

“Use of animal models with disease in Safety Pharmacology”

or

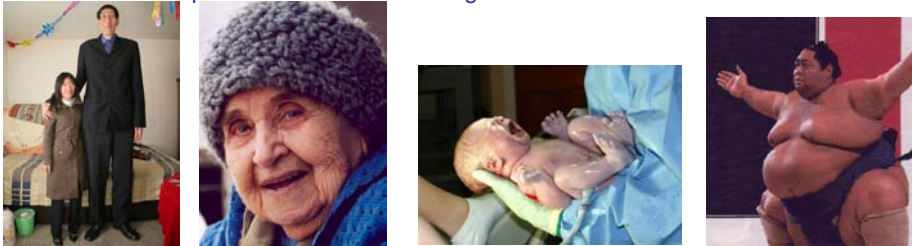
“You don’t give drugs to normal people!”

Robert L. Hamlin, DVM, PhD, DACVIM (Cardiology/Internal Medicine), Stanton Youngberg Professor of Veterinary Medicine, Professor of Biomedical Engineering, Professor Davis Heart and Lung Research Institute, Senior Attending Clinician, The Ohio State University; Scientific Director, QTest Labs

Which animal is the best surrogate for man?



We must develop safe and efficacious drugs for all!



Is it likely that these animals possess polymorphisms suitable for extrapolation?



Targets!





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**“U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research
(CBER) July 1997, ICH.”**

***Clear FDA Guidelines, June 18th, 2007:
“....recommend you conduct pre-clinical
testing, where appropriate and feasible,
in an environment that simulates actual
clinical conditions.” Clinical conditions
seldom refer to healthy persons!***

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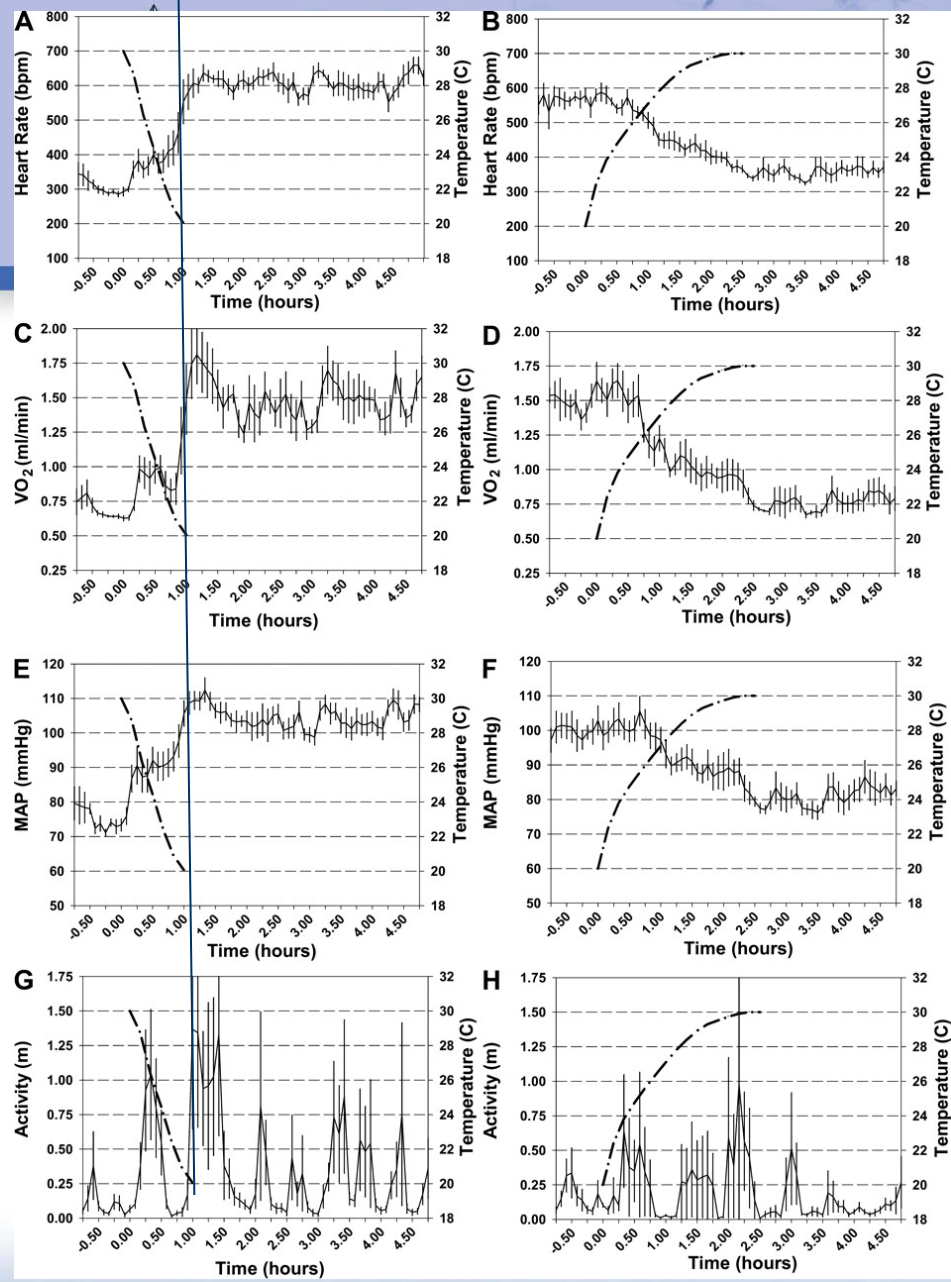


