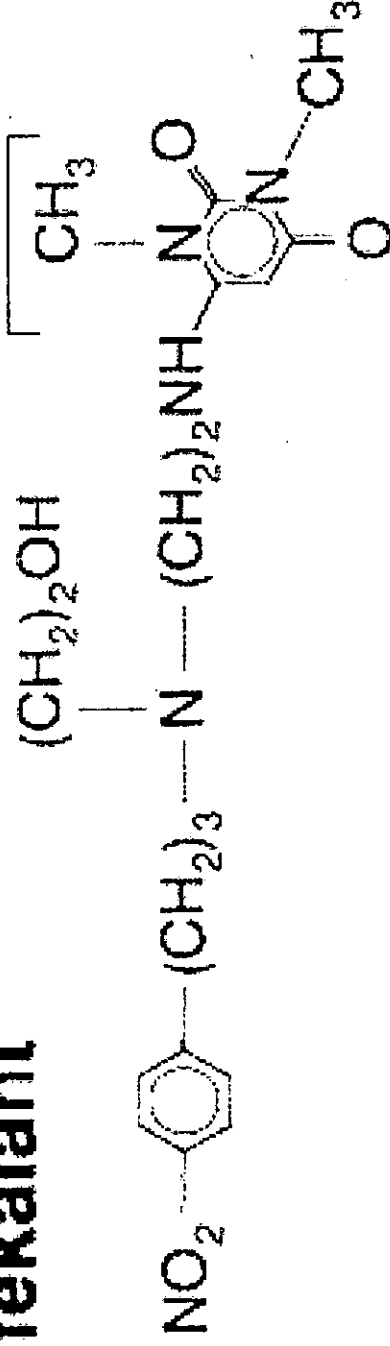


Nifekalant hydrochloride (NIF)

- Nifekalant hydrochloride (NIF), formally known as MS-551, is classified as a class III antiarrhythmic agent having a pirimidinedione structure.

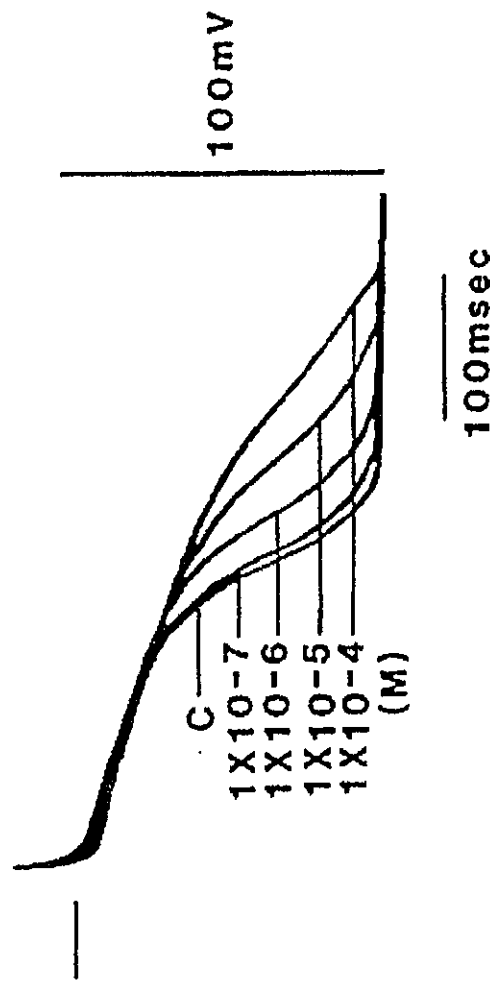
Nifekalant



Chemical structure of NIF

Electrophysiological effects of NIF (MS-551) in canine Purkinje fibers

- NIF prolongs the action potential duration (APD) and effective refractory period (ERP) in a concentration-dependent manner.
- NIF does not significantly affect other parameters including resting membrane potential, action potential amplitude and maximum upstroke velocity at phase 0 (V_{max}).



