Cardiovascular Safety Modelling

Teresa Collins
Translational Safety, Drug Safety and Metabolism
AstraZeneca

AstraZeneca

Overview

- Cardiovascular Safety- why is it important?
- What do we measure and when?
- Focus on QT models
- Focus on HR/BP models
- Case Study 1: Guinea Pig model
- Case Study 2: Dog risk assessment

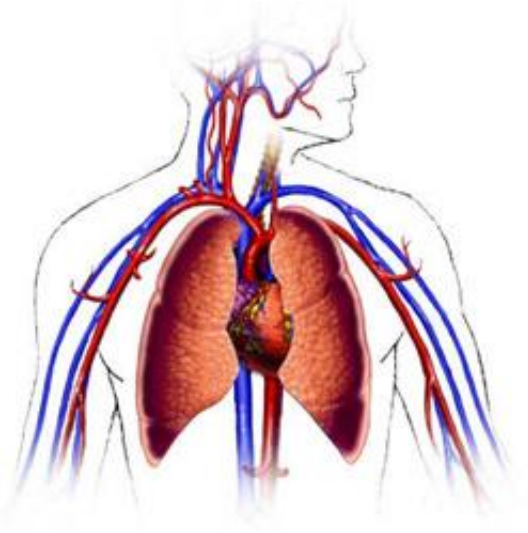
Why Study the Cardiovascular System?

Cardiovascular disease is the leading cause of death in the United States, accounting for over one quarter of all deaths every year.

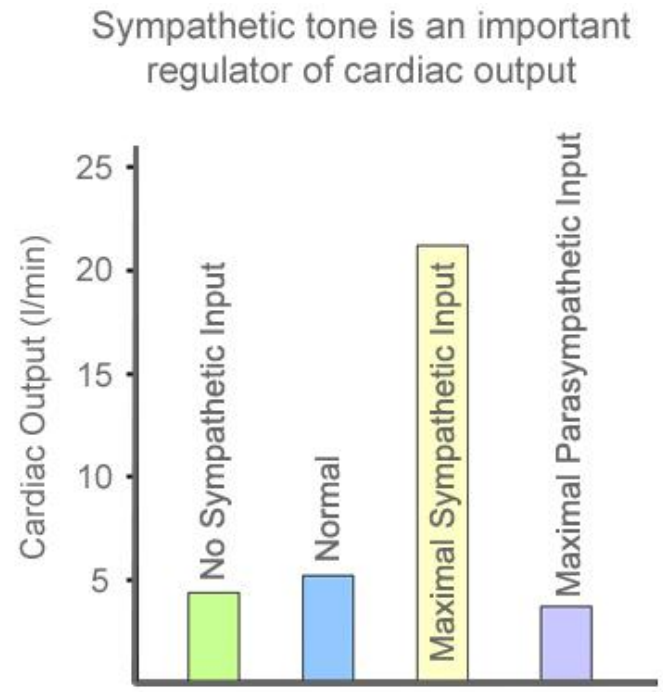
Some medical products intended to treat cardiovascular disease and other diseases have significant and potentially dangerous side effects related to their effects on the heart.

Cardiac safety concerns are a leading cause for the recall of marketed drugs and abandonment of drug development programs for any indication.

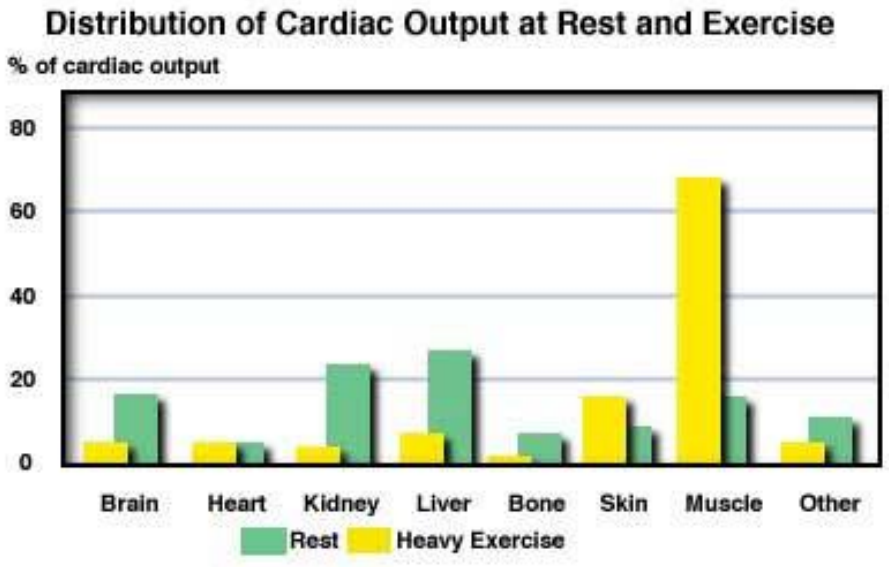
CSRC (www.cardiac-safety.org)



The Cardiovascular System
Its function is critical for life!



http://www.colorado.edu/intphys/Class/IPHY3430-200/012cardiovascular.htm



http://btc.montana.edu/olympics/physiology/graphics/CardOutput.JPG

Cardiac Output: volume of blood pumped by the heart in 1 minute interval (L/min)

Cardiovascular safety issues: a common cause of attrition

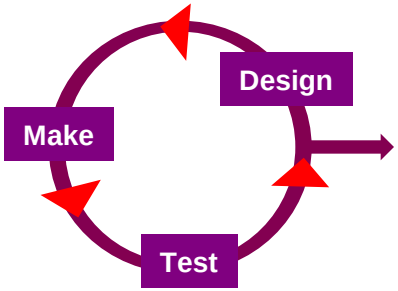
Phase	Preclinical	Non-clinical	Phase I	Phase I-III	Phase I-III	Phase III/ Approval	Post-Approval	Post-Approval
Information:	Causes of attrition	Causes of attrition	Serious ADRs	Causes of attrition	Causes of attrition	ADRs on label	Serious ADRs	Withdrawal from sale
Source:	ABPI (2008)	Car (2006)	Sibille et al. (1998)	ABPI (2008)	Olson et al. (2000)	BioPrint® (2006)	Budnitz et al. (2006)	Stevens & Baker (2008)
Sample size:	156 CDs stopped	88 CDs stopped	1,015 subjects	63 CDs stopped	82 CDs stopped	1,138 drugs	21,298 patients	47 drugs
Cardiovascular:	24%	27%	9%	35%	21%	36%	15%	45%
Hepatotoxicity:	15%	8%	7%	29%	21%	13%	0%	32%
Haematology/BM:	3%	7%	2%	3%	4%	16%	10%	9%
Nervous system:	12%	14%	28%	2%	21%	67%	39%	2%
Immunotox; photosensitivity:	7%	7%	16%	10%	11%	25%	34%	2%
Gastrointestinal:	5%	3%	23%	2%	5%	67%	14%	2%
Reprotox:	9%	13%	0%	5%	1%	10%	0%	2%
Musculoskeletal:	8%	4%	0%	5%	1%	28%	3%	2%
Respiratory:	1%	2%	0%	2%	0%	32%	8%	2%
Renal:	6%	2%	0%	5%	9%	19%	2%	0%
Genetic tox:	5%	5%	0%	0%	0%	0%	0%	0%
Carcinogenicity:	0%	3%	0%	3%	0%	1%	0%	0%
Other:	4%	0%	0%	2%	4%	16%	2%	2%

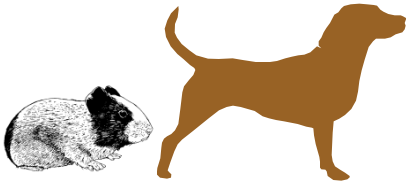
0% 1-9% 10-19% >20%

Adapted from Redfern WS et al. The Toxicologist 2010; 114 (S-1), 1081.

CV risk assessment during Drug Development

Target Selection → Lead Generation → Lead Optimization → Pre-clinical → Clinical





In silico

In vitro
Panel of targets including ion channels

In vivo
Guinea-pig model; Monitoring in single-dose dog studies:

Clinical
Clinical Monitoring; Adverse events; TQT Study

How can we predict CV risk earlier?

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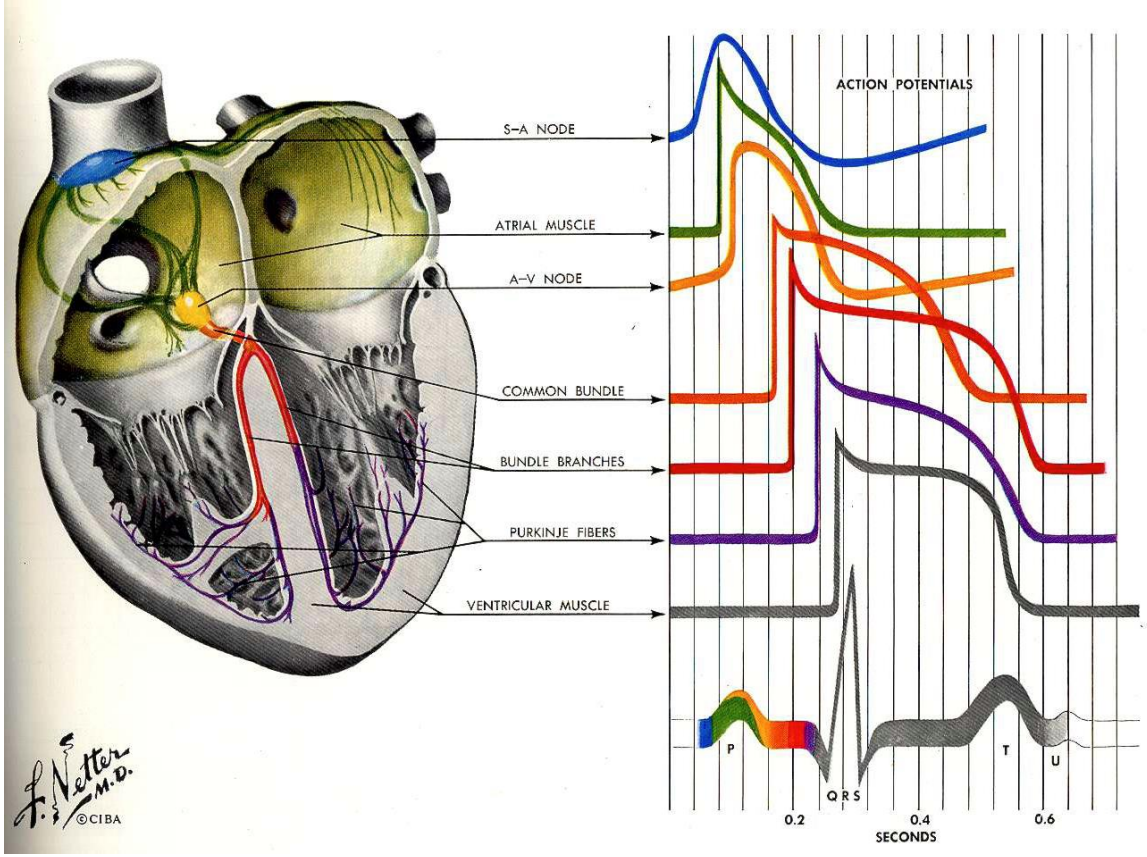
Background biology
ECG



Excitation initiated in the sino-atrial node spreads through the heart

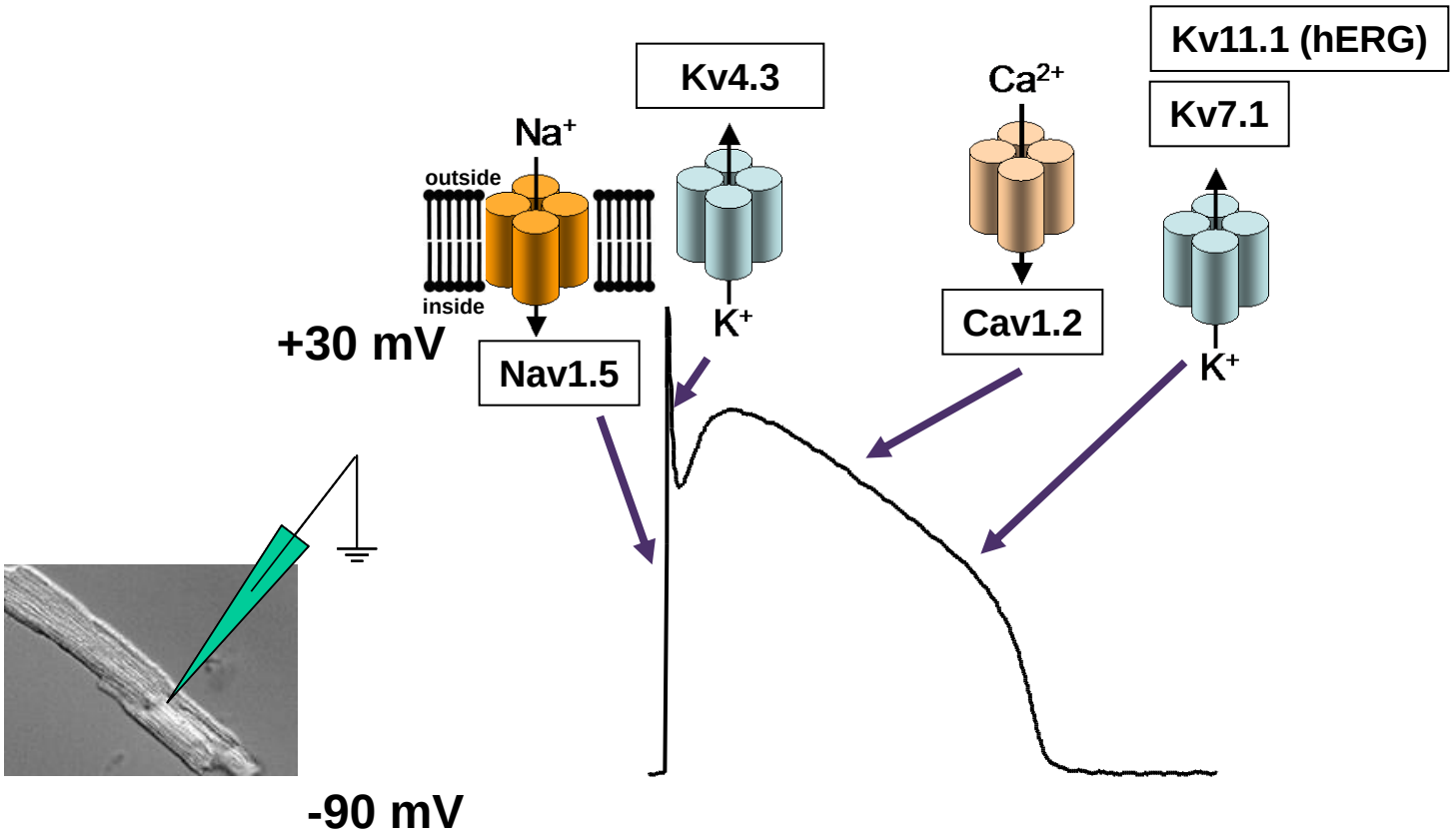
Action potential morphology varies according to cardiac region

The wave of excitation can be detected on the body surface: the electrocardiogram (ECG)