**Safety
Pharmacology
Society**

***For those of you
who balk at using
diseased (not “naïve”)
animals...***

you already are!!

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AALAS/NIH/USDA →

Heavy viscera,
lighter brains,
immune-compromised,
clotting activated

“Good” for the mouse



You study 80
to 100 million
per year.

The LD₅₀'s for both IP ephedrine and salicylic acid are ~50% lower at 20° than at 30°.

“It’s always been that way!”

Gerhard Zbinden: Don’t do something just because it’s always been done that way, because you can, or because others do!



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“.....experiments conducted under highly standardized conditions (eg., on normal animals) may reveal local ‘truths’ with little external validity (to patients with disease).”

S Helene Richter, Joseph P Garner & Hanno Würbel, 2009

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I know what a diseased animal is, but what is a naïve animal?

Is it gnotobiotic?

Is it vaccinated?

Are all parameters of the CBC and SMA normal?

Has it every been used in a previous study?

Does it behave “normally“?

Is it not diseased (i.e., not showing signs/symptoms)...not absent from health (i.e., asymptomatic but will not live life span determined by apoptosis)?

Does it make a difference (more/less predictive) if it is naïve/diseased?



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My opinion.....

We should savor and exploit (not shy away from) genetic, epigenetic, and developmental heterogeneities in our surrogate populations in the hope of achieving greater statistical power or control. (i.e., Make statisticians happy!) Everybody knows that toxicity occurs much more ubiquitously in patients with multiple risk factors.

You can search for torsadogenicity in the best-controlled study on a million “identical” rats and never get the correct answer for man. You can ligate the left main coronary artery of a million guinea pigs and never learn anything about myocardial ischemia for man. You can give doses of atropine (lethal to man) to most rabbits and not get toxicity. Digitalis, ACE inhibitors, antiarrhythmics, beta blockers, and diuretics have profoundly different pharmacology/toxicology in normals than in subjects with heart failure....and on and on!

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“The primary goals of preclinical safety evaluation are:

- (1) to identify an initial safe dose and subsequent dose escalation schemes in humans (**Do they mean healthy humans (yes in phase I, no in phases II and III?)**);
- (2) to identify potential target organs for toxicity and for the study of whether such toxicity is reversible (**Do they mean normal target organs?**);
- (3) to identify safety parameters for clinical monitoring (**Do you monitor normal patients?**).”

Is there anybody who does not know that adverse events to drugs occur more commonly in patients because they are sick?

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“Preclinical safety testing should consider:

- (1) Selection of the relevant animal species;
- (2) age;
- (3) *physiological state*;
- (4) the manner of delivery, including dose, route of administration, and treatment regimen; and
- (5) stability of the test material under the conditions of use.”



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“In recent years, there has been much progress in the development of animal models that are thought to be similar to the human disease. These models **may?** provide further insight, not only in determining the pharmacological action of the product, pharmacokinetics, and dosimetry, but **may?** also be useful in the determination of safety (e.g., evaluation of undesirable promotion of disease progression). In certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals. The scientific justification for the use of these animal models of disease to support safety should be provided.”

What about providing the scientific justification for the use of healthy animals? Do we have knowledge of sensitivity and specificity of our present paradigms?

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Issues for animal models with disease (for later discussion):

- **Cost**
- **Availability**
- **Necessity/Demand**
- **Sensitivity (usually 1/specificity)**
- **Which diseases? Which conditions?**
- **Data supporting or refuting.**
- **Acceptability**
- **Interpretability**

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Examples of the value of using animal models with disease (not to be restricted to electrophysiology, but to all parameters that, if affected, translate to morbidity and/or mortality).