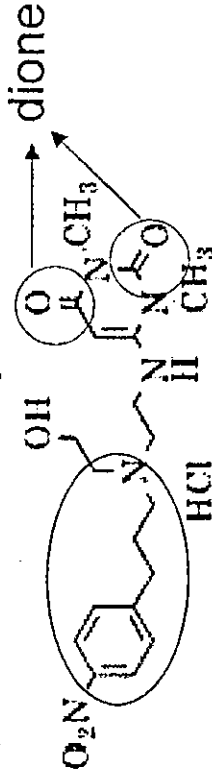
NIF vs Amiodarone: structure

Nifekalant

~ Nifekalant hydrochloride

~ 5-[2-[(N-2-hydroxyethyl)-3-(4-

n-phenenyl)propylaminoethylamino]-1,3-dimethyl-1H-3H-pyrimidine-2,4-dione]nonahydrochloride



~ $C_{19}H_{27}N_5O_5 \cdot HCl$ pyrimidinedione

~ 441.91

~ 171 ~ 175°C

~ Pale yellow to yellow crystal or crystalline powder

~ Very soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and practically insoluble in ethyl ether

Chemical name

Structural formula

Molecular formula

M.W.

m.p.

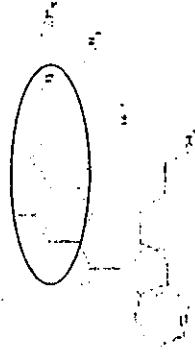
Description

Solubility

Amiodarone

~ Amiodarone hydrochloride

~ 2-butyl-3-benzofuran-4-[2-(diethylaminoethoxy)-3,5-bis(phenyl)ketone]hydrochloride



~ $C_{25}H_{29}N_2O_3 \cdot HCl$

~ 681.78

~ ca. 160°C (decomposition)

~ White to slightly yellow crystalline powder

~ Soluble in methanol and dichloromethane, slightly soluble in ethanol(95), very slightly soluble in water and hexane

NIF vs Amiodarone: pharmacology

- Amiodarone is multi channel blocker (different action by short and long term)
- Nifekalant is pure K channel blocker

Pharmacological action of Class III

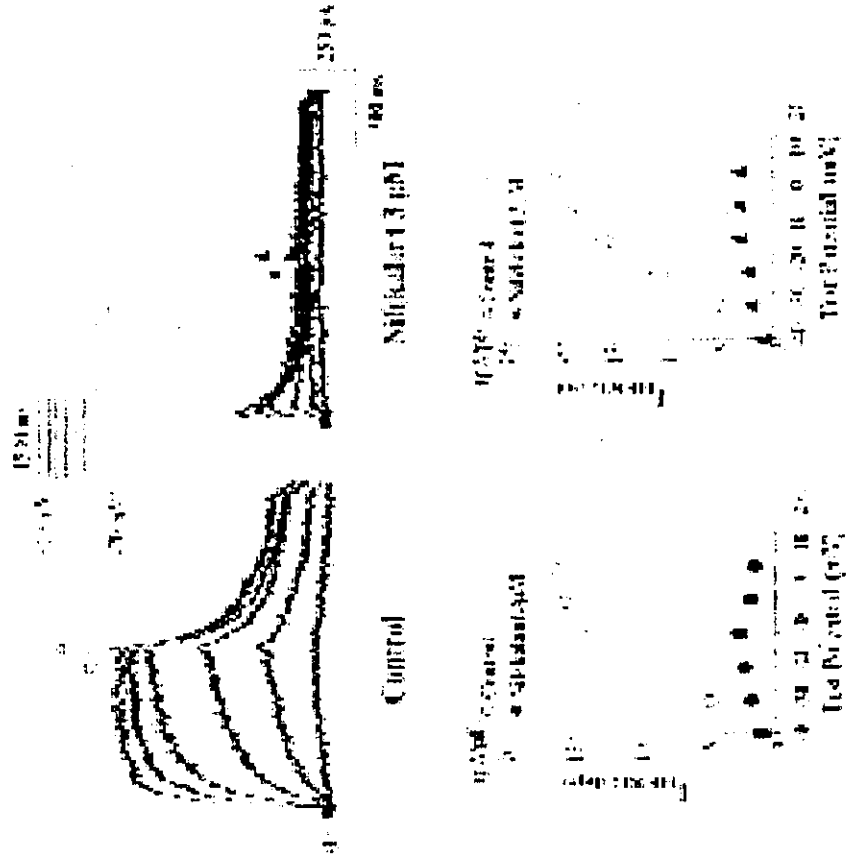
The Shelton Gambel: A New Approach to the Classification of Antiarrhythmic Drugs

