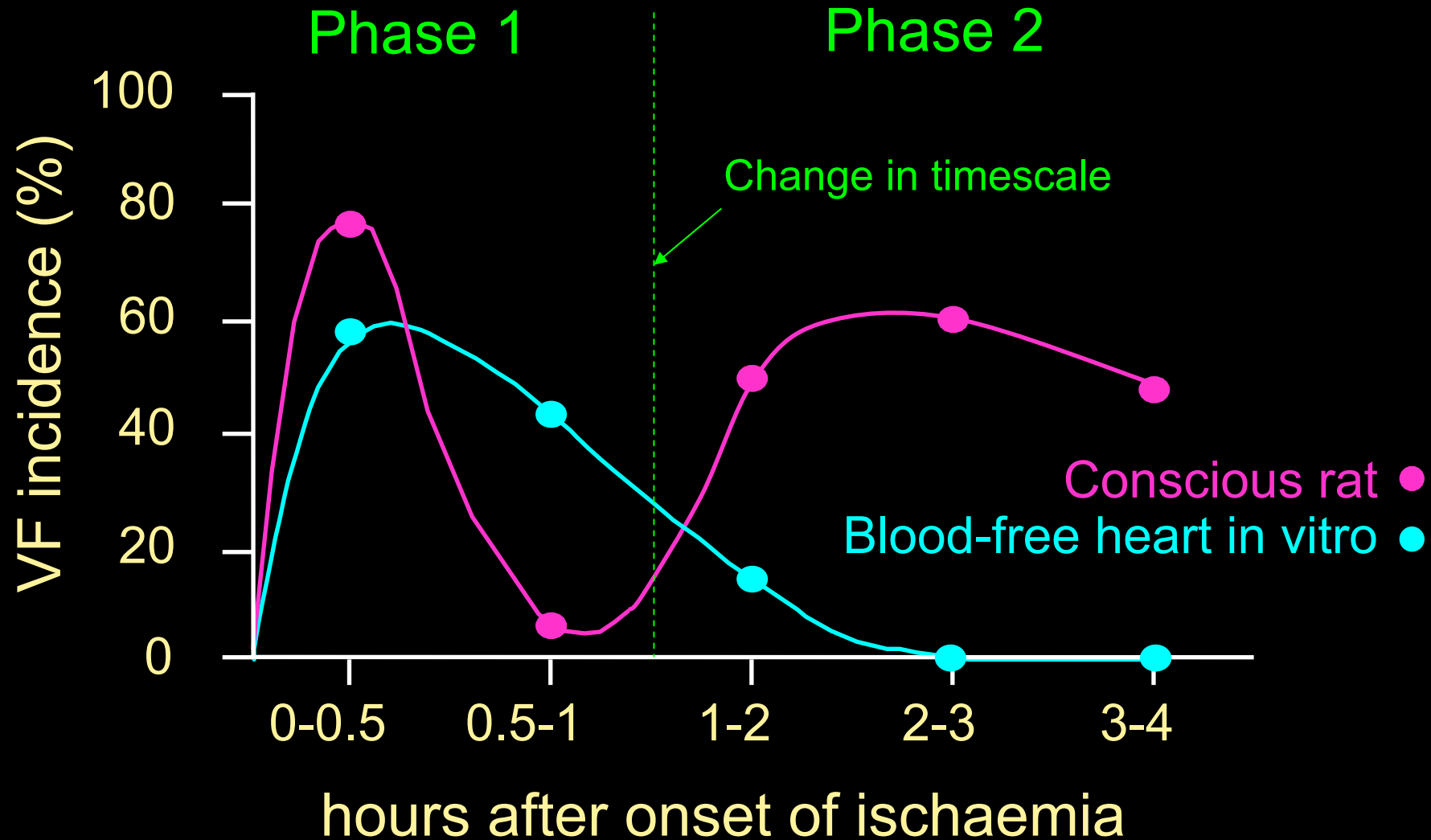
- Arguably less important than phase 1 (ischaemic VF)

Dogs with severe ischaemia die of phase 1 VF
Survivors have small infarcts and low VF risk

Curtis MJ. Cardiovasc Res 39: 194-215, 1998

- Mechanisms much less well understood
Clearly different from phase 1 VF:

Phase 2 VF absent in blood free hearts in vitro



Mechanism of infarct-induced VF?