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While not a model of disease? This model demonstrates the value of altered physiology/pharmacology for enhancing sensitivity to detect toxicity.

Table 1

Influence of α_1 -adrenoceptor stimulation by methoxamine on the induction of torsades de pointes (TdP) by class III antiarrhythmic agents in the anaesthetised rabbit

Agent	No methoxamine		Methoxamine		Reference
	# of rabbits with TdP	Dose at TdP	# of rabbits with TdP	Dose at TdP	
Clofilium	3/10 (30%)	2.2 mg/kg	20/20 (100%)	0.2 mg/kg	Carlsson et al., 1990
Clofilium	4/6 (67%)	4.6 mg/kg	8/10 (80%)	2.6 mg/kg	Buchanan et al., 1993
Clofilium	0/10 (0%)		8/10 (80%)		*
Almokalant	1/6 (17%)	34.7 mg/kg	6/7 (86%)	0.4 mg/kg	Carlsson et al., 1993a,1993b
Dofetilide	1/6 (16%)	0.5 mg/kg	11/16 (69%)	1.3 mg/kg	Buchanan et al., 1993
E-4031	0/6 (0%)		9/16 (56%)	0.4 mg/kg	Buchanan et al., 1993
D-sotalol	0/6 (0%)		6/10 (60%)	10.4 mg/kg	Buchanan et al., 1993
Ibutilide	0/6 (0%)		2/16 (13%)	1.0 mg/kg	Buchanan et al., 1993

*; J Matz, personal communication.