C Pollard

Background biology

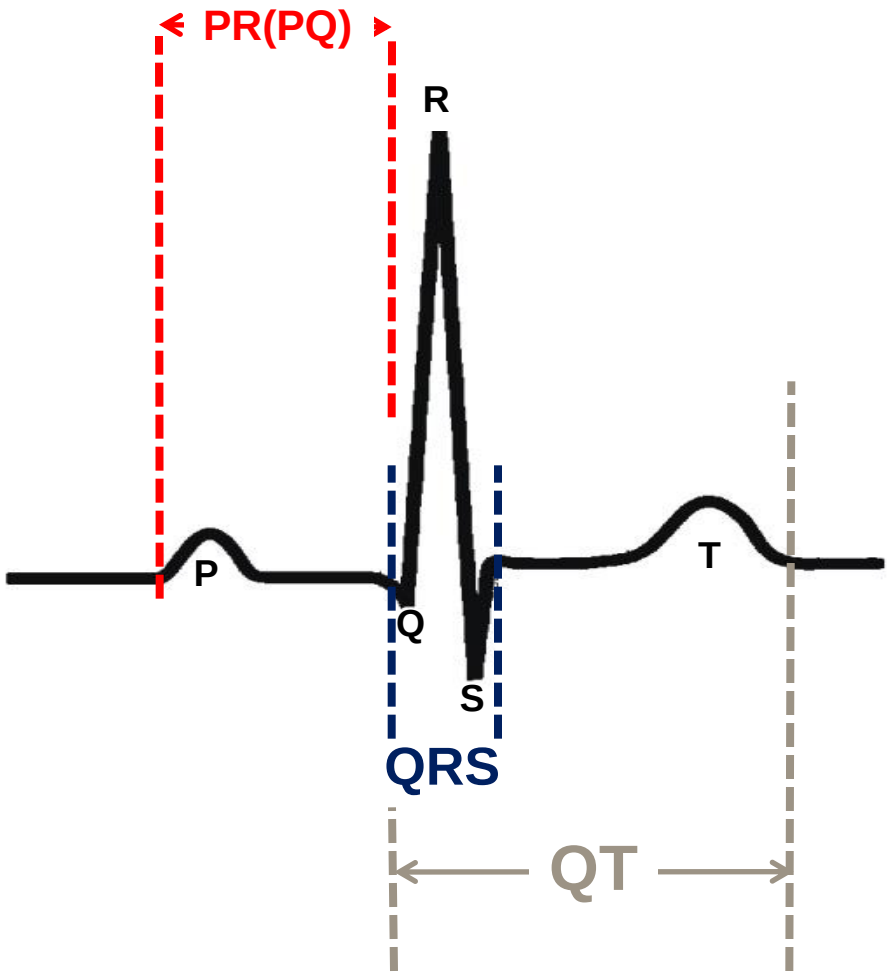
Key channels underlying ventricular action potentials



Molecular understanding fundamental to preventing / minimising ECG risk

Bers (2001). Excitation-Contraction Coupling and Contractile Force. Kluwer Academic Publishers, Netherlands. ISBN 0-7923-7157-7.

Background biology
Information derived from PR, QRS & QT intervals



PR(PQ): an index of conduction through the atrio-ventricular node

QRS: an index of conduction through the ventricles

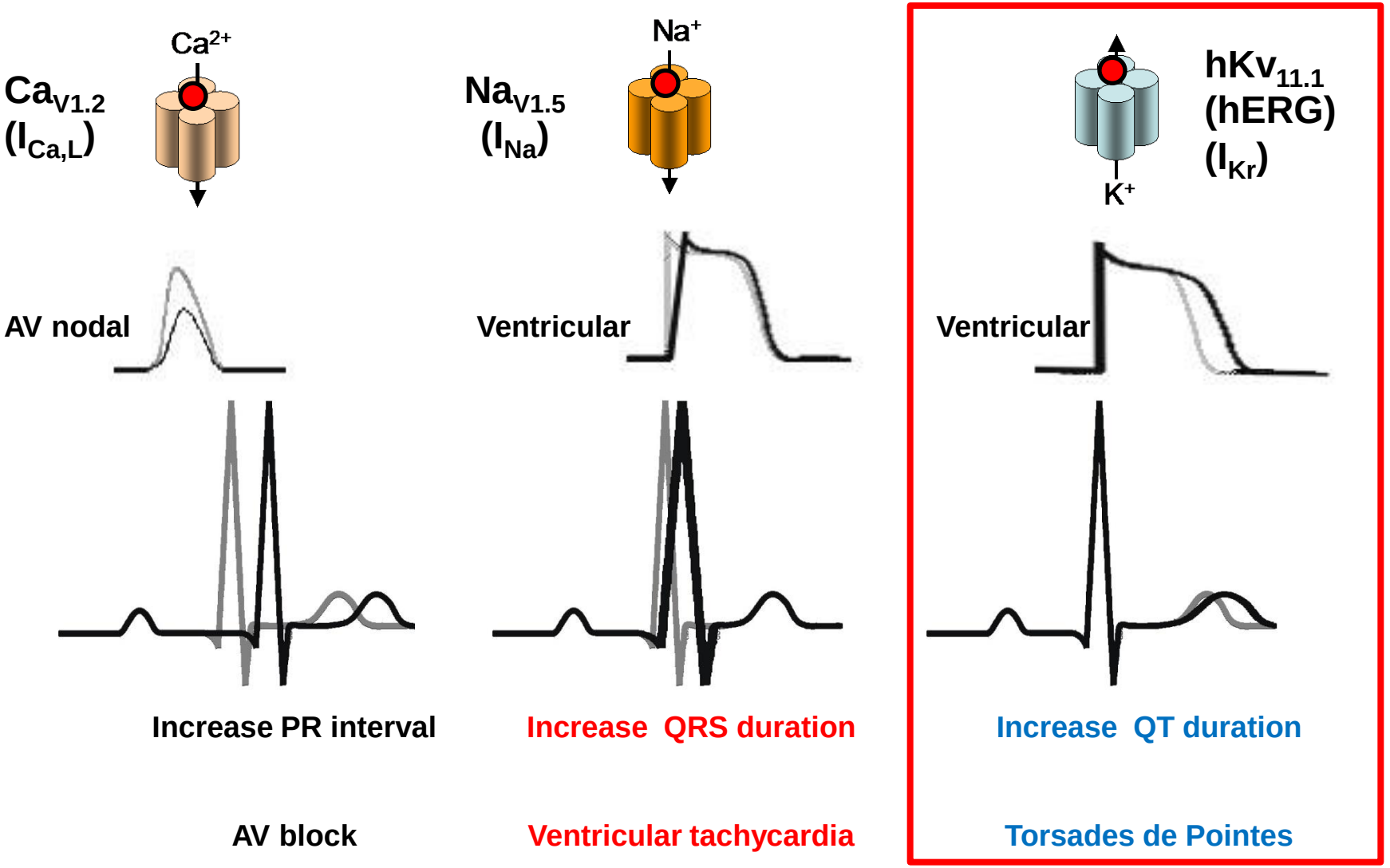
QT: an index of action potential duration in the ventricles

RR: Heart rate

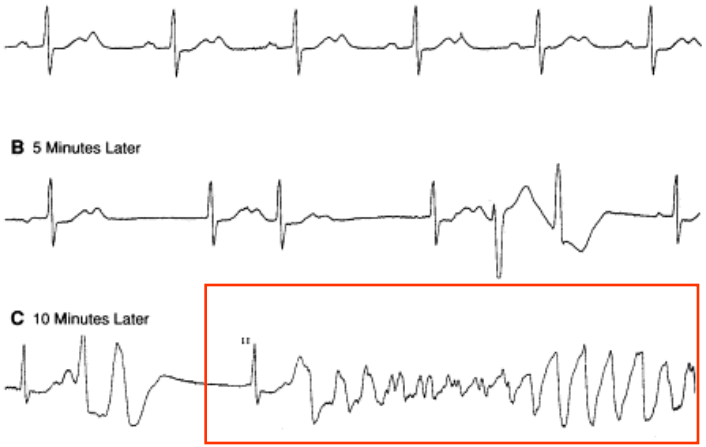
C Pollard

What's the problem

Effect of channel block on action potentials & ECG



QT interval and TdP



Torsades de pointes (TdP) is a life-threatening form of Ventricular tachycardia

The majority of drugs that promote TdP inhibit potassium current (IKr) channels in cardiomyocytes and cause a prolongation of the QT interval on the surface electrocardiogram (ECG).

In vivo and clinic: QT interval (ECG)
Pre-clinical in vitro: human ether-a-gogo–related gene (hERG) assay is widely used as a model for the effect of compounds on IKr conduction

General guideline: provisional **30-fold** safety margin between the maximally reached free plasma concentration and the in vitro 50% inhibitory concentration (IC50) for IKr inhibition
Redfern et al., Cardiovasc Res. 2003 Apr 1;58(1):32-45

QT: Notable Drug Withdrawals

Table 1 Drugs withdrawn from the US market as a result of QT-associated proarrhythmia

Compound	Class	Year withdrawn (reference)
Astemizole	Antihistamine	1999 (1)
Cisapride	Prokinetic agent	2000 (2)
Grepafloxacin	Fluoroquinolone antibiotic	1999 (3)
Lidoflazine	Calcium channel blocker	Never approved in the United States
Sertindole	Antipsychotic agent	Rejected by the US Food and Drug Administration in 1996
Terfenadine	Antihistamine	1997 (4)
Terodiline	Antimuscarinic agent	1993 (5)

QT as a Safety Biomarker
Whellan et al; CPT 2009: 86 (1)

Factors effecting QT

Heart rate and circadian rhythm are important factors when analysing drug effects on QT interval

Heart rate, calculated from RR interval is commonly corrected for with respect to QT (QTc)

Bazett $QTcB = QTxRR^{-0.5}$

Fredericia $QTcF = QTxRR^{-0.333}$

Other factors affecting QT/QTc interval:

Genetic (Long QT Syndrome)
Food intake
Obesity
Physical activity
Electrolyte disturbances
Blood glucose concentrations
Blood pressure
Alcoholism
Presence of U-wave

Table 2 Variation of average QTc with age and gender

	Age, 20–29 years	Age, 70–79 years
Males	387 ms (351–426)[a]	401 ms (363–446)[a]
Females	400 ms (362–440)[a]	410 ms (369–459)[a]

[a]Averages are the means at 2% of the 98th percentile.

Pharmacokinetic –Pharmacodynamic Modeling in the Data analysis and interpretation of Drug-induced QT/QTc prolongation Piotrovsky AAPS Journal 2005 7 (3) E609

QTc PKPD Modelling

Translational

Parkinson et al
Chain et al
Ollerstam et al

Mechanistic

Cardiac Safety Simulator
Combination of ion channels, hERG trafficking, electrolyte levels etc and population variability
http://www.simcyp.com/ProductServices/Cardiac+Safety+Simulator/

In vitro predictor

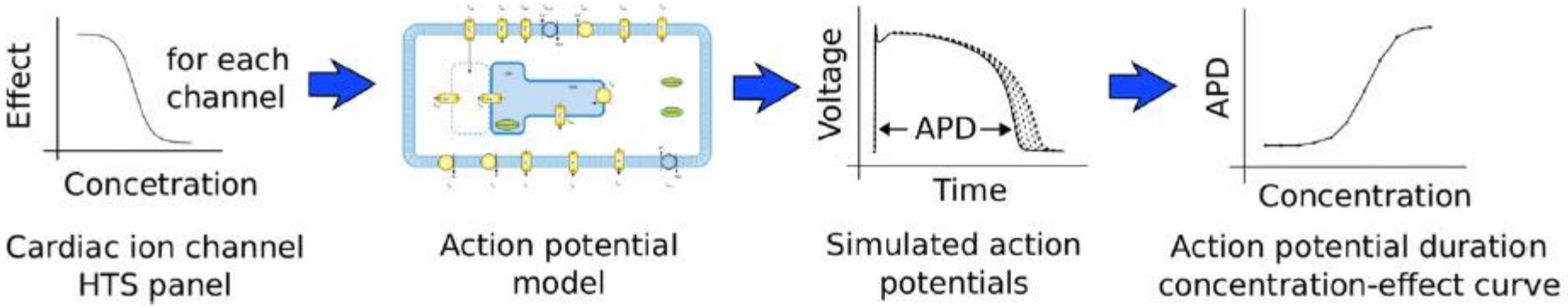
isAP model
(in silico Action Potential)

Mechanism based

Jonker et al
Ikr to Clinical QTc

isAP (in silico Action potential) Model

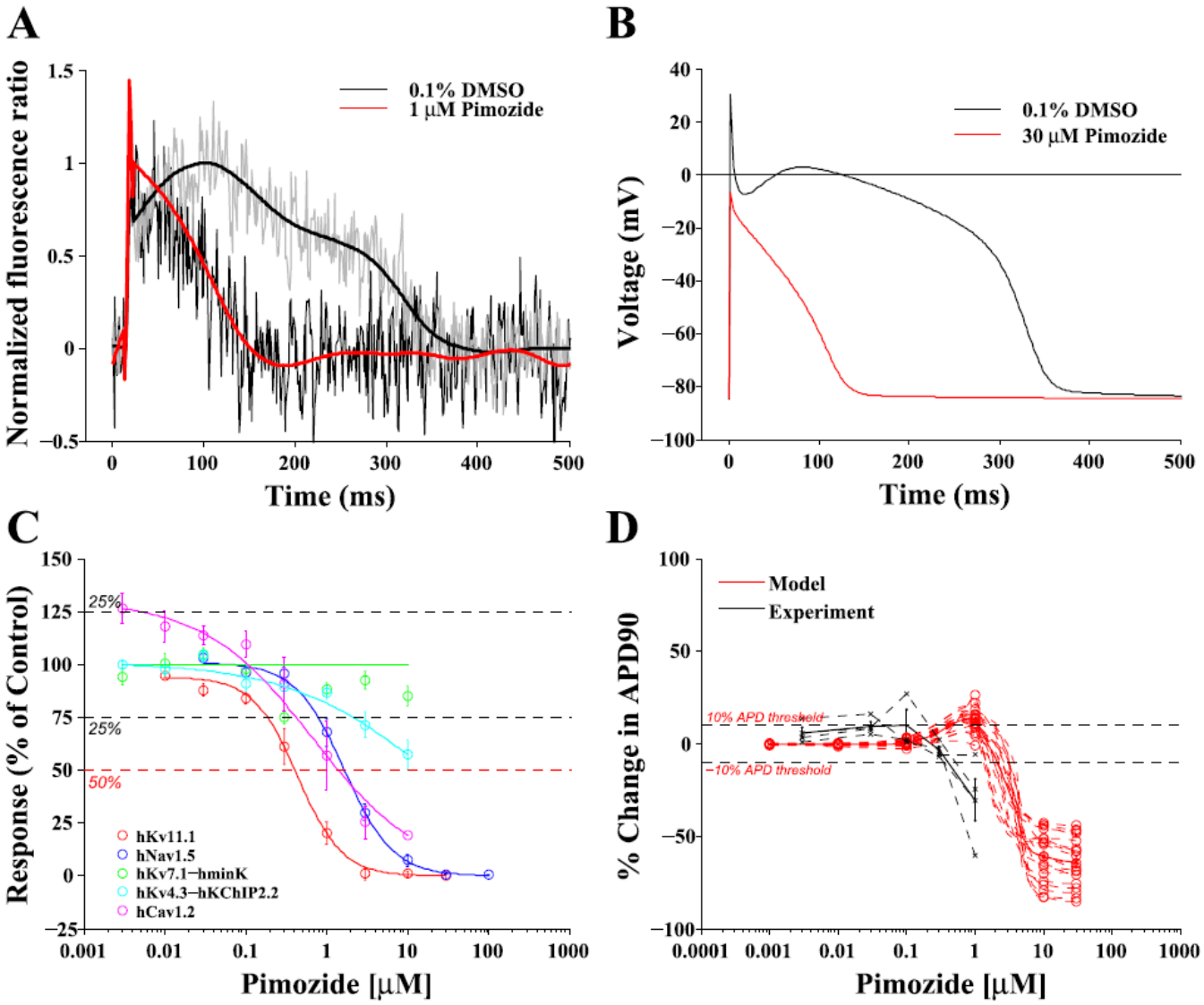
R.C. Elkins et al. / Journal of Pharmacological and Toxicological Methods 68 (2013) 112–122