DRUG	CHANNELS			RECEPTORS			PUMPS		
	Na	Ca	K	If	α	β	M ₂	A ₁	Na-K ATP _{ase}
	Fast	Med	Slow						
Nifekalant				●					
Amiodarone(Short-term)	△			●					
Amiodarone(Long-term)				○	△				○

Relative potency of block: ○=low. △=moderate. ●=high

Effect of NIF on the HERG current (I_{Kr}/I_{HERG}) expressed in a HEK293 cell

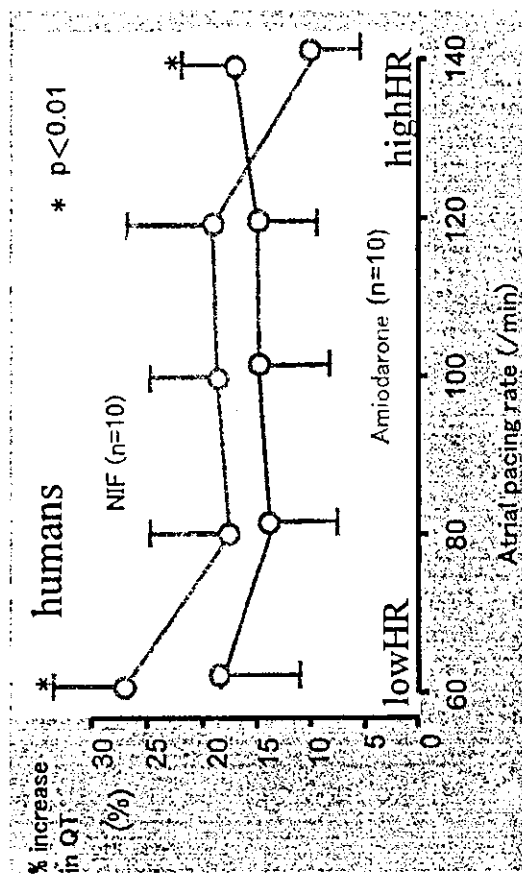
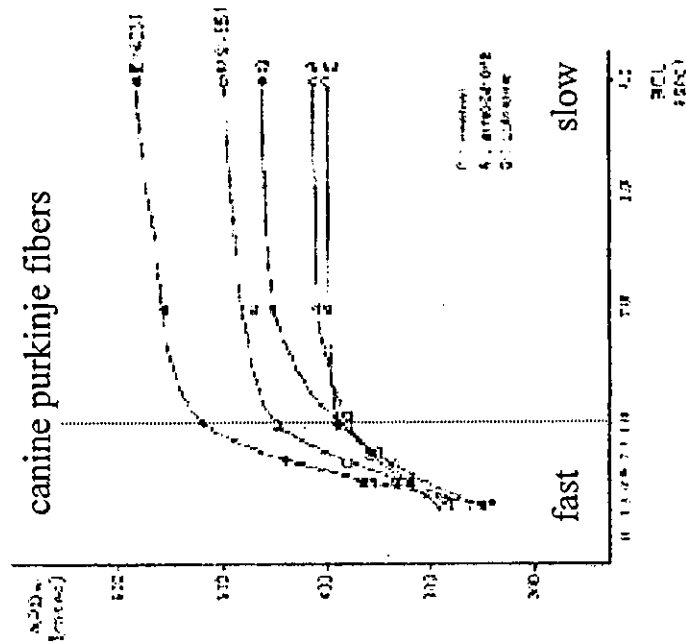
- NIF inhibited HERG channels, suggesting the selective inhibition of the rapid component of the delayed rectifier K^+ current (I_{Kr}).