L. Carlsson / *Pharmacology & therapeutics* 119 (2008) 160-167

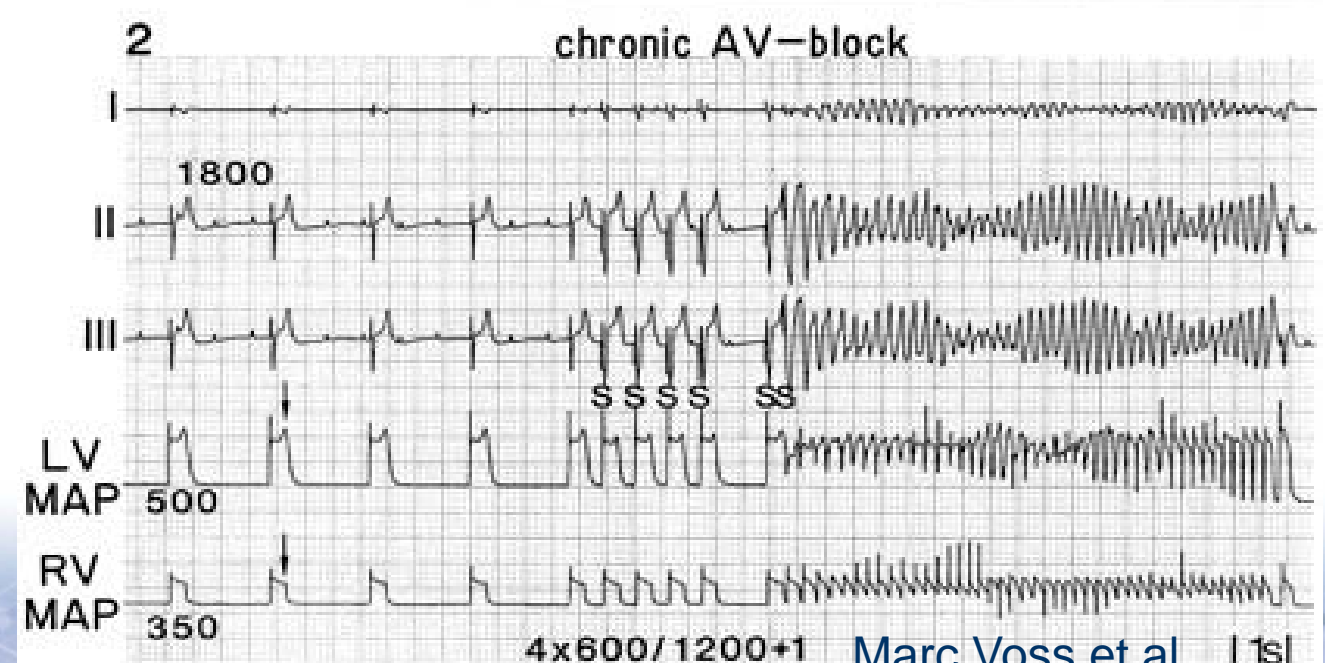
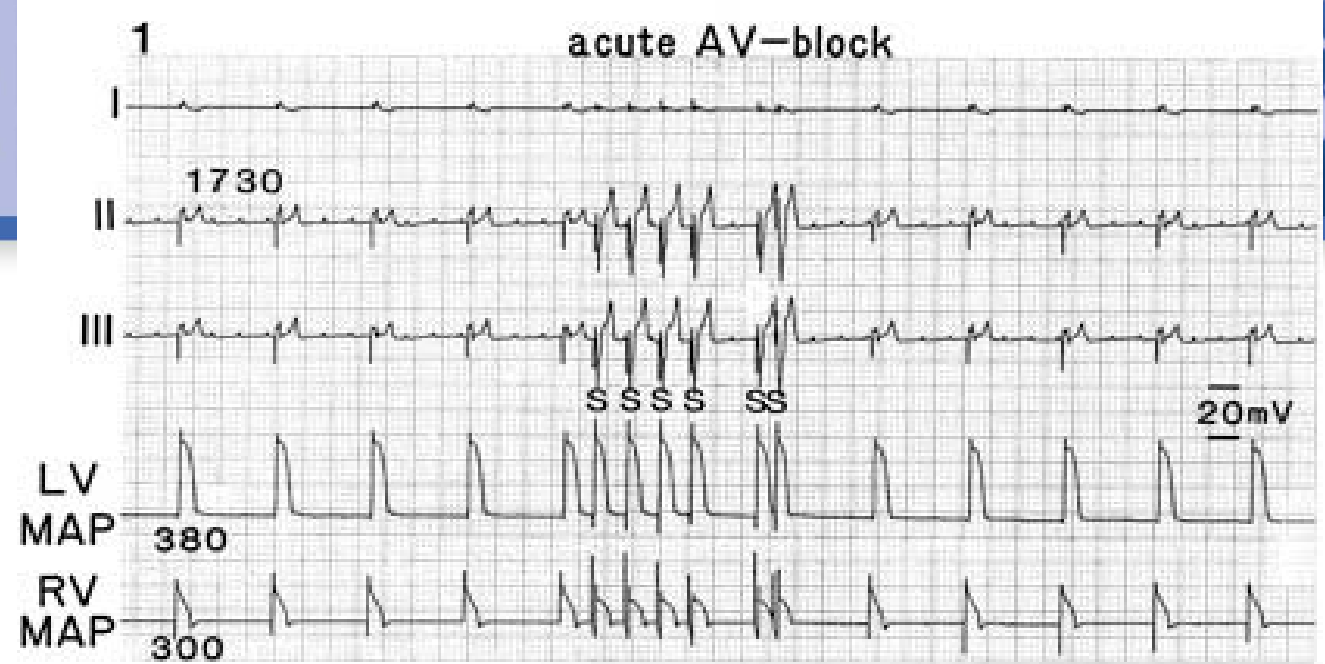
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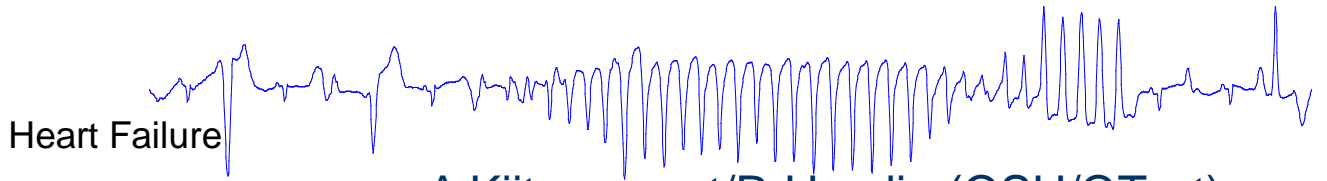