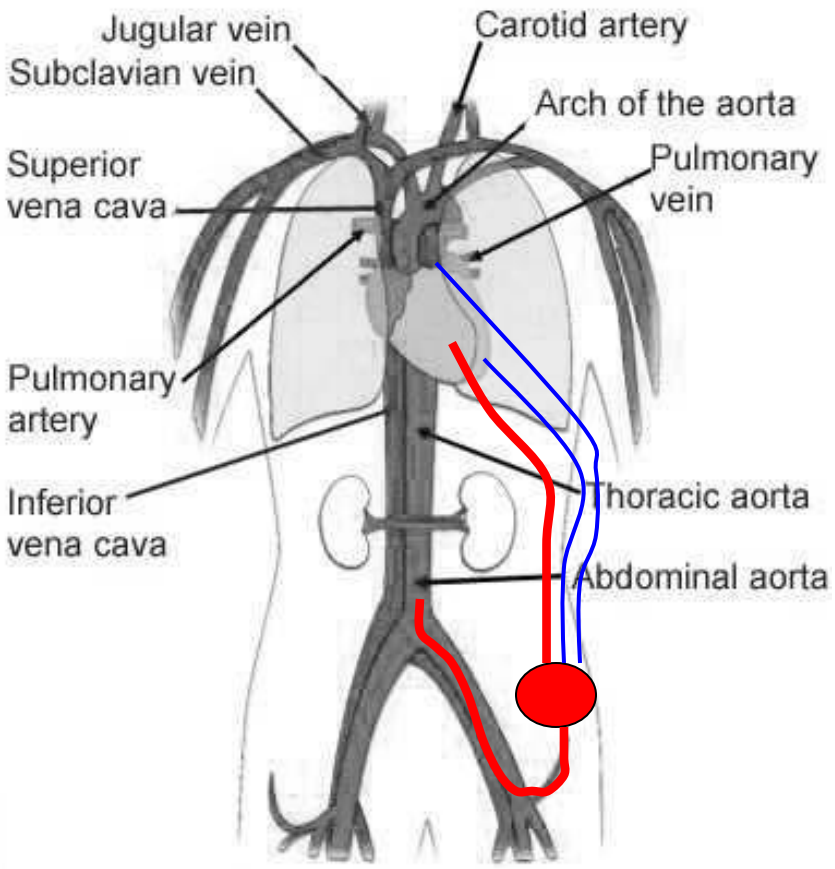
Hund and Rudy (canine epicardial model), adapted for midmyocardial cells by Benson

Could we predict Human outcome in the future?

Pimozide- Mixed ion channel blocker



Dog In vivo Surgical set-up



Pressure catheters positioned in:

Descending aorta – for arterial blood pressure

Left ventricle – for left ventricular pressure

ECG leads placed directly on epicardial surface of heart

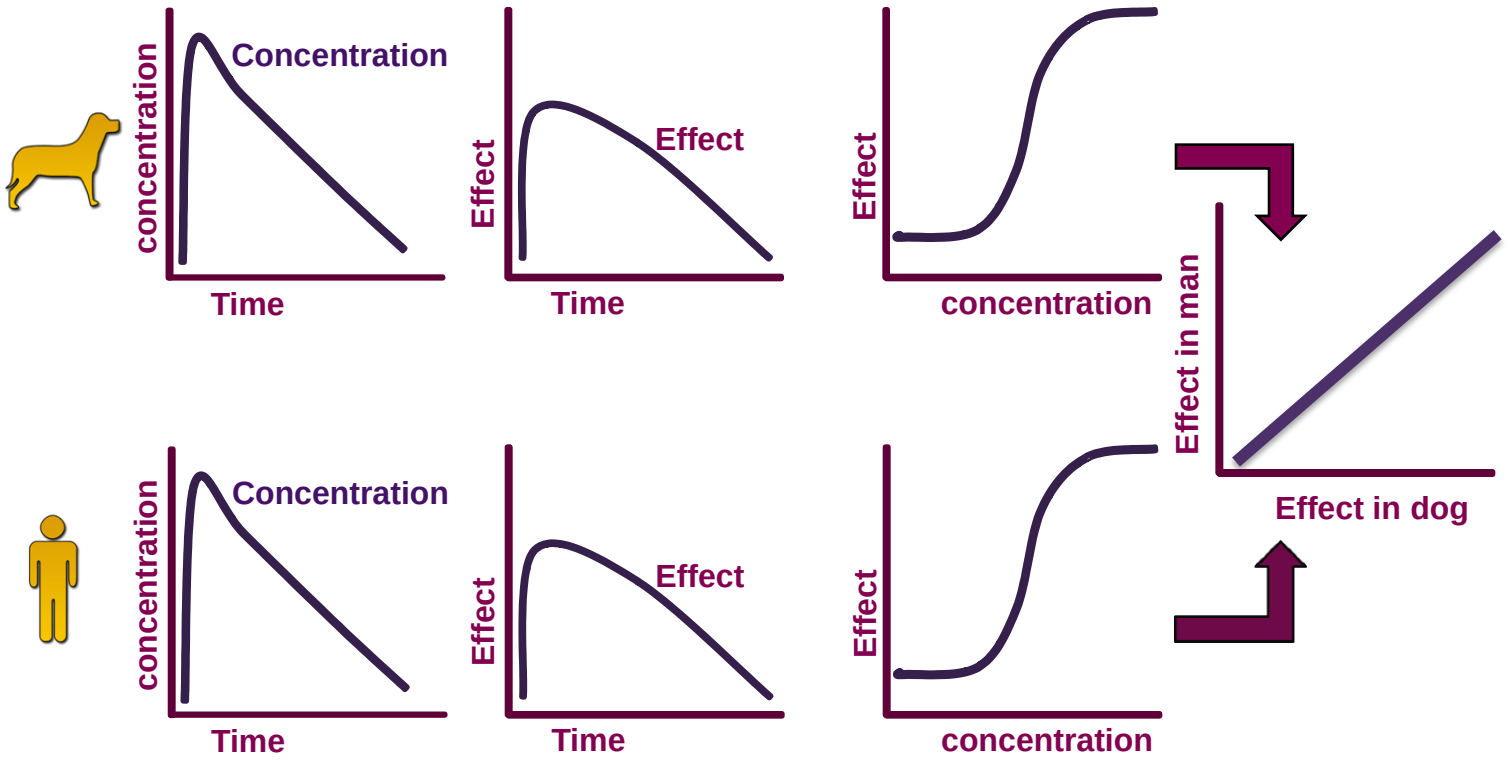
Dog Study design

- Each dog receives a vehicle dose and 3 dose groups on 4 separate dosing days.
- This can be in an ascending dose design or latin square (randomised) design

- Doses are chosen based upon tolerability data in the dog and any other previously identified risks (e.g. Rat, Guinea Pig telemetry).

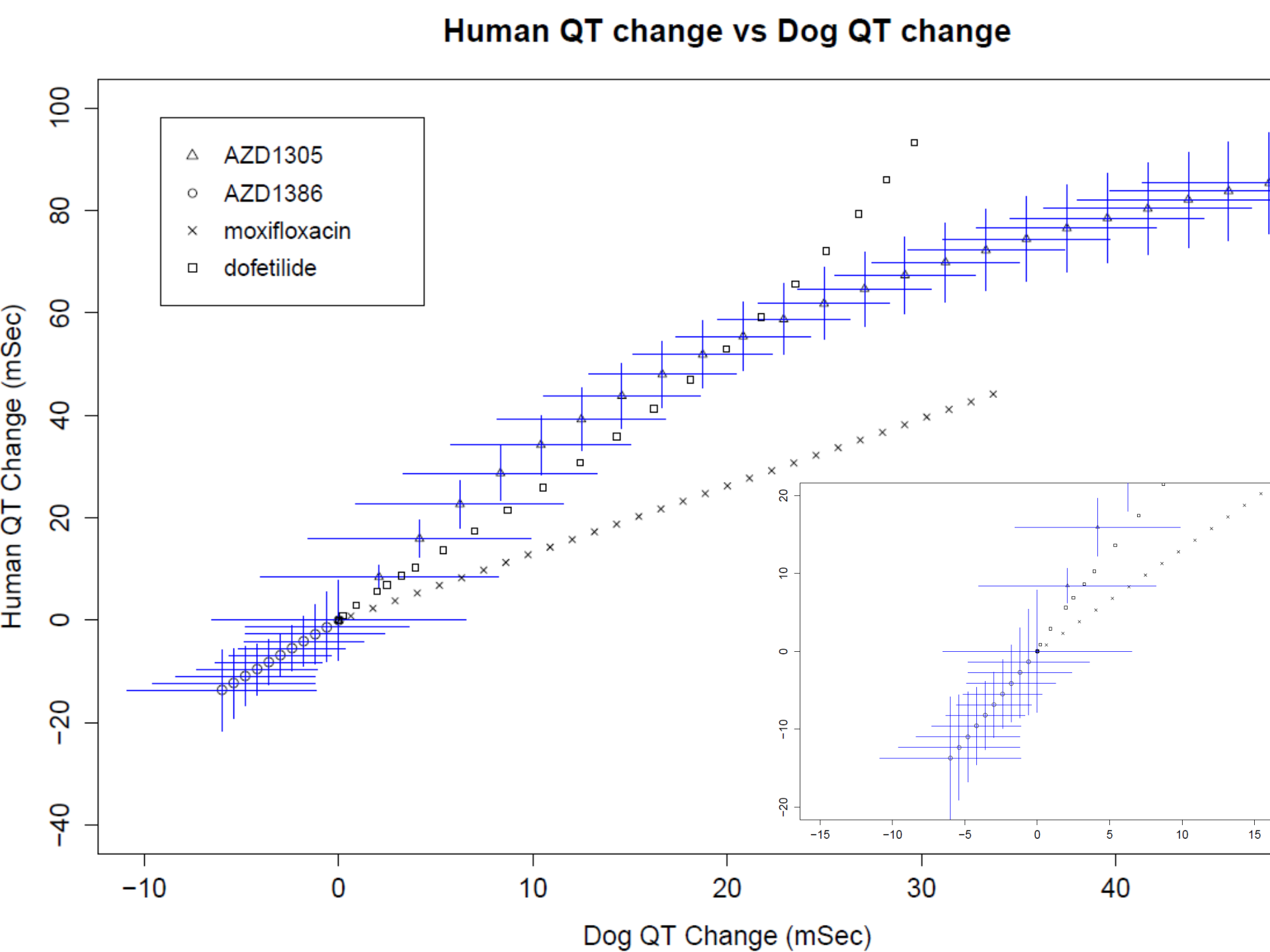
- PK: typically 3 time-points
- PD: typically 12 time-points

Parkinson Translation



Compounds: AZD1305 AZD1386 moxifloxacin, dofetilide (Data from Ollerstam)

Consistent translational relationship at low delta-QTc intervals
- 2.5–8 ms in dog would correspond to a 10 ms change in human
- Journal Pharm + Tox Methods 68 (2013) 357

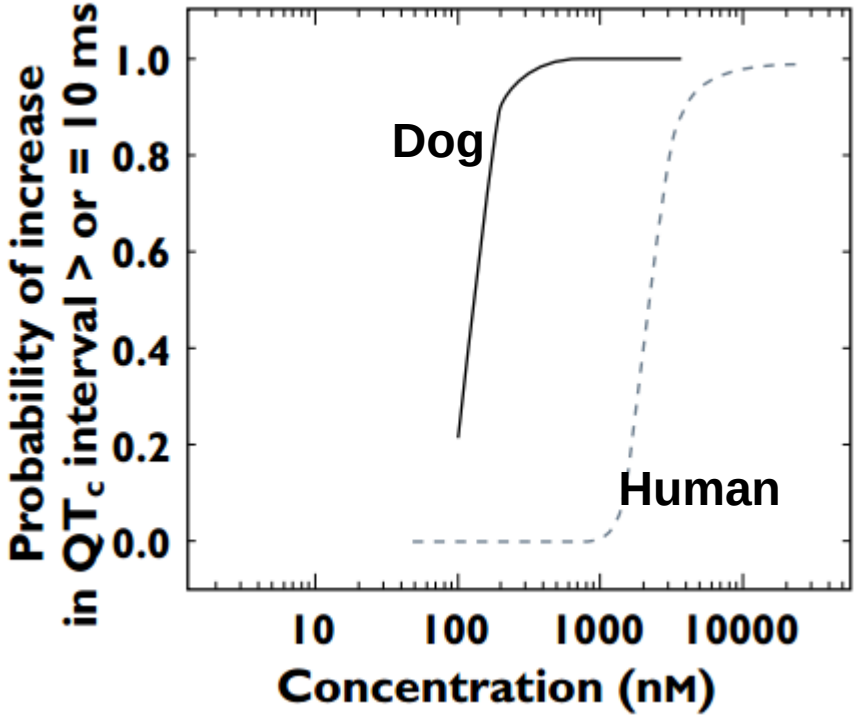

Human QT change vs Dog QT change
AZD1305
AZD1386
moxifloxacin
dofetilide
Human QT Change (mSec)
Dog QT Change (mSec)
100
80
60
40
20
0
−20
−40
−10
0
10
20
30
40
−15
−10
−5
0
5
10
15

Clinical Prediction of QTc

Chain *et al.* (TI Pharma)

- Cisapride, d-sotalol, moxifloxacin
- PKPD relationship modelled in Dog and Man (2xPhD students)
- Does look at the probability of reaching 10 ms (WinBUGS)

$$\text{Probability of} \geq 10\ \text{ms prolongation (at } C) = \text{step}\left(0.00001^{F(\text{Gender})} \cdot \text{Slope} - \frac{10\ \text{ms}}{C}\right)$$



Identifying the translational gap in the evaluation of drug-induced QT_c interval prolongation

Anne S.Y. Chain,[1]* Vincent F.S. Dubois,[1]* Meindert Danhof[1], Miriam C.J.M. Sturkenboom[2,3] & Oscar Della Pasqua[1,4] on behalf of the Cardiovascular Safety Project Team, TI Pharma PKPD Platform

Assessing the Probability of Drug-Induced QTc-Interval Prolongation During Clinical Drug Development

ASY Chain[1], KM Krudys[2], M Danhof[1] and O Della Pasqua[1,2]

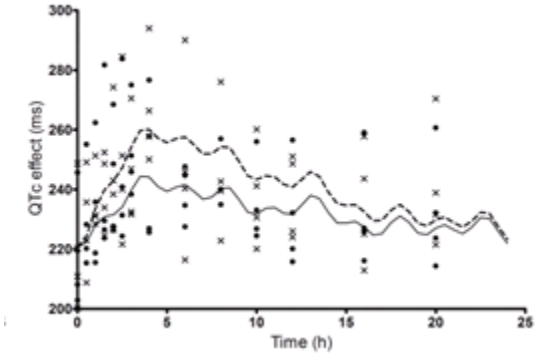
CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 90 NUMBER 6 | DECEMBER 2011

http://onlinelibrary.wiley.com/doi/10.1111/bcp.12082/pdf

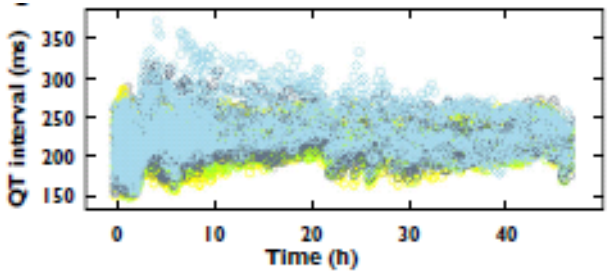
Comparison of two approaches

- Single versus multiple cosine functions for baseline fitting
- Linear drug effect
- QTc correction carried out during fitting in Chain *et al*
- Chain et al have a higher frequency of measurements
- No obvious differences in Data capture (similar analysis software and technology)