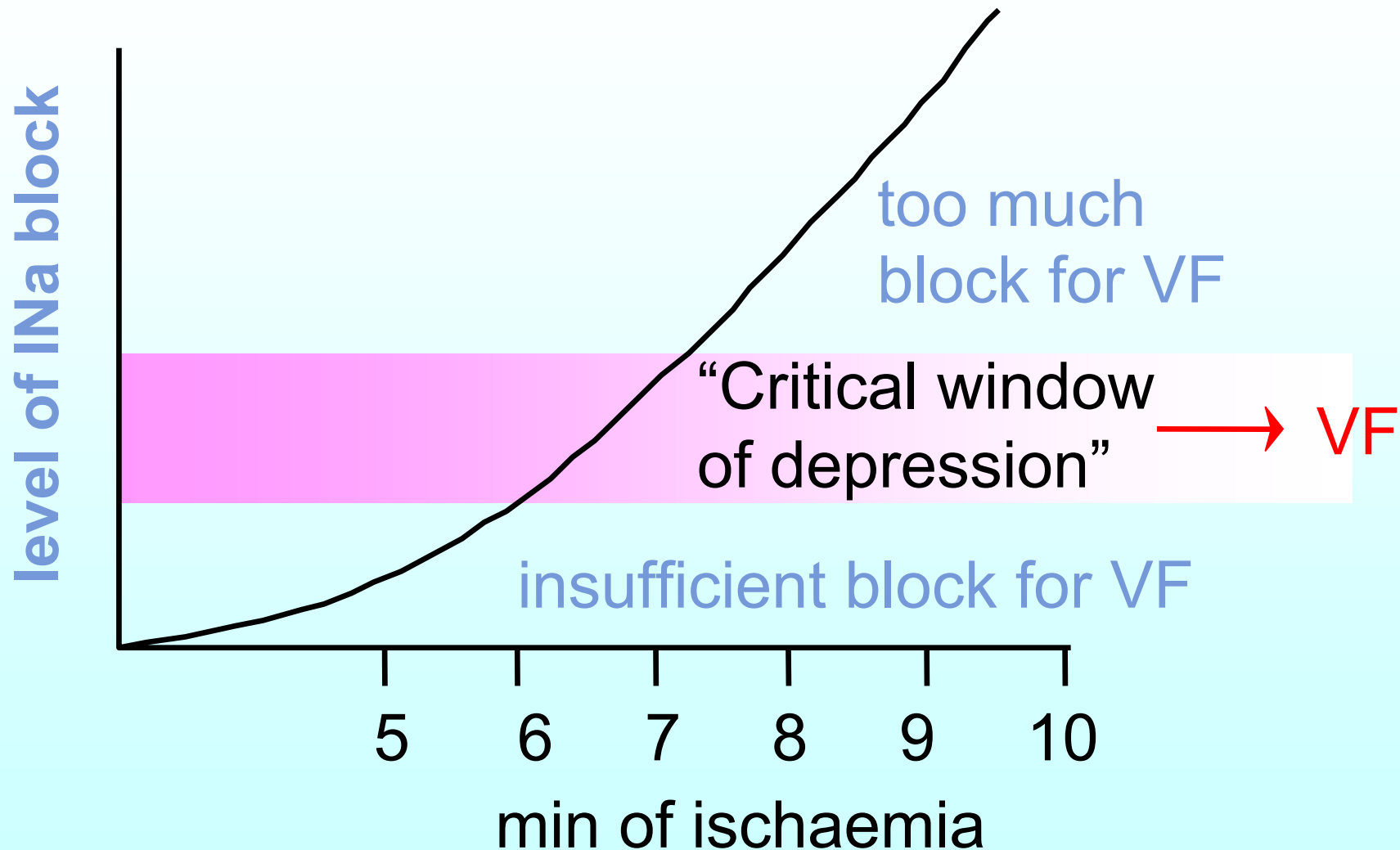
- Does the hiatus (between phase 1 and 2 in vivo) give a clue?