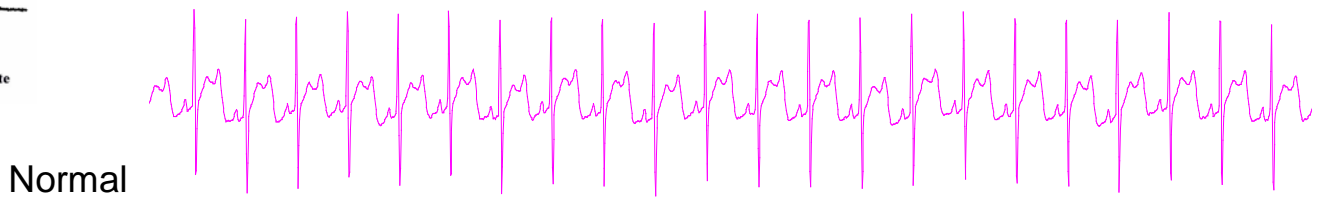
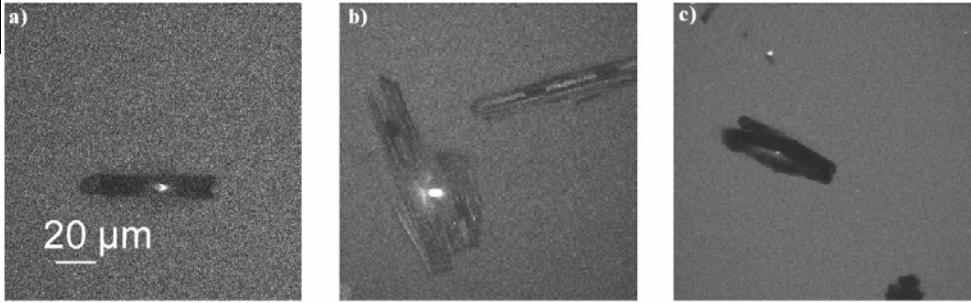
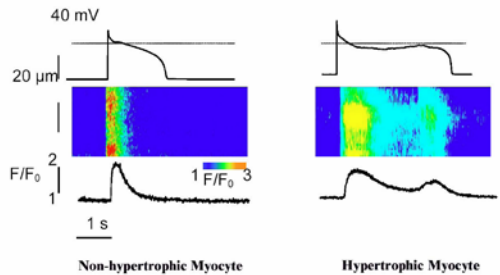
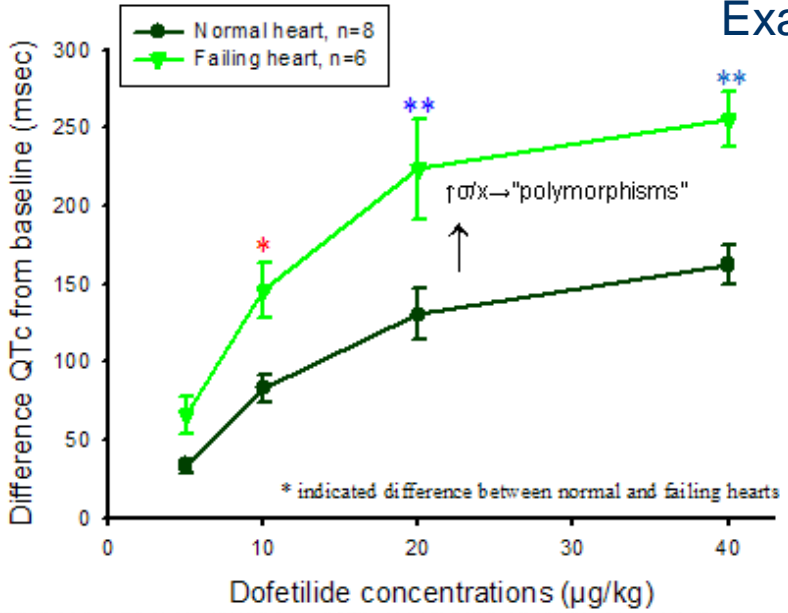
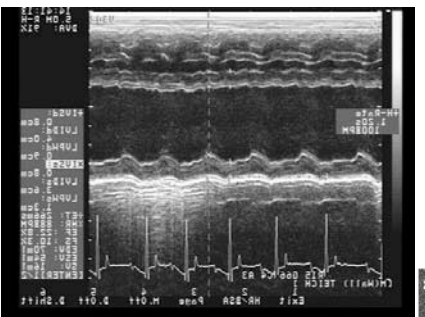
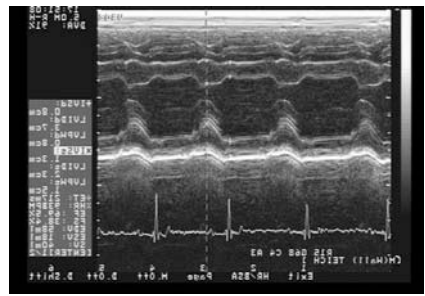