AZD1305



Moxifloxacin



QTc Summary

- QT translation is relatively well studied, still relatively small number of compounds assessed
- AZ Dog studies appear more sensitive to QTc changes than the other reported studies
- In general Human QTc changes are larger than dog -more likely to reach 10 ms at a lower concentration

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Factors affecting HR and BP

Factors affecting heart rate:
Tachycardia: physical exercise, sleep, anxiety, stress, illness, ingestion
Bradycardia: Sepsis, fever, hypoxia, hyperthyroidism, cardiomyopathy, valvular heart disease

Factors affecting Blood pressure:
Age
Circadian rhythm
Exercise
disease
Alcohol
Stress
obesity
Blood volume (dietary salt intake)
Vascular Resistance –related to length and radius of vessel
Viscosity of Blood

HR/BP system

Heart rate (HR, bpm)): measured from RR interval from ECG
Blood pressure (mmHg): measured using a sphygmomanometer or pressure catheter

MAP=mean arterial pressure
Systolic pressure= maximum pressure
Diastolic pressure= minimum pressure

$$\mathrm{MAP} \approx P_{\mathrm{dias}} + \frac{1}{3}(P_{\mathrm{sys}} - P_{\mathrm{dias}}).$$

Basic principles:

CO=HR.SV	CO= cardiac output mL/min, SV = stroke volume mL/beat
MAP=TPR.CO	TPR= total peripheral resistance

Hemodynamic PKPD Modelling

Translational

Langdon et al

Mechanistic

Francheteau *et al*
Snelder *et al*

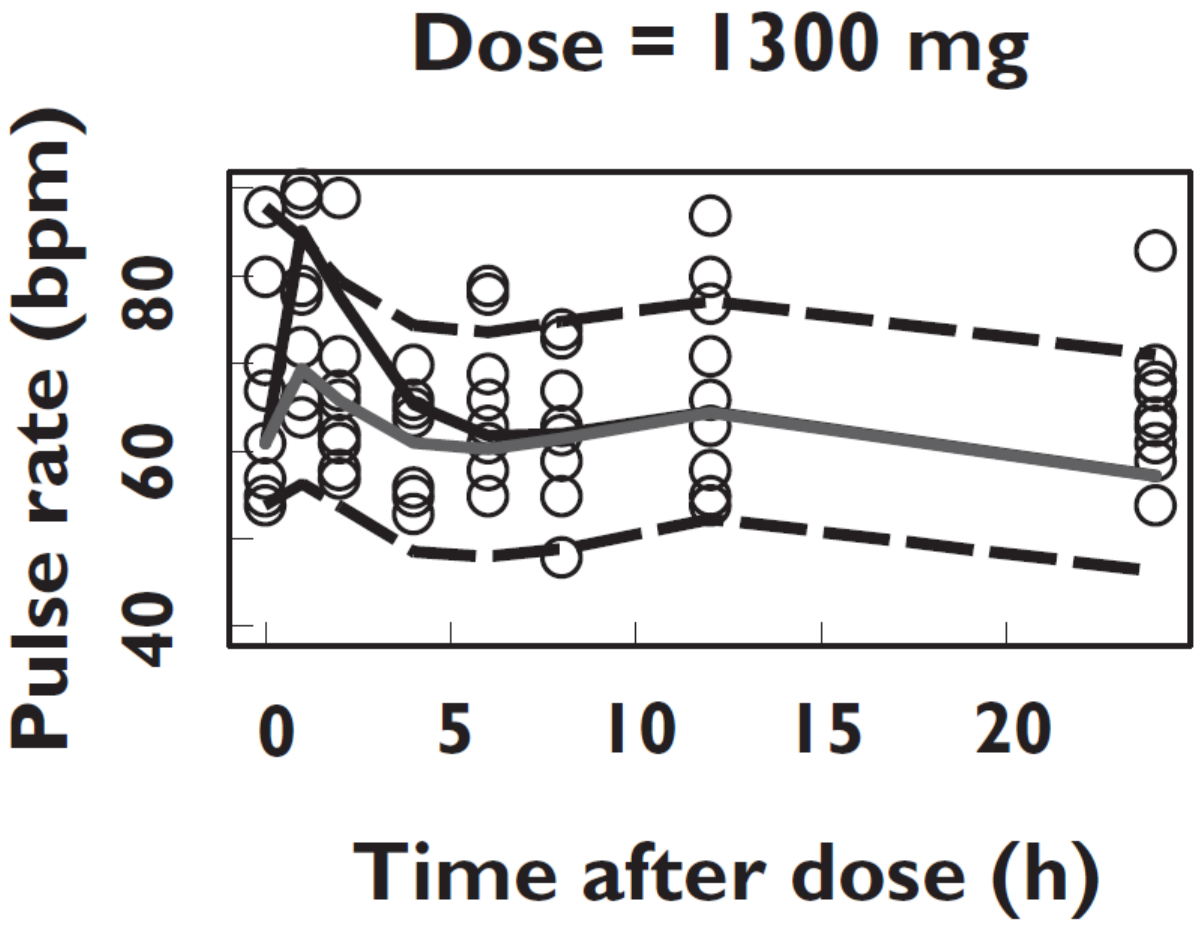
Mechanism based

eg VEGF inhibition
Curwen et al Clin Cancer Res 2008; 14(10)

Translational HR modelling

Dog makes reasonable prediction of Human HR change

Drug effect: Linear (Slope typical value 2.3 fold higher in dog)
Baseline: cosine function
HR modelled, sBP not modelled



Grey 50th quantile of simulation

Black 50th quantile using of simulation using dog slope

Internal Regulatory Controls

Baroreceptor reflex: Baroreceptors in the high pressure receptor zones. Result: Autonomic adjustment of mean arterial pressure, altering both the force and speed of the heart's contractions, and TPR.

Renin-angiotensin system (RAS): activating an endogenous vasoconstrictor angiotensin II. Result: long-term adjustment of arterial pressure drop

Aldosterone release: released in response to angiotensin II or high serum potassium levels. Aldosterone stimulates sodium retention and potassium excretion by the kidneys. Result: increased fluid retention, and indirectly, arterial pressure.

Baroreceptors in low pressure receptor zones
-regulate the secretion of antidiuretic hormone (ADH/Vasopressin), renin and aldosterone. Result: increased in blood volume =cardiac output, arterial blood pressure.

Can a simple model capture all this?
How to include drug effects in an otherwise well controlled homeostatic system?

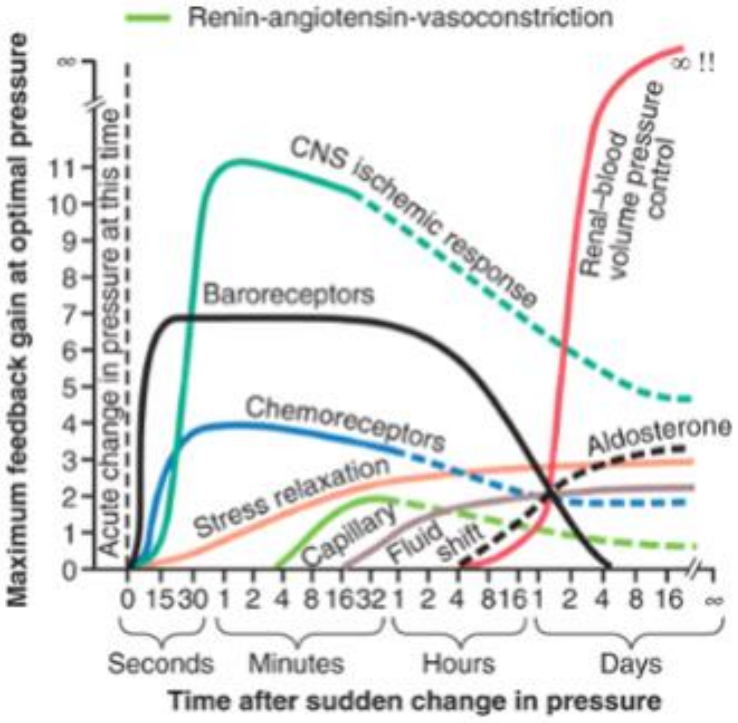
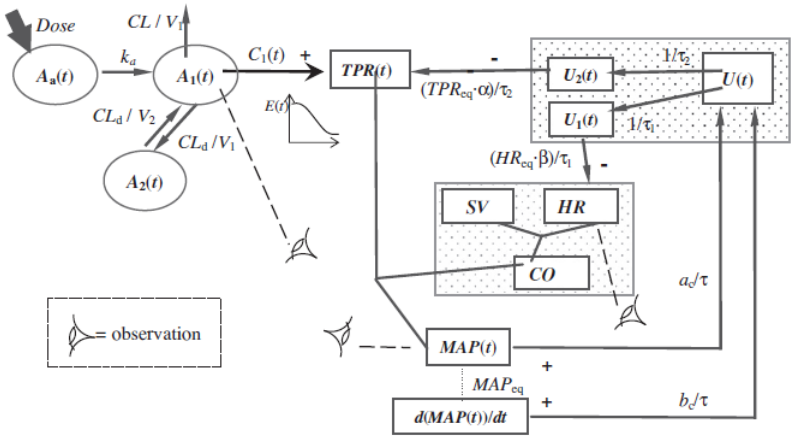


Figure 19-16 Approximate potency of various arterial pressure control mechanisms at different time intervals...

Guyton & Hall 2010

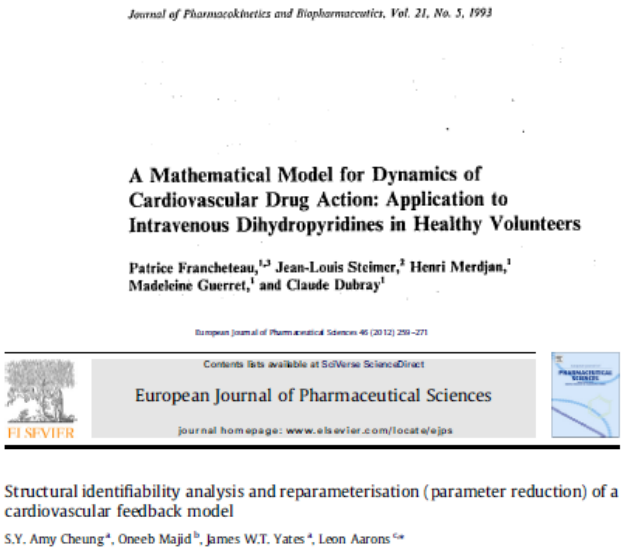
Francheteau *et al*



Dihydropyridines (L-type calcium channel blockers) affect total peripheral resistance, vasodilators, in healthy volunteers

System parameters could therefore be used to predict drug effects in pre-clinical stage

Updated by Cheung et al to address structural identifiability issues.



Journal of Pharmacokinetics and Biopharmaceutics, Vol. 21, No. 5, 1993

A Mathematical Model for Dynamics of Cardiovascular Drug Action: Application to Intravenous Dihydropyridines in Healthy Volunteers

Patrice Francheteau,[1,2] Jean-Louis Steimer,[3] Henri Merdjan,[1] Madeleine Guerret,[1] and Claude Dubray[1]

European Journal of Pharmaceutical Sciences 46 (2012) 259–271

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

ELSEVIER

Structural identifiability analysis and reparameterisation (parameter reduction) of a cardiovascular feedback model

S.Y. Amy Cheung[a], Oneeb Majid[b], James W.T. Yates[a], Leon Aarons[c,*]

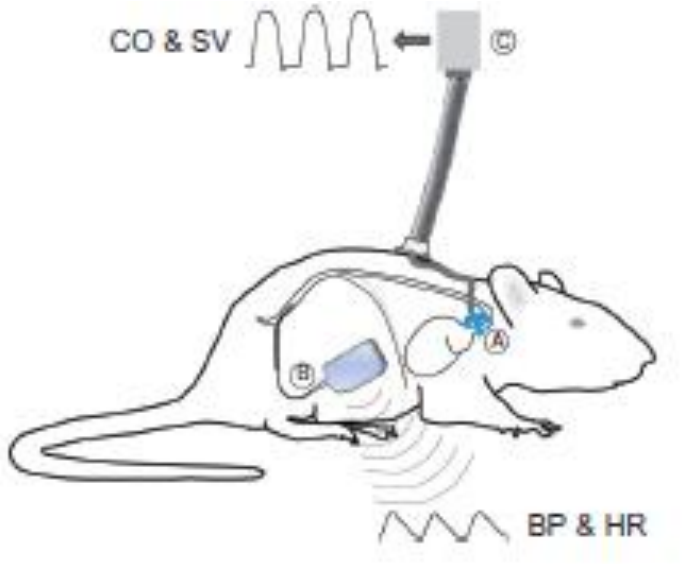
Snelder *et al*

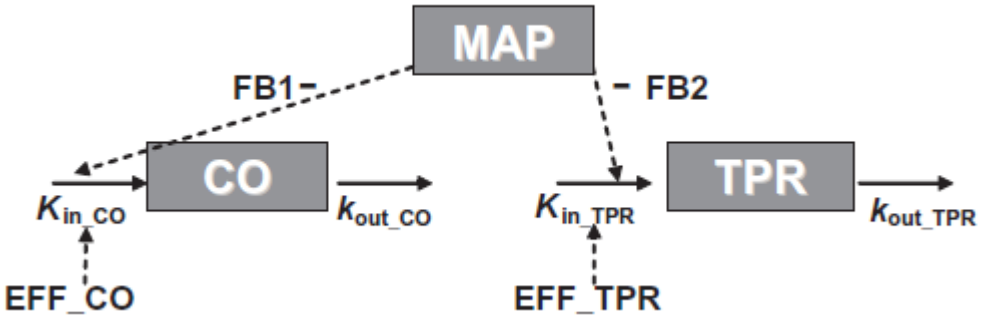
Studied 6 anti hypertensive drugs in spontaneously hypertensive rats

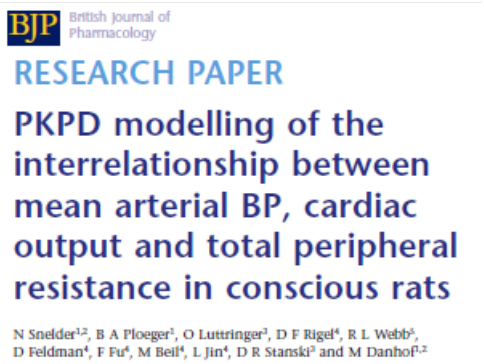
Study 1: different compound each day (MAP and HR)
Study 2: Varied doses MAP and CO

CO measured using an aortic flow probe, has to be hardwired unlike radiotransmitter for ECG and BP measurements

Proportional feedback of MAP on CO and TPR






BJP British Journal of Pharmacology

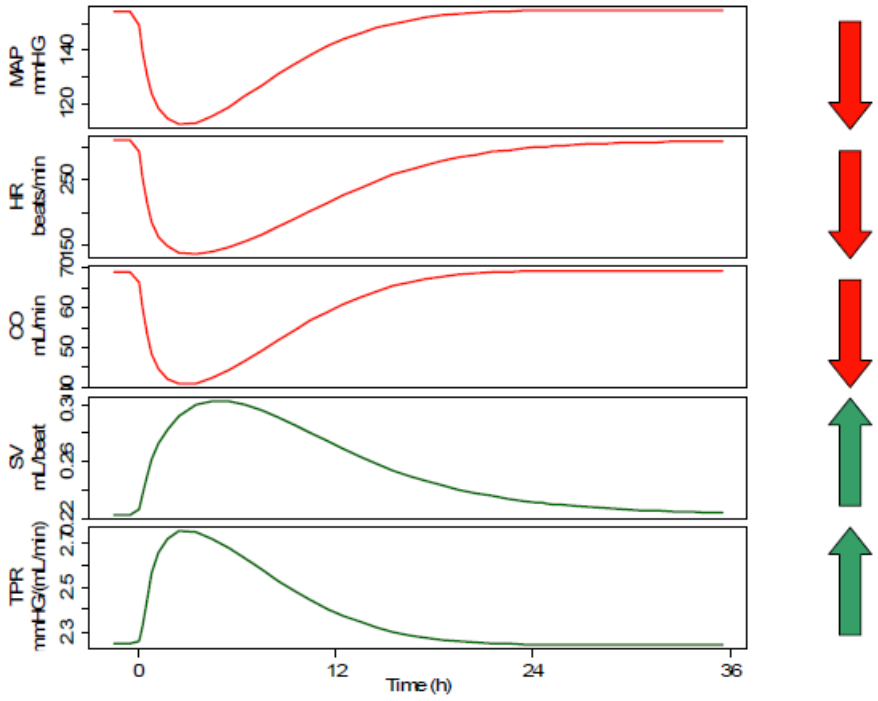
RESEARCH PAPER

PKPD modelling of the interrelationship between mean arterial BP, cardiac output and total peripheral resistance in conscious rats