Phase 1 VF disappears owing to closure of the critical window of I_{Na} depression

Hondeghem, 1978

But it is unclear how the window opens again

The critical window is necessary for phase 1 VF



Role of I_{Ca_L} dependent conduction in phase 2 VF?

Cranefield proposed this in 1970s

Never tested thoroughly

- Idea that local catecholamines activate I_{Ca_L}
- This current then carries slow conduction
- Ischaemic region can then conduct re-entrant wave
- Ca 'overload' may also initiate abnormal automaticity

Clinical trial of verapamil failed to test hypothesis

Drug dose too low (to avoid vascular effects)

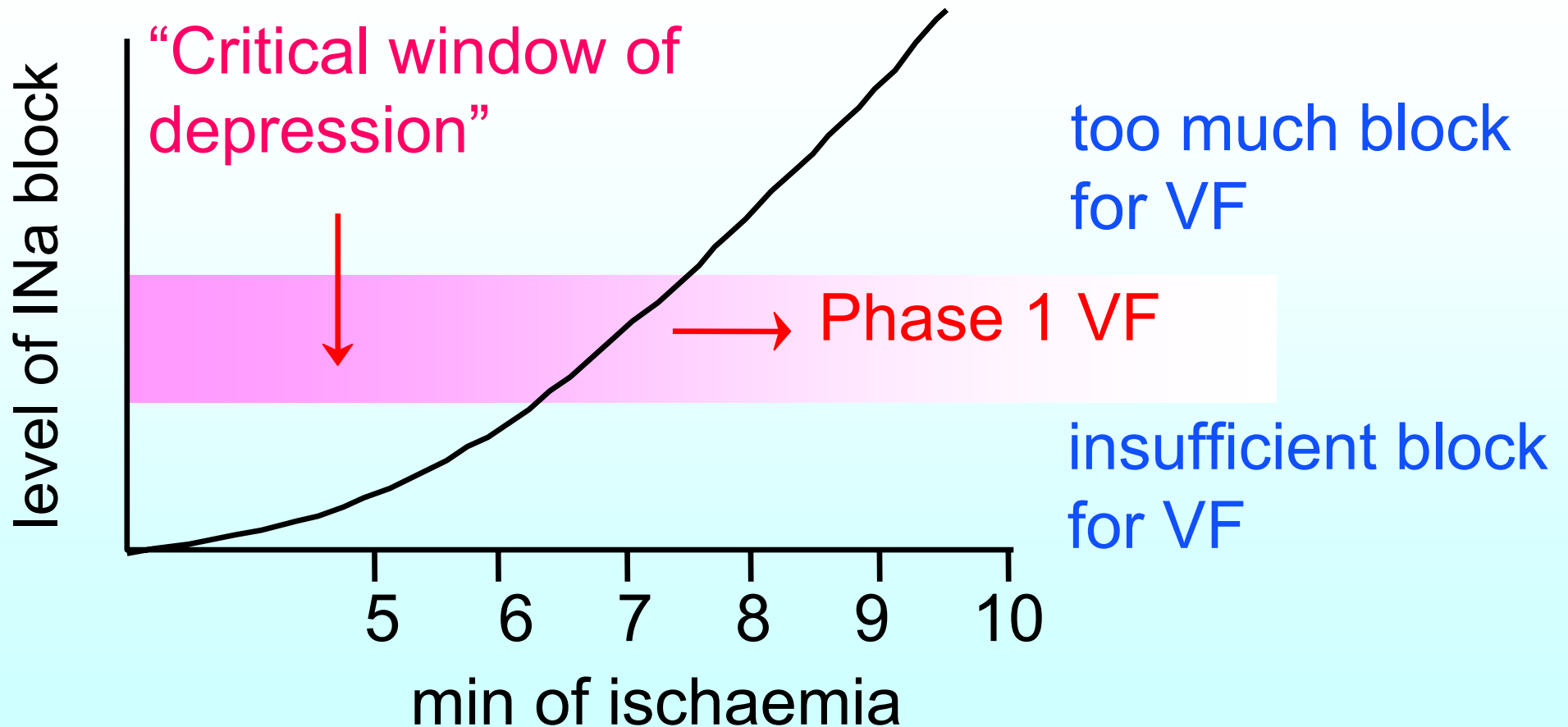
Summary and conclusion

It is clear that the links between ischaemia, infarction and VF are complex

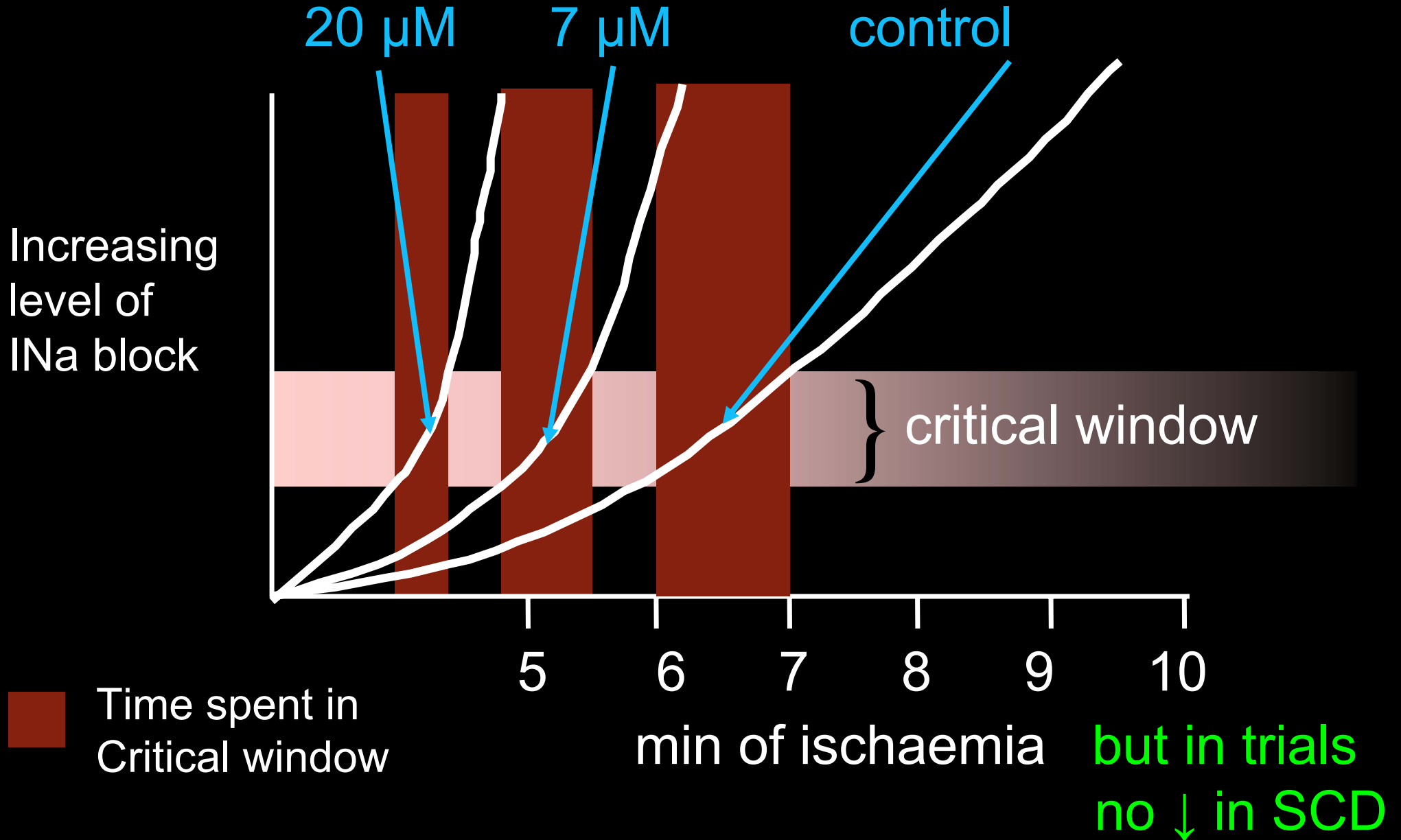
- There are multiple mediators and modulators
- There is redundancy (pathophysiological reserve)
- There is time dependence