D-SOTALOL



Example 1.

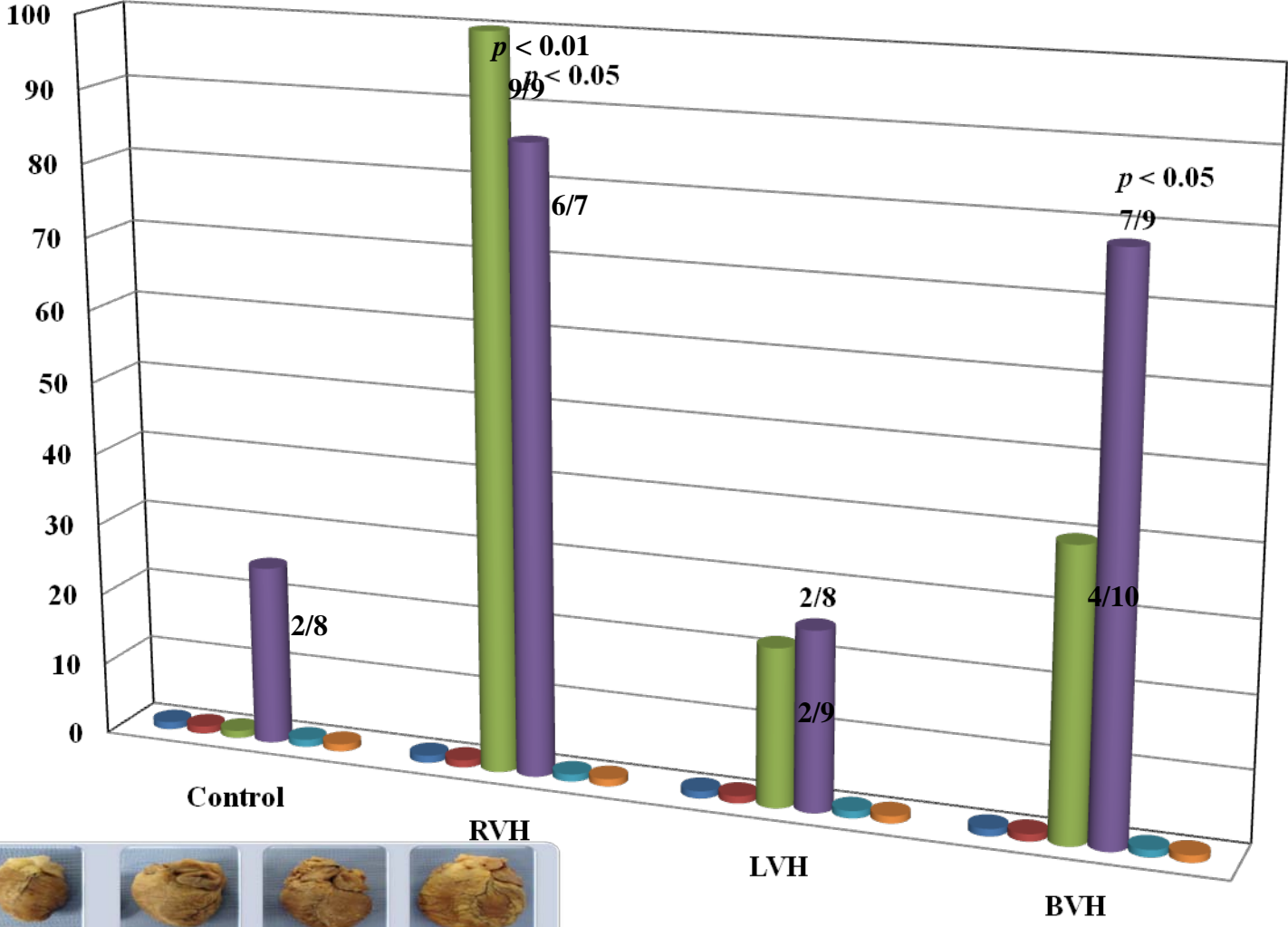




Anusak Kijawornrat

A Kijawornrat/R Hamlin (OSU/QTest)

Incidence of TdP (%)