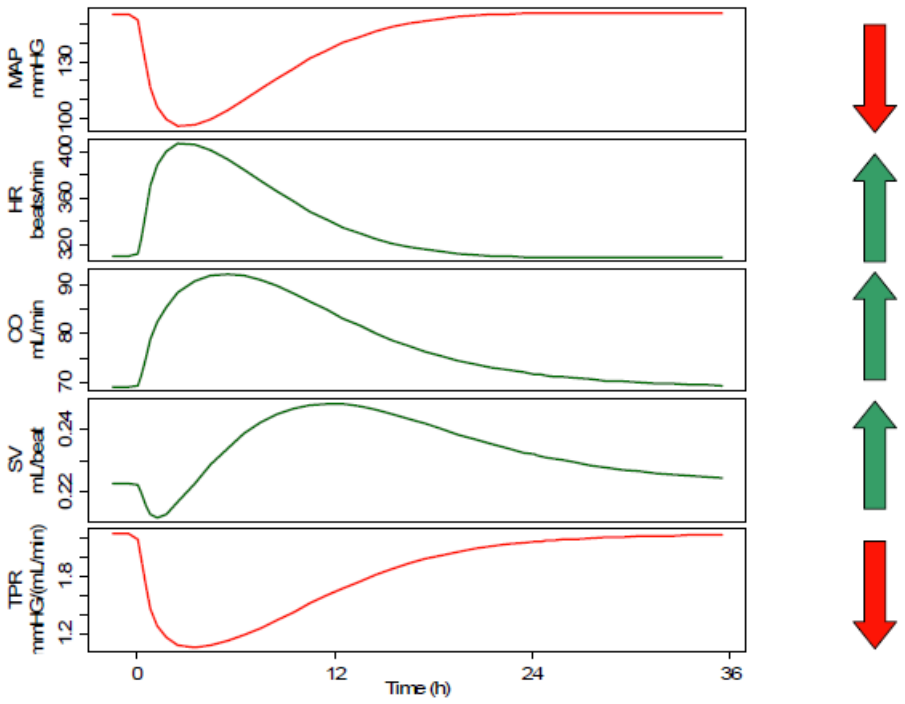
N Snelder[1,2], B A Ploeger[1], O Luttringer[3], D F Rigel[4], R L Webb[5], D Feldman[4], F Fu[4], M Beil[4], L Jin[4], D R Stanski[3] and M Danhof[1,2]

Snelder *et al*

Effect on HR

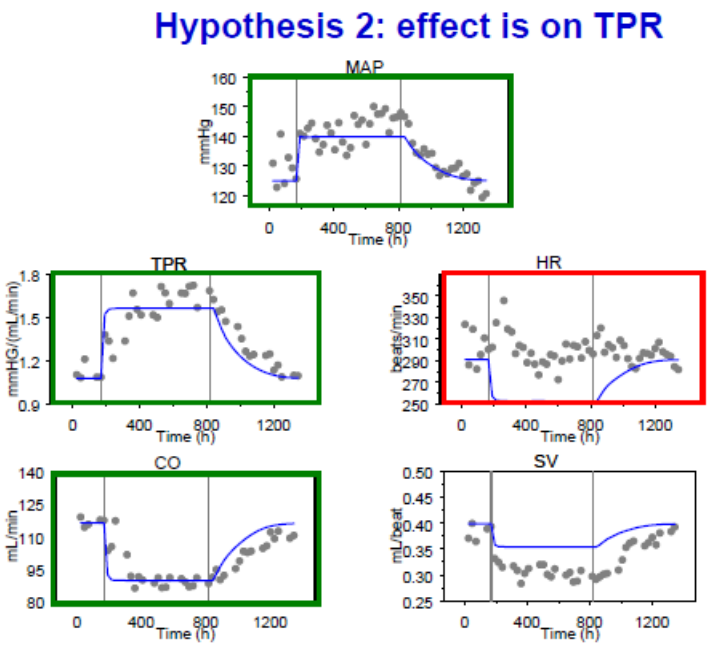


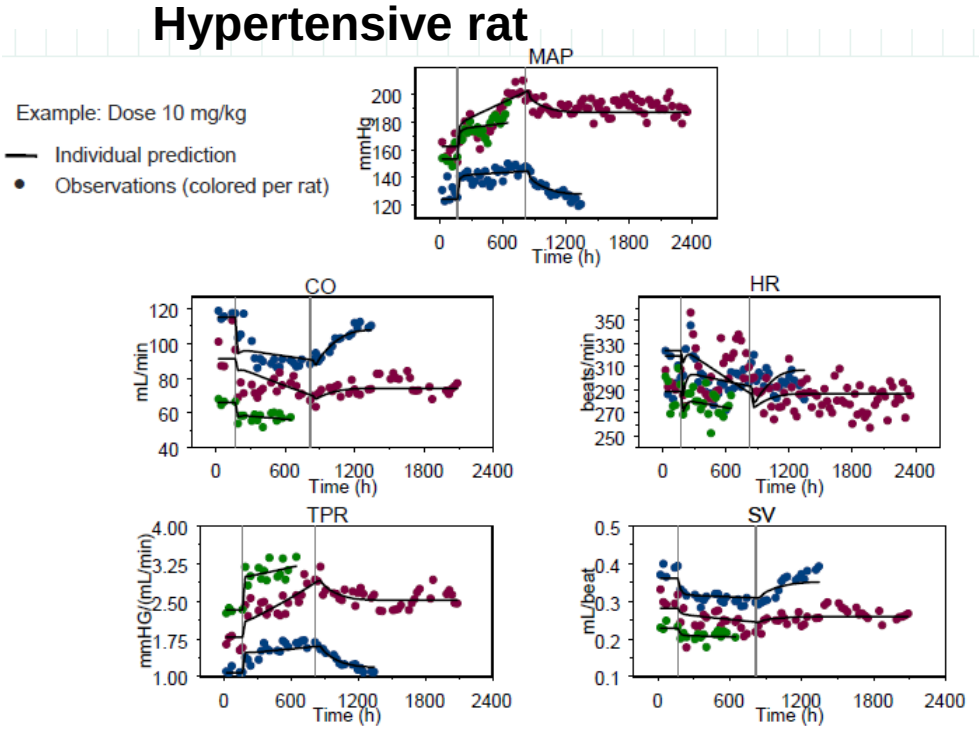
Effect on TPR



Provides mechanistic understanding that can be applied to drugs with unknown mechanism on hemodynamics

Application to Fingolimod





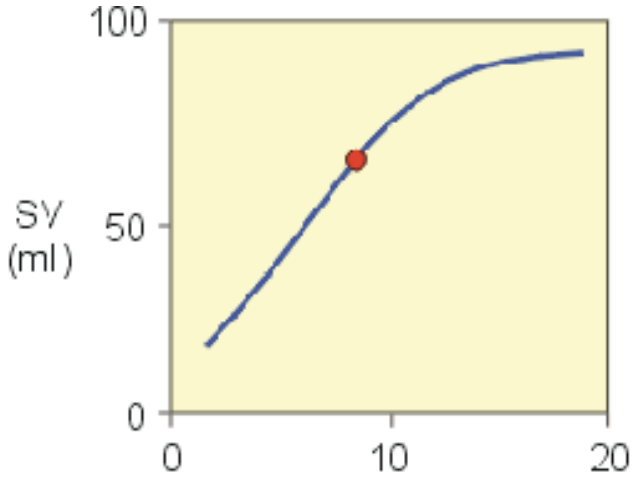
- The effect of fingolimod on the CVS was described by a combination of 3 effects:
  - Fast positive effect on TPR: log-linear model
  - Slow positive effect on TPR: linear model
    - Slow structural effect only in hypertensive rat at high doses
  - Transient negative effect on HR: power model
    - Tolerance was described by feedback model - type 1

Overview

- Cardiovascular Safety- why is it important?
- What do we measure and when?
- Focus on QT models
- Focus on HR/BP models
- Case Study 1: Guinea Pig model
- Case Study 2: Dog risk assessment

Case study 1

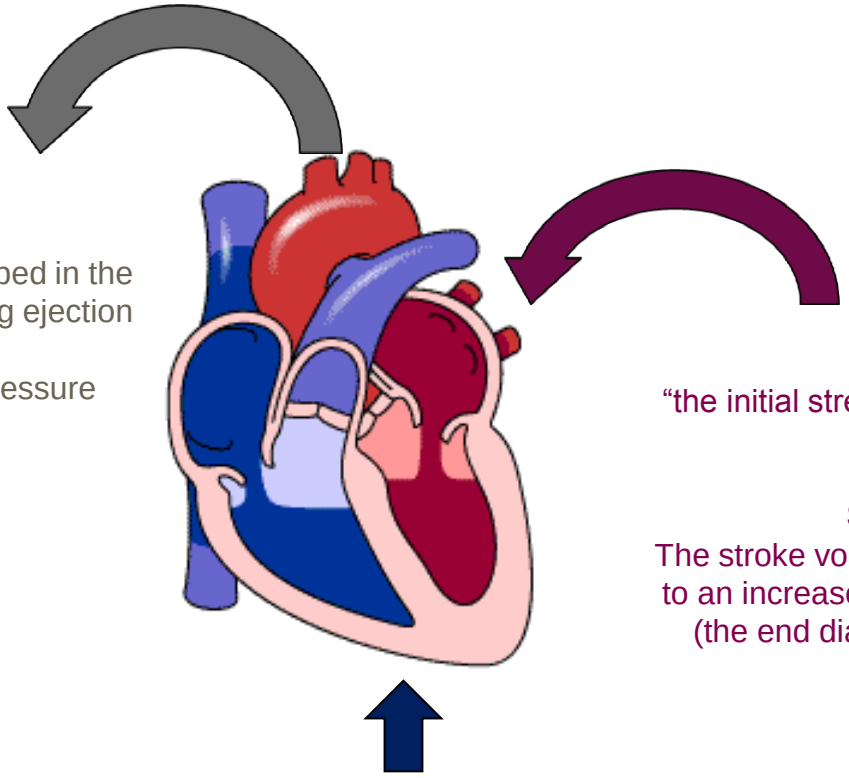
Contractility



Afterload

The tension or stress developed in the wall of the left ventricle during ejection

Closely related to aortic pressure



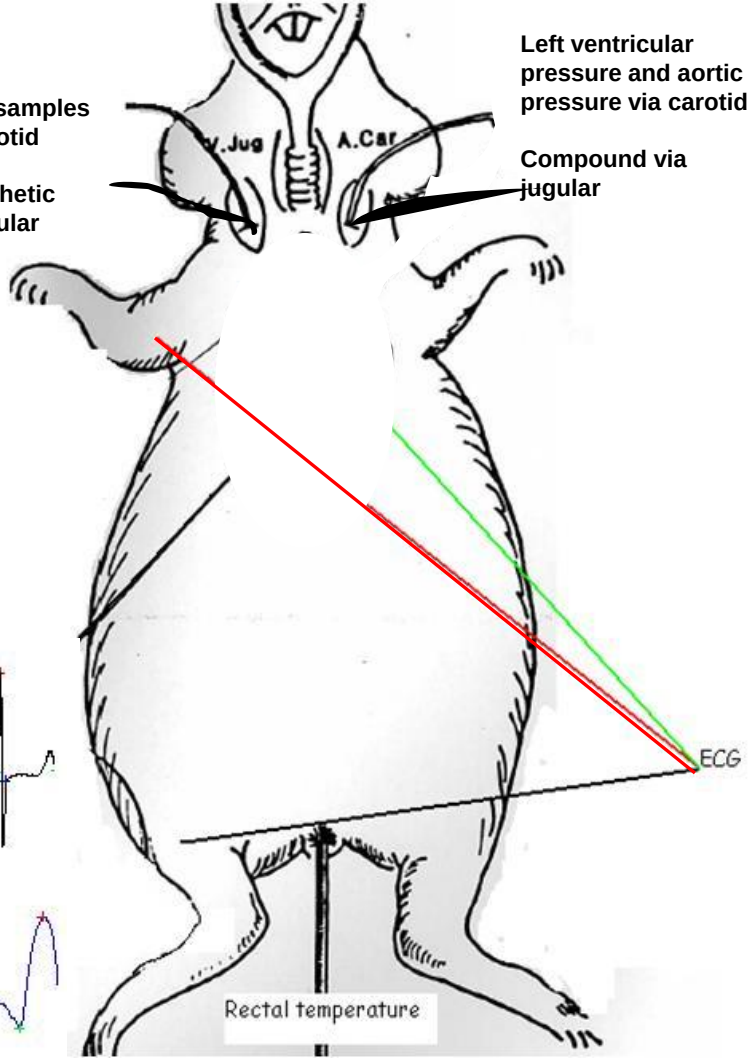
Preload

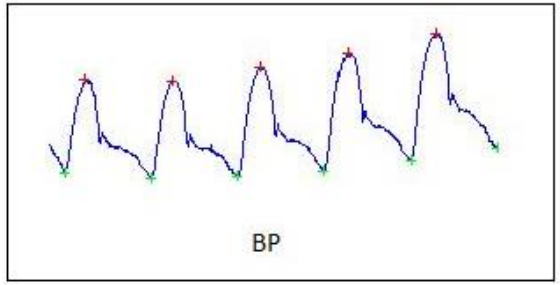
"the initial stretching of the cardiac myocytes prior to contraction"

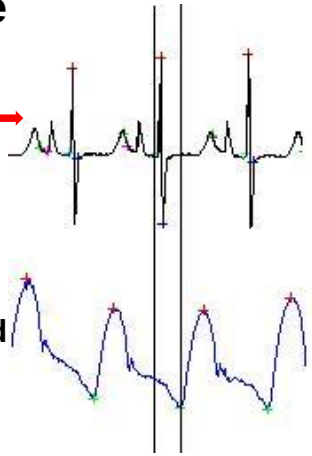
Starling's Law of the heart
The stroke volume of the heart increases in response to an increase in the volume of blood filling the heart (the end diastolic volume) when all other factors remain constant.