Only when the mediators sufficient and necessary for VF are known will we be able to target VF rationally

Targeting abnormal conduction via I_{Na} block carries a risk of promoting re-entry – ischaemia blocks I_{Na}

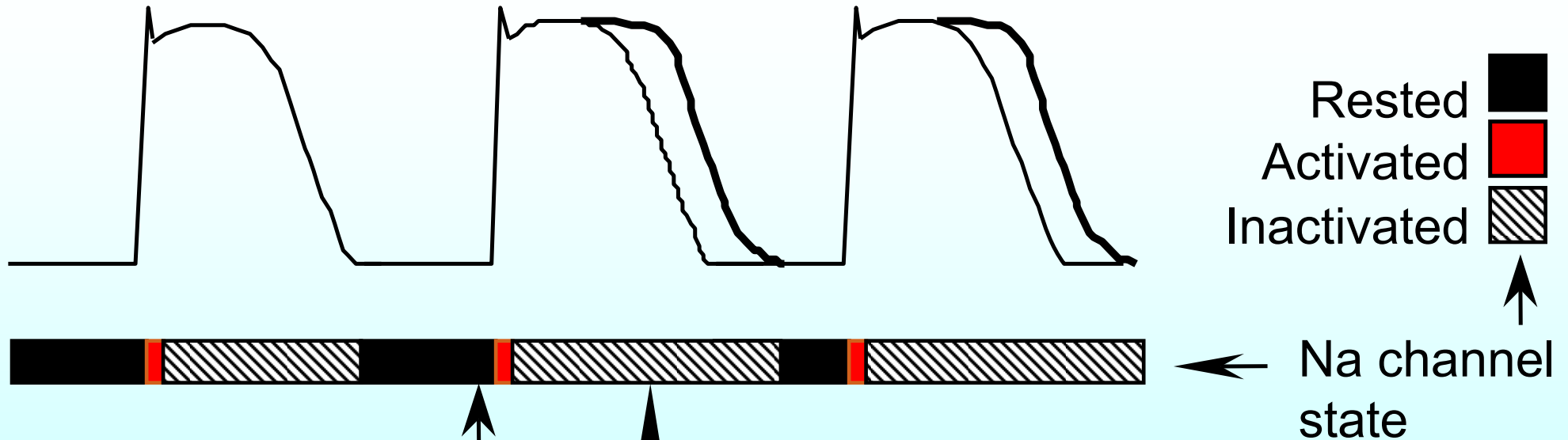


In theory, lidocaine may reduce the 'critical window'