- vehicle
- cilobradine
- dofetilide
- clofilium
- terfenadine
- diltiazem



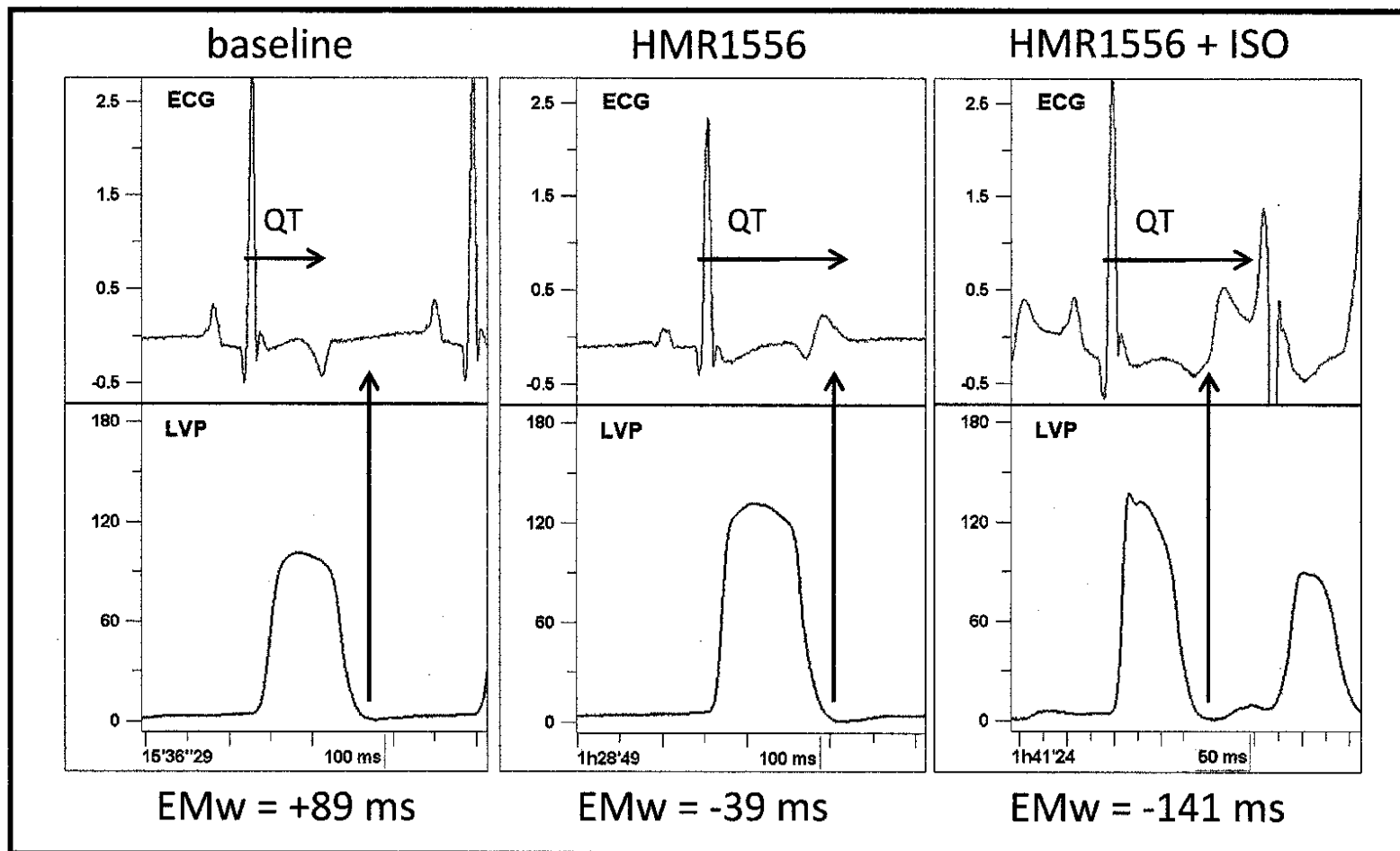
			
Control 2.24±0.04 n = 8	RVH 3.26±0.11* (p < 0.05) n = 9	LVH 3.33±0.07* (p < 0.05) n = 9	BVH 3.88±0.14* (p < 0.05) n = 10

Yaowalok Panyasing

Y Panyasing/A Kijawornrat/R Hamlin (OSU/QTest)

Example 4.

Induction of Torsades de Pointes after HMR1556 (1.5 mg/kg IV) and Isoproterenol (2.5 μ g/kg IV) in the anaesthetised beagle dog model.



HJ van der Linde et. al. The Electro-Mechanical window: a risk marker for Torsade de Pointes in a canine model of drug induced arrhythmias. British Journal of Pharmacology (2010).