Direct
Sympathetic effects on degree of sarcomere shortening

Anaesthetised G-pig model

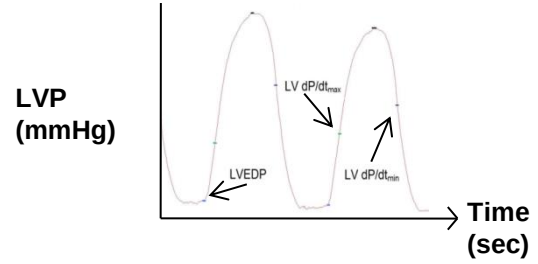




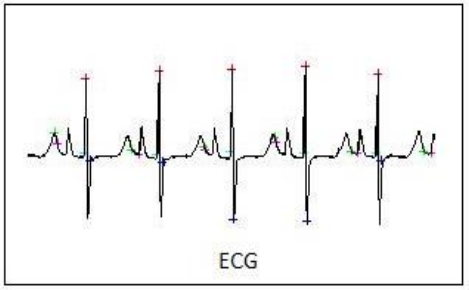


Hemodynamics
Blood pressure
Heart rate
QA interval

QA and LV dP/dt_{max} are reported to be inversely related



Contractility
Left Ventricular pressure
dP/dt Max
dP/dt Min



ECG
PR, QRS, QT, QTc, RR intervals

K Philp

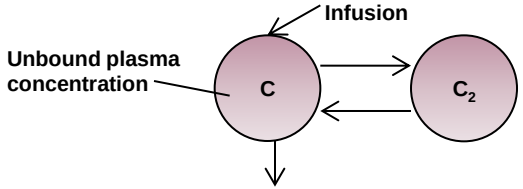
Closed chest surgery under sinus rhythm
Sympathetic system not compromised apart from anesthesia

Guinea Pig Closed Chest model

PKPD modelling details

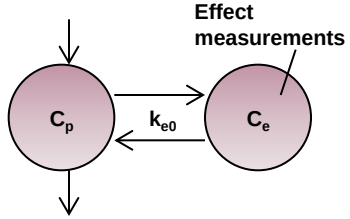
PK model: 2 compartment IV infusion

Parameters: V, V_2, Cl, Cl_2 (not reported)



Link Model: distributional delay between plasma concentration and site of effect

Parameter: k_{e0} (reported as $t_{1/2}$ k_{e0} in minutes)



PD model: exponential model (empirical)

Parameters: a, b (related to shape of curve)

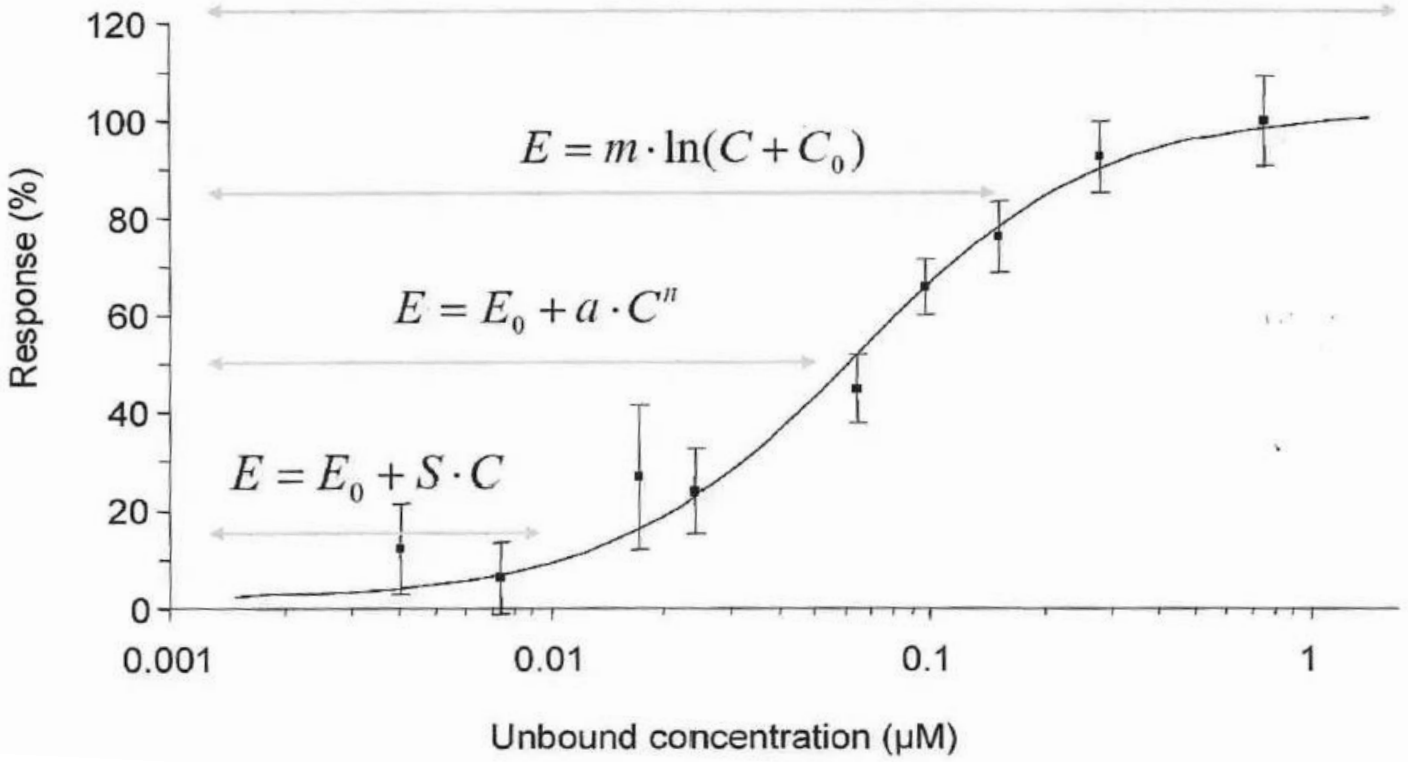
Secondary parameter: e.g. C_{eu}10% equates to unbound concentration (umol/L) of fitted curve giving 10% effect

$$E_{\text{Effect}} = a \cdot C_{eu}{}^{b}$$

Modelling set-up based on:
Lindhardt E and Gennemark P. J Bioinform Comput Biol 12(3): 1450010, 2014.
Open source code: http://www.mathworks.com/matlabcentral/fileexchange/43521-preclinical-pkpd-modeling

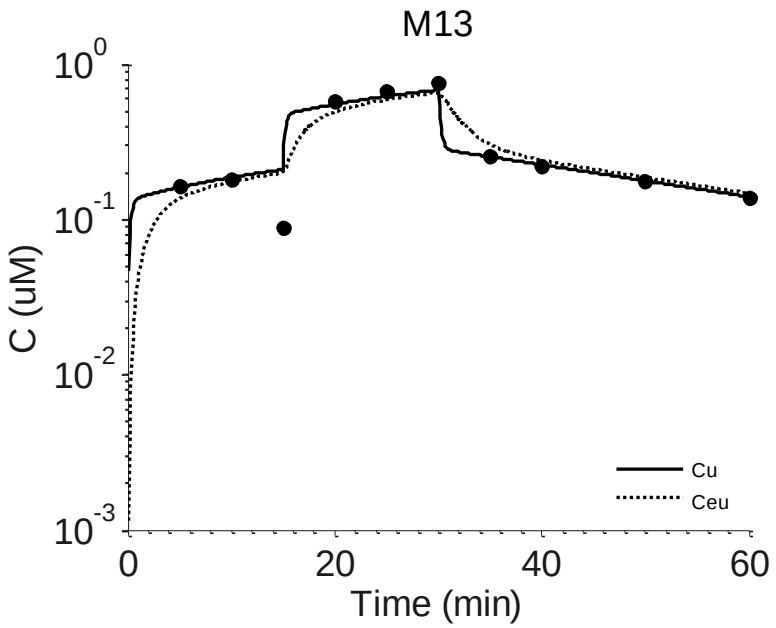
Model gallery

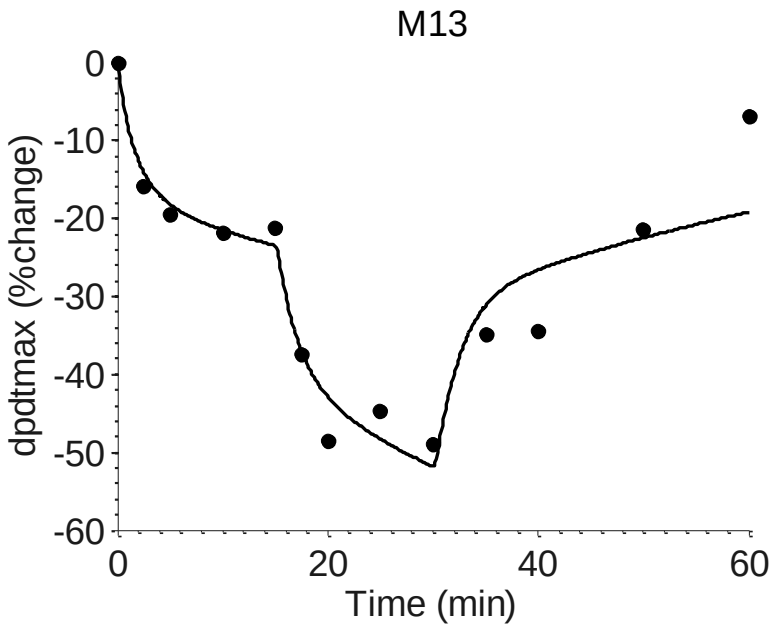
$$E = E_0 + \frac{E_{max} \cdot C^n}{EC_{50}^n + C^n}$$



J Gabrielsson

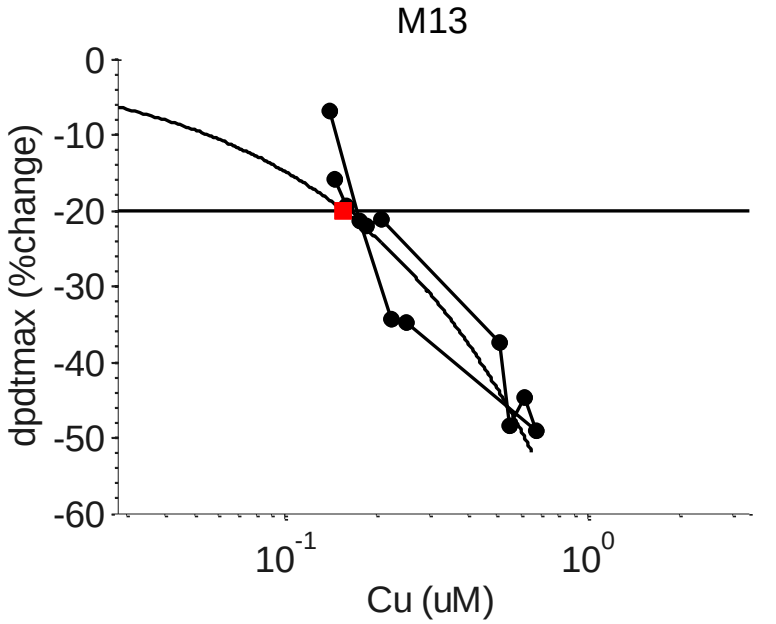
dpdtmax (%change)





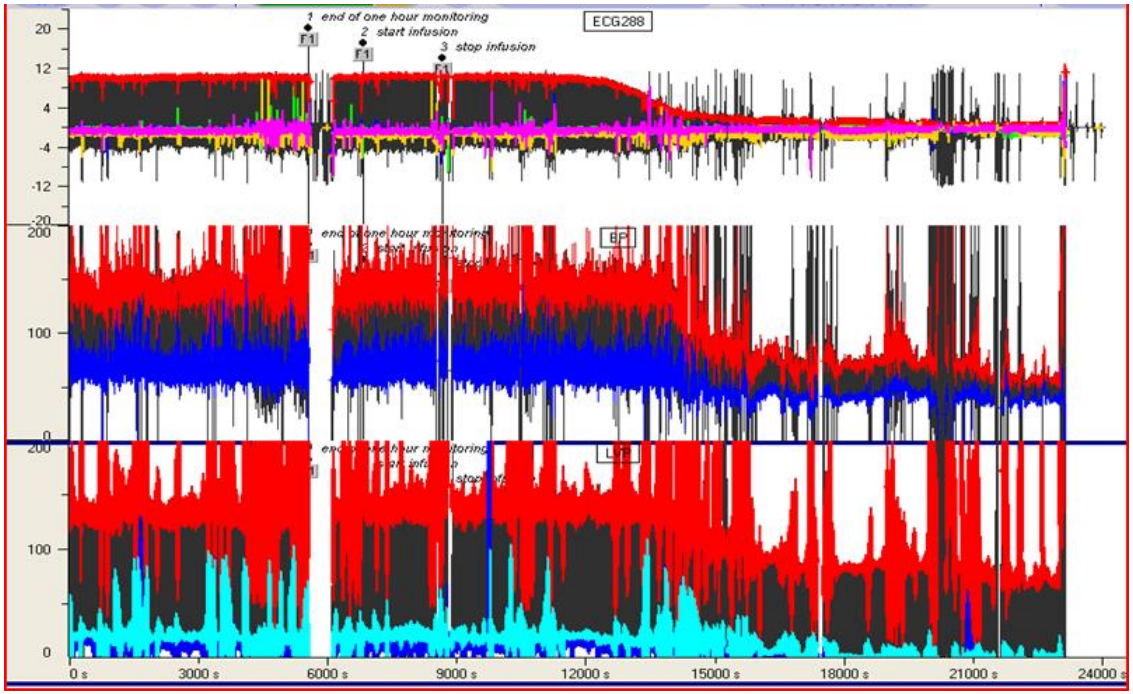
	M13
$t_{1/2}$ ke0 (min)	1.5
a	-69
b	0.66
Ceu-20% (µmol/L)	0.16

Observation

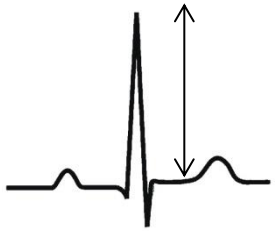


Case study 2

R wave amplitude changes in the Dog



R wave amplitude



ECG

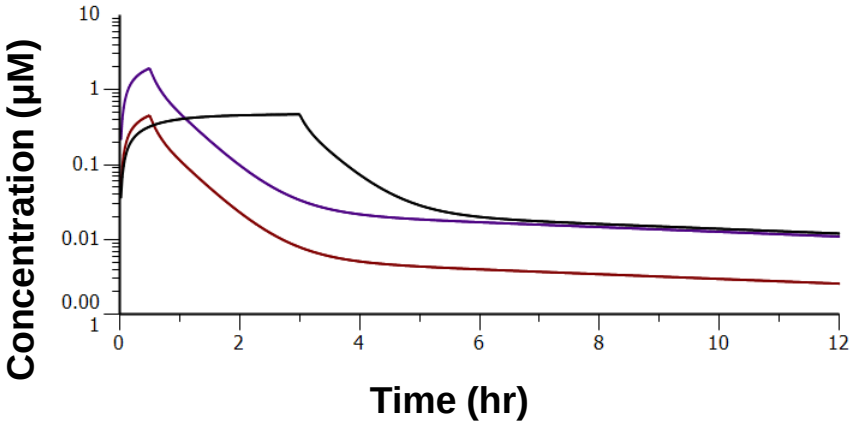
BP

LVP

J Moors

Infusion scenarios

Could a longer infusion mitigate against CV effects?