(Jpn J Electrocardiol 2000;20:195-201)

Reverse use-dependent effect

- In canine Purkinje fibers, the prolongation of APD by NIF (MS-551; $10^{-5}M$) was exaggerated at slower heart rates.
- This reverse use-dependence effect was also found in humans.



*data from Dr.Matsuda (Tokyo Women's Medical Univ)

(Jpn J Electrocardiol 1993;13:19-31)

NIF vs Amiodarone: action

Nifekalant

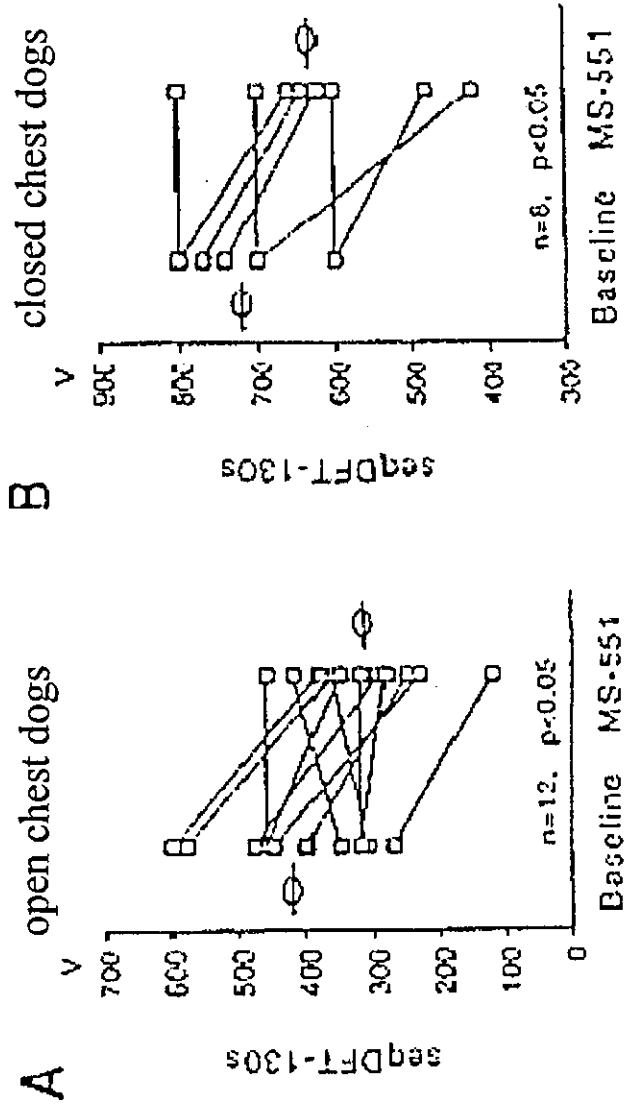
- Pure K channel blocker(selective I_{Kr} blocking agent)
- Reverse use-dependent effect
- Defibrillation threshold improve
- Negative inotropic effect (+/-: may be positive inotropic effect)

Amiodarone

- Multi channel blocker(different action by short and long term)
- Use-dependent effect
- Defibrillation threshold unchanged
- Negative inotropic effect (+)