Targeting abnormal conduction indirectly via $I_{K_{misc}}$

Ventricular action potentials, normal rate



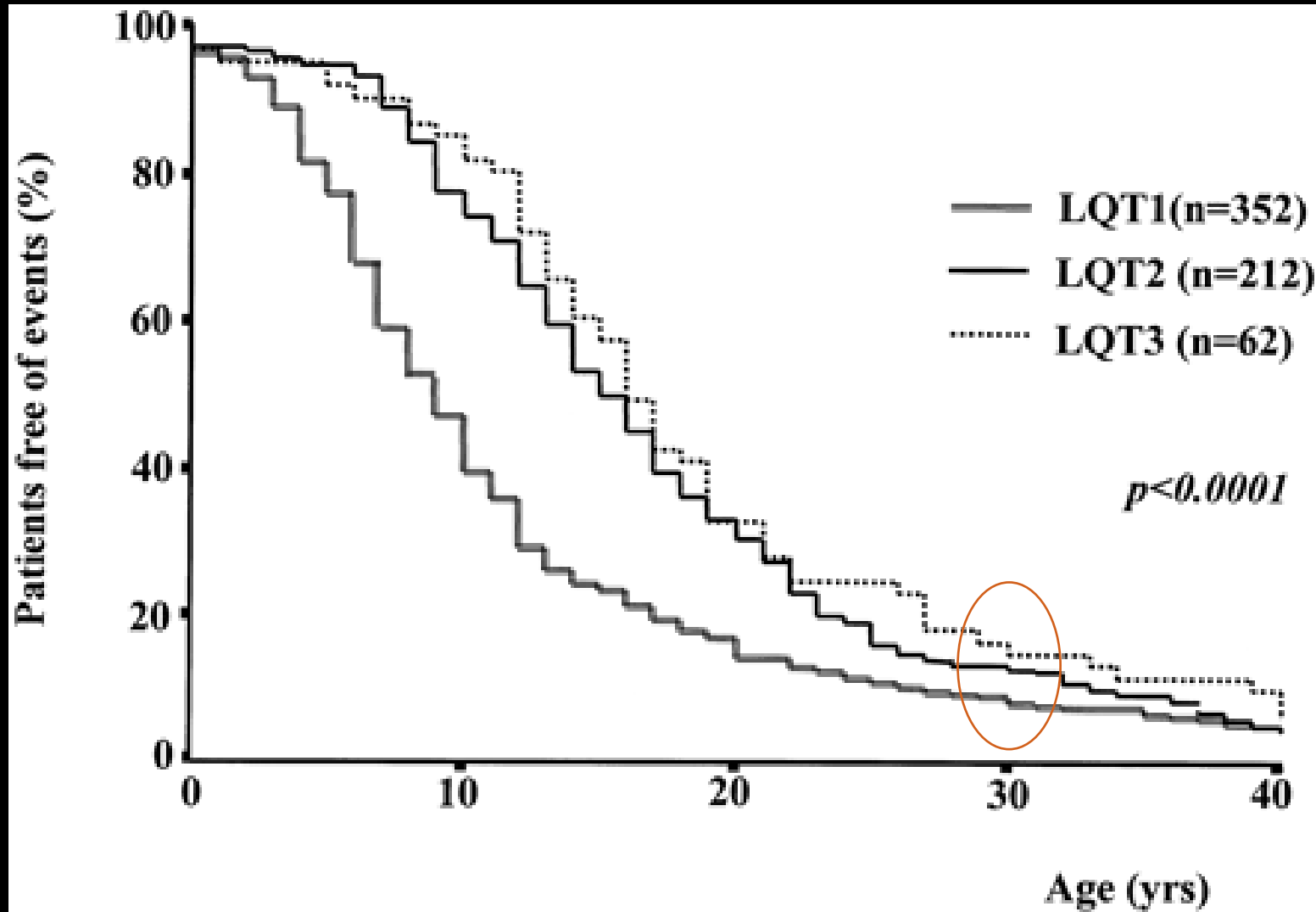
Give I_{K_r} blocker

Na channel stays inactivated for longer

Thus excitability (rested state time) reduced

However, the most studied target, I_{K_r} , is tainted . . .