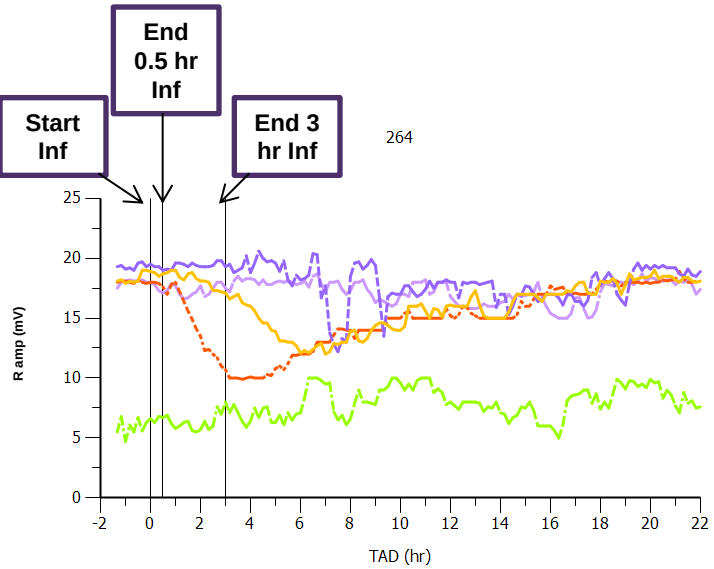
If the 3 hour infusion is most similar to 0.85 mg/kg over 0.5 hour –AUC driven

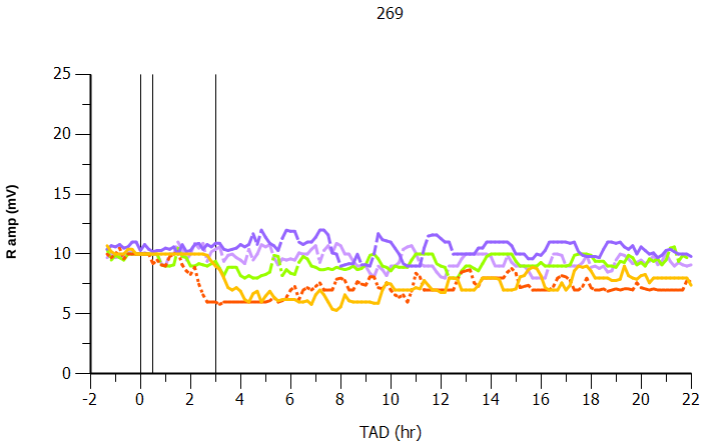
If 3 hour infusion most similar to 0.2 mg/kg over 0.5 hour – Cmax driven

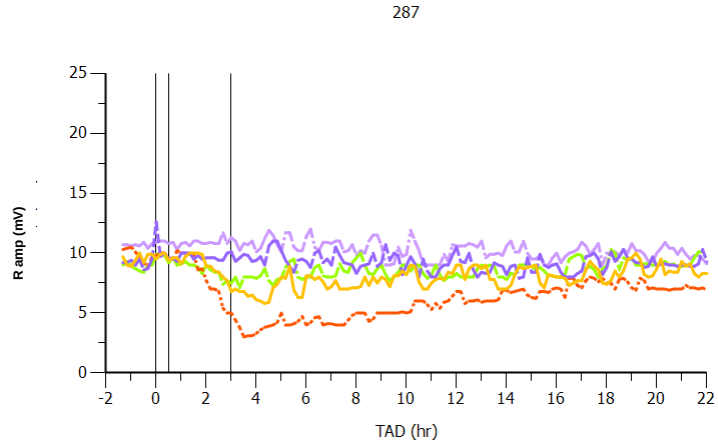
Dose (mg/kg)	Infusion Duration (hr)	Infusion rate (mg/kg/hr)	Cmax (µM)	AUC (µM*h)
0.85	0.5	1.7	1.9	1.7
0.85	3	0.28	0.5	1.7
0.2	0.5	0.4	0.5	0.4

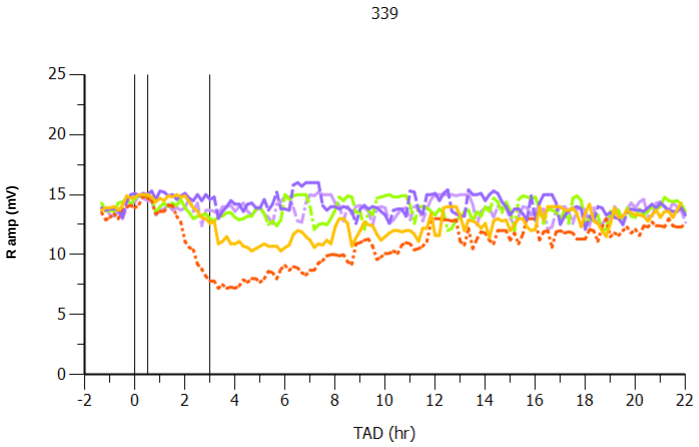
R wave amplitude changes

0.5 hr Vehicle
0.5 hr 0.2 mg/kg
0.5hr 0.85 mg/kg
3 hr vehicle
3 hr 0.85 mg/kg



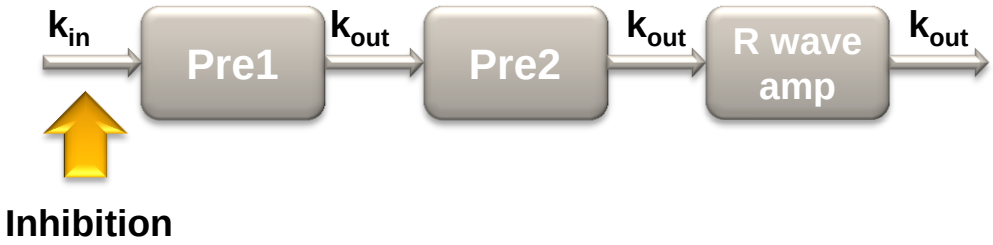






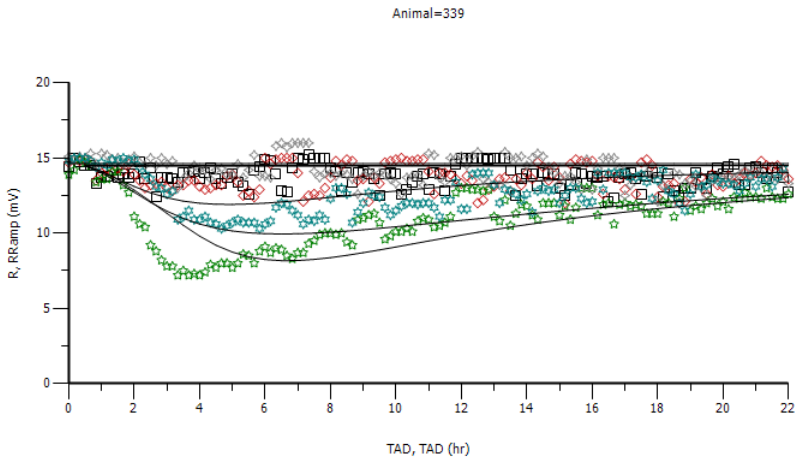
Modelling Approach

-Transduction model to capture the onset in delay



-To date, not reached a satisfactory output in terms of modelling

-Used a statistical approach to prove AUC driven outcome



Conclusions

Beyond QT ambition for pre-clinical Cardiovascular safety assessment

- Hemodynamic models
- Contractility and other effects

We must understand the species/system we study in order to translate effects in Human

- Structural morphology
- Expression differences

Need more routine feedback from the clinic in order to better understand translation of drug induced CV effects

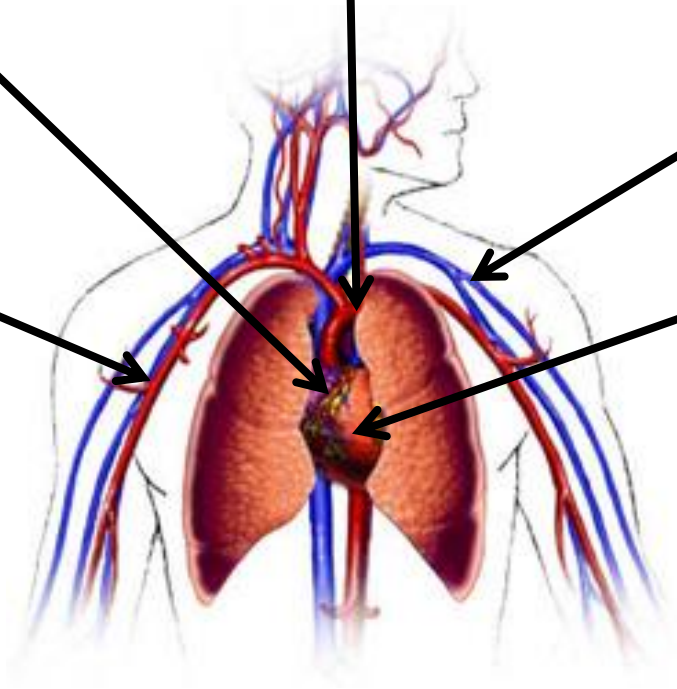
Thanks for listening!

Any questions?

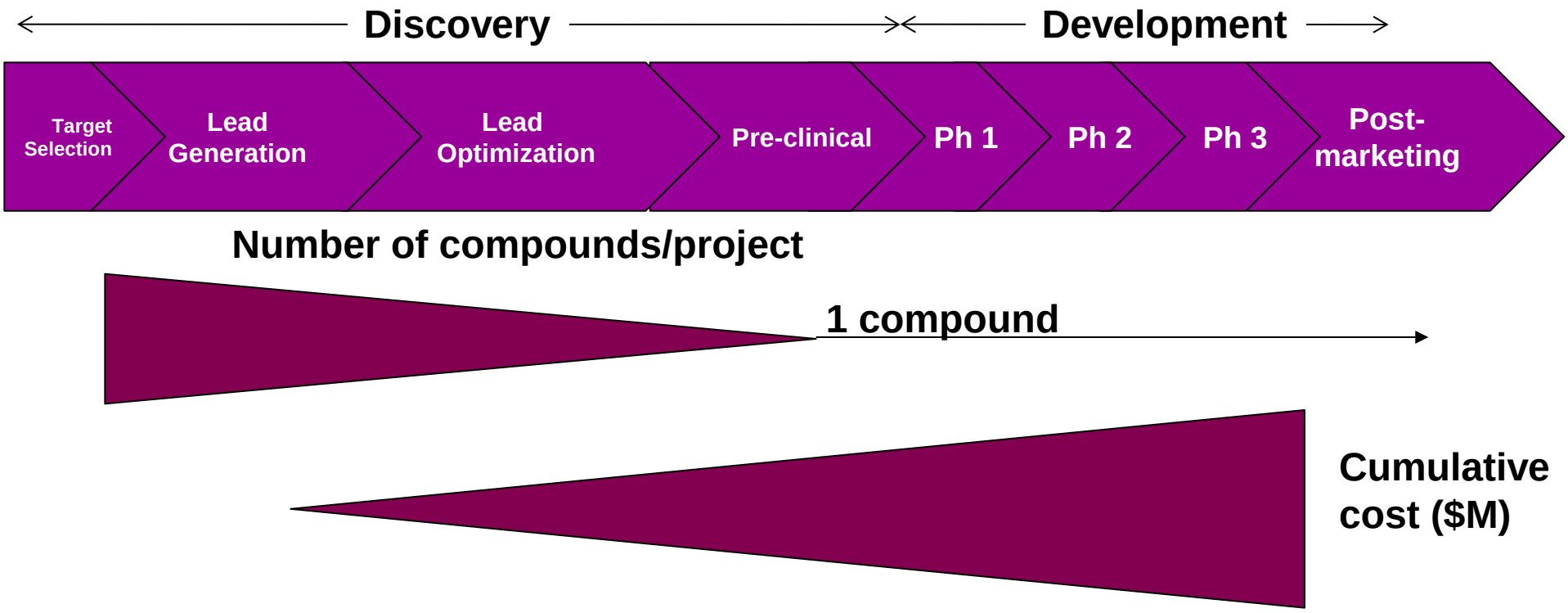
Back ups

The Cardiovascular System

Many recipients of new medicines already have cardiovascular disease!



Drug Discovery & Development Context



Lead Optimization is the critical phase to try to avoid safety issues:

- **Cheap to fail**
- **Greatest chemical choice – can try to avoid CV risk**

Guidance for level of changes

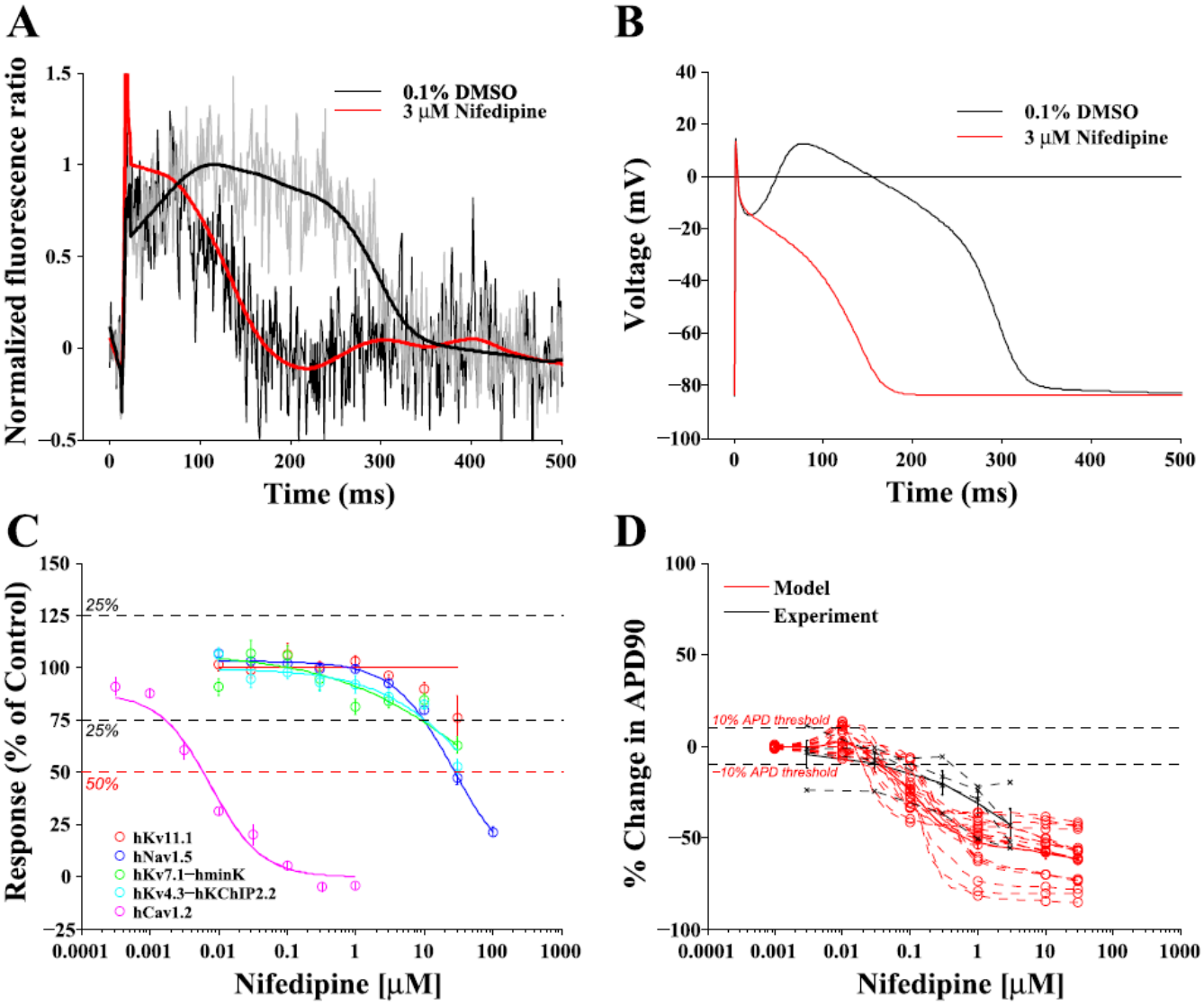
Table 1: Suggested margins for changes in HR, BP and QTc that should be detected in safety pharmacology studies. Effect margins in animals are best practice suggestions and require validation. Adapted from [10].

Goal	Parameter	Effect limit in man	Effect limit in animals
ICHS7A/B	HR	>110 bpm or 40 bpm increase	>40 bpm
(identify catastrophic effects)	BP	Change >30 mmHg (same posture)	>30 mmHg
- general stopping rules	QTc	500 ms or 60 ms increase	>30 ms in dog
			>60 ms in monkey
Predict large clinical trials	HR	5–10 bpm	5–10 bpm
	BP	2–5 mmHg	2–5 mmHg
	QTc	5–10 ms	2–6 ms in dog
			5–10 ms in monkey

[10] D. Leishman, T. Beck, N. Dybdal, D. Gallacher, B. Guth, M. Holbrook, B. Roche, and R. Wallis, "Best practice in the conduct of key nonclinical cardiovascular assessments in drug development: Current recommendations from the Safety Pharmacology Society," *Journal of Pharmacological and Toxicological Methods*, vol. 65, no. 3, pp. 93–101, 2012.