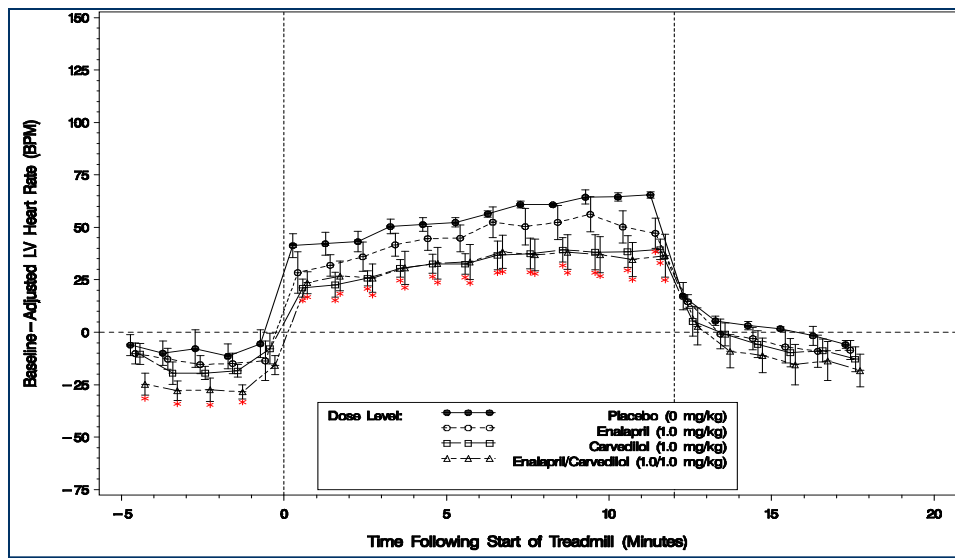
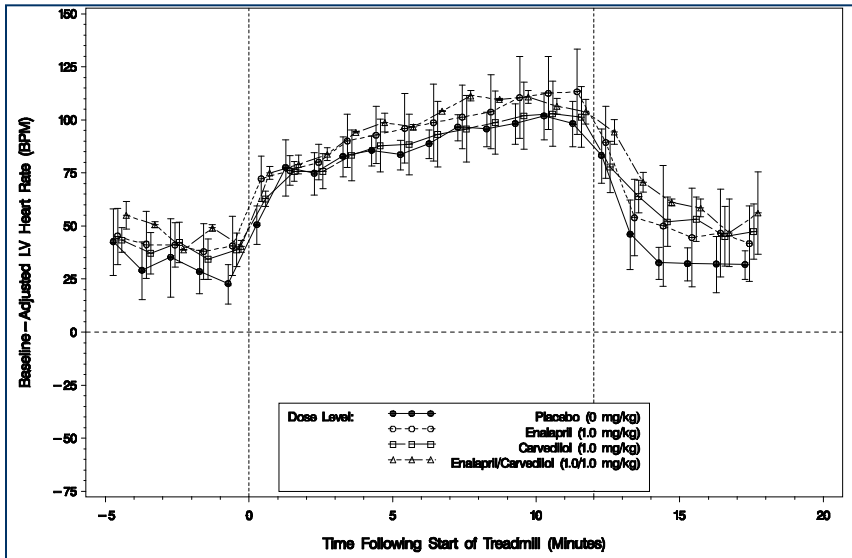


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Example 5.

	Rest	Exercise	Recovery
Normal	NS	NS	NS
Heart Failure	C+E Decrease	C and C+E Decrease	NS





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Models to consider:

- Aged....costly and simple
- Diabetes....type I, but we're interested in type II
- Obesity....relatively expensive
- Hypertension....inexpensive and facile depending upon type
- Heart failure....inexpensive and facile depending on type
- Hypertrophy....inexpensive and facile
- Concomitant drugs....least expensive and facile

Studies for exploitation of those models:

- General toxicology....No!
- To evaluate efficacy and mechanisms....Yes and yes!
- All Safety Pharmacology....No!
- "Lead" compounds....Yes!
- "Lead" compound....Yes, yes!

Why?

- to increase sensitivity (decrease specificity minimally?)
- to comply with FDA suggestion
- it "sounds reasonable"
- not costly
- requires moderate surgical skill
- humane

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However,

don't even consider animal models with disease if you are satisfied with the Toxicology/Safety Pharmacology paradigm as it exists! **Don't do something just because you can! (GZ) It must make a difference! (GZ) The FDA seems to think it does!**

Clear FDA Guidelines, June 18th, 2007:

“....recommend you conduct pre-clinical testing, where appropriate and feasible, in an environment that simulates actual clinical conditions.”

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Thanks for your kind attention, and I look forward to stimulating criticisms, questions/answers and discussion.



Mackenzie deserves safe and efficacious drugs!

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QUESTIONS



We will now open the phone lines for discussion.
If you would like to speak click the hand icon
below the participants list.



Reminders:

Continue discussion on the SPS Blog



THANK YOU FOR ATTENDING.
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