Kaplan-Meier cumulative survival curves

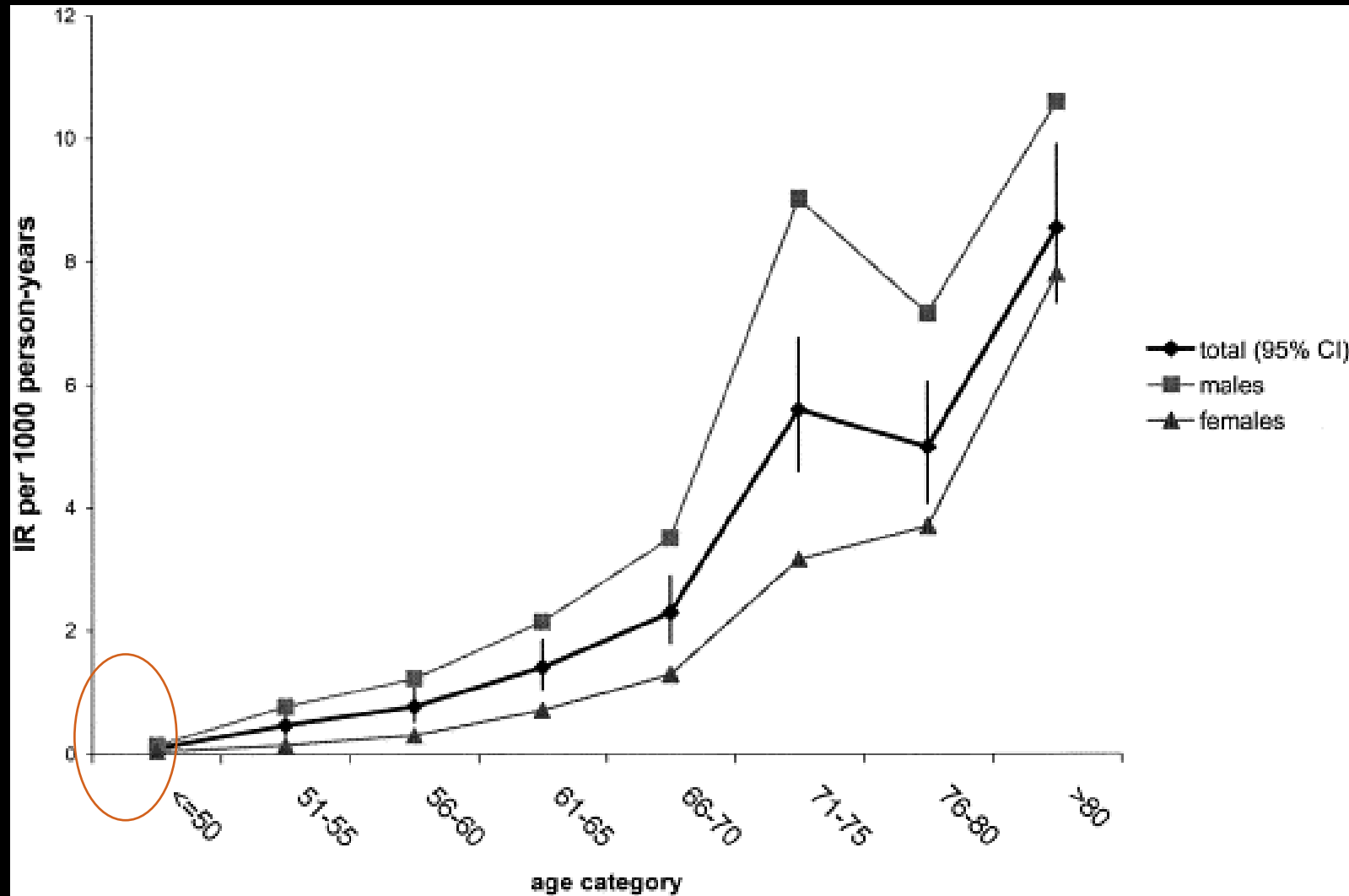


(Schwartz PJ et al., 2001)

However

SCD is a lethal condition affecting hardly anyone under the age of 50

SCD incidence in the general population



SCD vs LQTS

The lower prevalence, and the different epidemiology explain why of the 300,000 SCDs reported in the US each year, only up to 1,000 are thought to be due to LQTS

Oddly there is not 300 times the research spend on SCD vs LQTS, and 300 times the number of papers currently published