L Bergenholm

Nifedipine Calcium channel blocker



Ollerstam

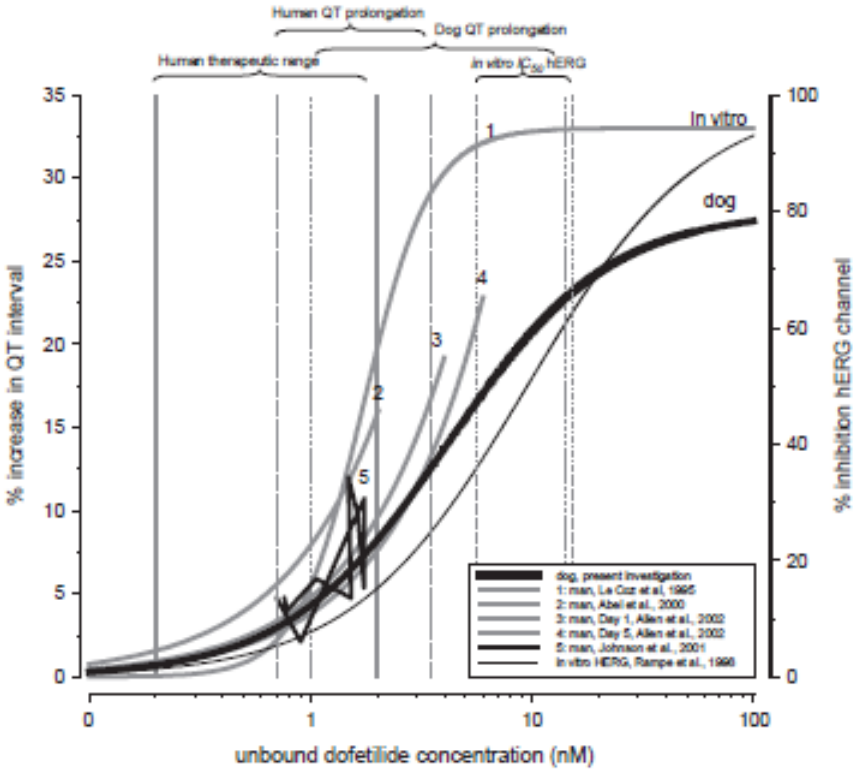


Fig. 6. Comparison of the concentration–effect relationships in dogs (present investigation) and humans as reported by (Abel et al., 2000; Allen et al., 2002; Le Coz et al., 1995) and (Johnson et al., 2001). Reported relationships were recalculated to unbound (free) nM concentrations (protein binding values were taken from (Smith et al., 1992)) and expressed as a percentage of the reported predose value. The thin black line represents the IC_{50} for hERG inhibition scaled to a secondary *y*-axis as reported by (Rampe et al., 1998), potencies with confidence intervals being expressed as free concentration: IC_{50} in vitro: 9.5 nM (5–15 nM); EC_{x50} dog: 4 nM (2.3–6 nM); QT EC_{x50} human: 2 nM (0.5–3.5 nM, based on (Le Coz et al., 1995)); therapeutic effective concentration human: 1.2 nM (0.4–2 nM).

Approx 2 fold difference between Dog and Human of dofetilide

Jonker

Dofetilide in Human

Both affinity and activity to hERG applied to in vivo data using operational model of pharmacologic agonism

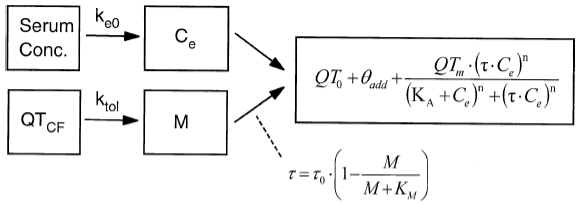
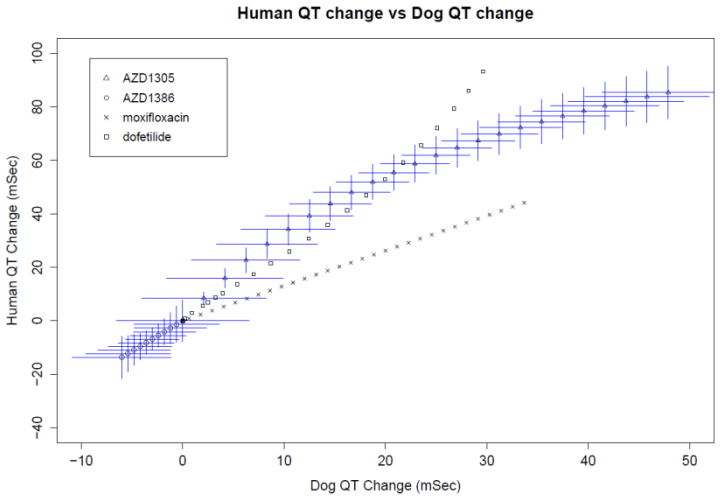


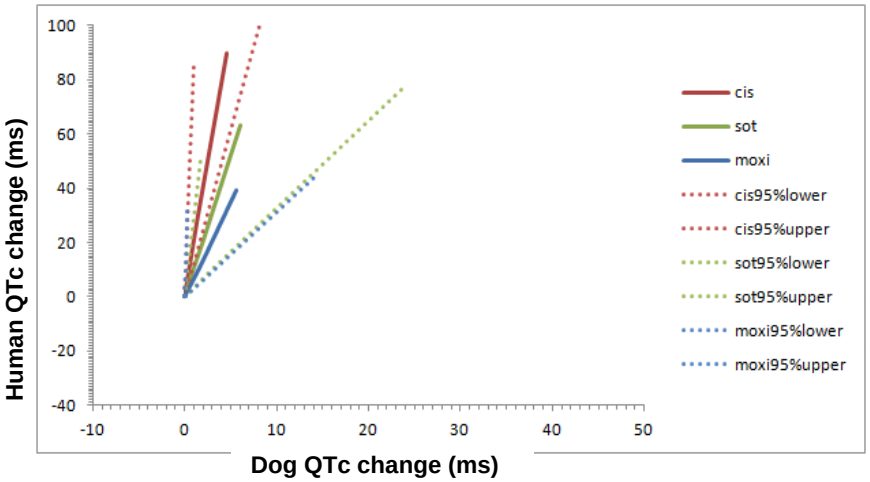
Fig 3. Schematic representation of final pharmacodynamic model. Refer to the text for clarification of the operational model that was implemented with an effect compartment and a feedback compartment for the response. C_e, Dofetilide effect site concentration; QT_{CF}, QT response; k_{e0}, rate constant for drug transfer to effect compartment; k_{tol}, rate constant for tolerance development; M, amount in feedback compartment; QT_0, average QT_{CF} value in each subject at baseline; θ_{add}, residual variability in QT_0; QT_m, maximum QT prolongation relative to baseline; τ, transducer ratio; n, slope factor; K_A, dissociation constant of dofetilide; τ_0, transducer ratio in absence of tolerance development; K_M, factor determining extent of tolerance development.

Translational relationship

Parkinson



Chain



Moxifloxacin:
Human slopes are within two fold
Dog slopes are almost 14 fold different
Chain et al -not as sensitive to QT change in Dog as AZ

Confidence in QTc Translation

AZ perspective

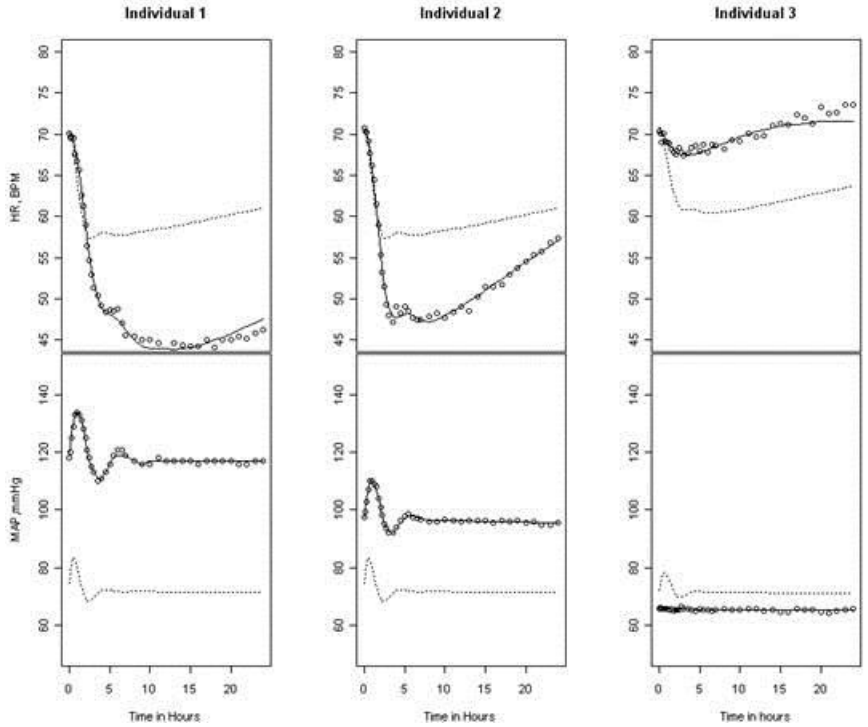
Confidence	High	Medium	Low
Mechanism	hERG	Mixed effects or unclear mechanism	Unknown or other
Dog Telemetry	"Modellable" Concentration dependent effects	"Modellable" Concentration dependent effects OR technically difficult to model effects	Technically difficult to model effects OR no observable effect OR effects following multiple dosing
Tox Studies	Predictable Concentration dependent effects	Predictable Concentration dependent effects OR Difficult to model effects	Technically difficult to model effects OR Effects only evident following multiple dosing
	↓	↓	↓
Prediction of Clinical QTc effect range (based on Parkinson paper)	Effects in Dog below 20 ms Effects in Dog above 20 ms	Effects in Dog below 20 ms Effects in Dog above 20 ms	Should not make prediction
Example	2.5–8 ms in dog would correspond to a 10 ms change in human	>20 ms change in Dog would correspond to >25 ms change in human	

Cheung *et al*

Applied to α1A/1L-adrenoceptor, partial agonist developed for the treatment of stress urinary incontinence

Side effect: increased peripheral resistance

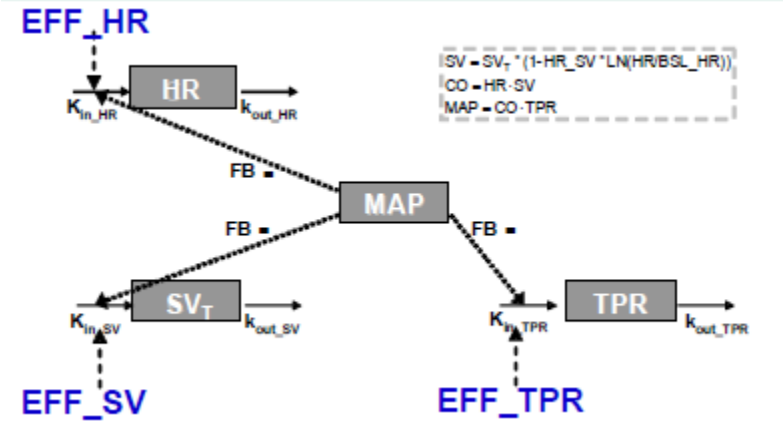
Individual and population predictions



Snelder *et al*

Simultaneous fitting of all compounds gave drug independent system parameters

Model further expanded to include HR and SV



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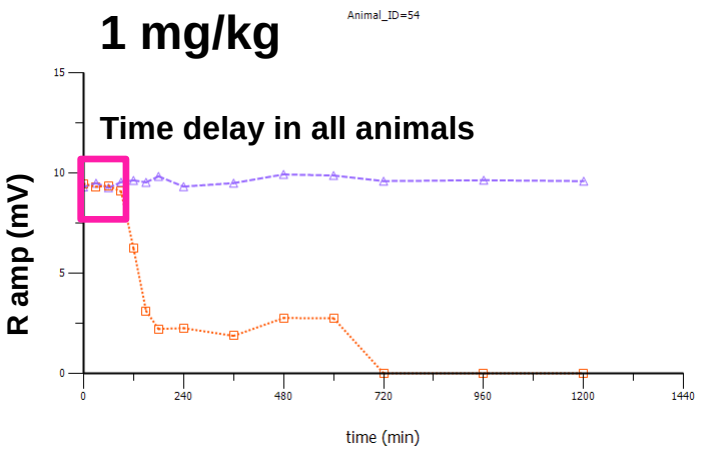
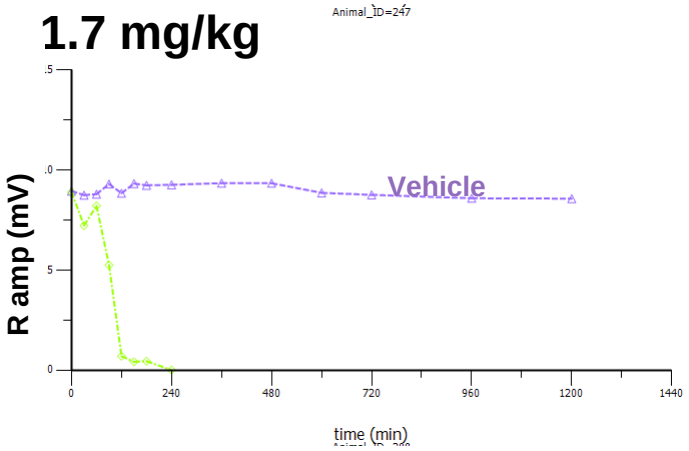
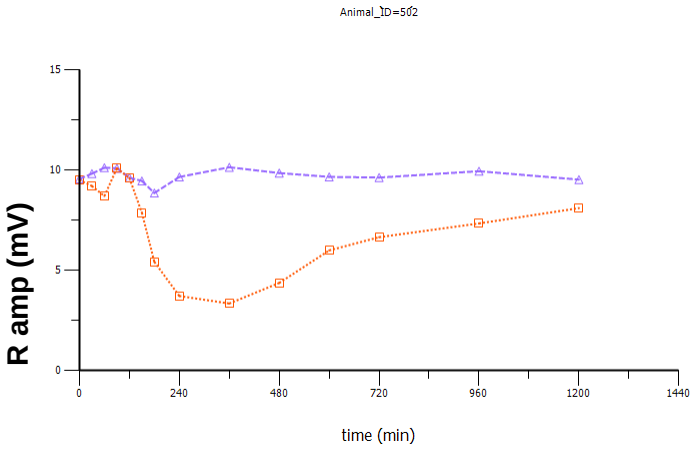
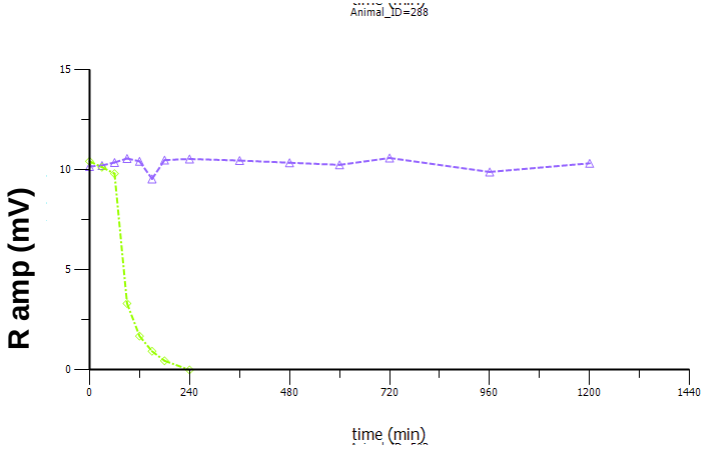
Dog data 30 minute infusion









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