Improvement of defibrillation efficacy

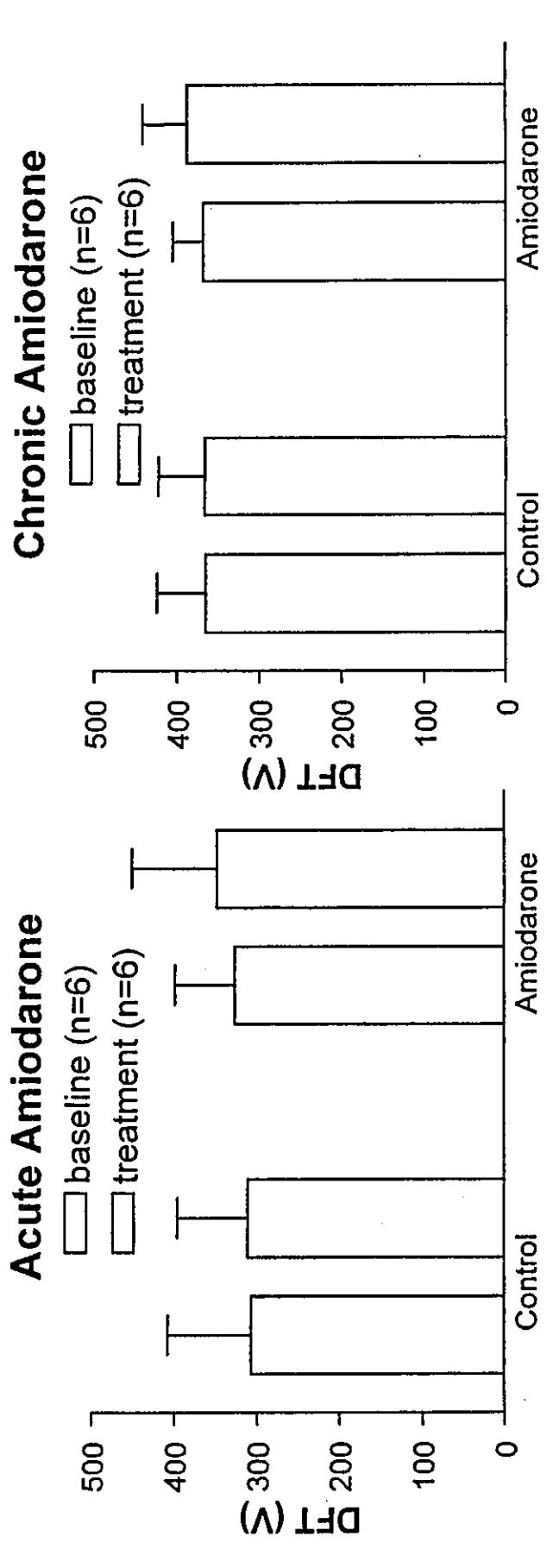
- In the anesthetized dogs, NIF (MS-551) decreased defibrillation threshold (DFT).



(J Am Coll Cardiol 1997;29:688-692)

No change in defibrillation threshold (DFT) by amiodarone

- Neither acute nor chronic administration of amiodarone changed DFT in the anesthetized dogs.



(J Am Coll Cardiol 2002;40:375-383)

NIF vs Amiodarone: action

Nifekalant

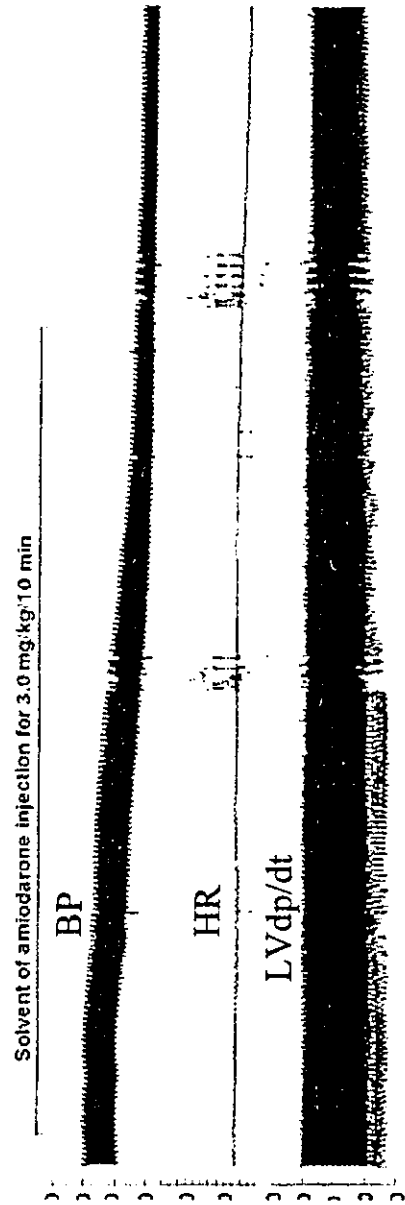
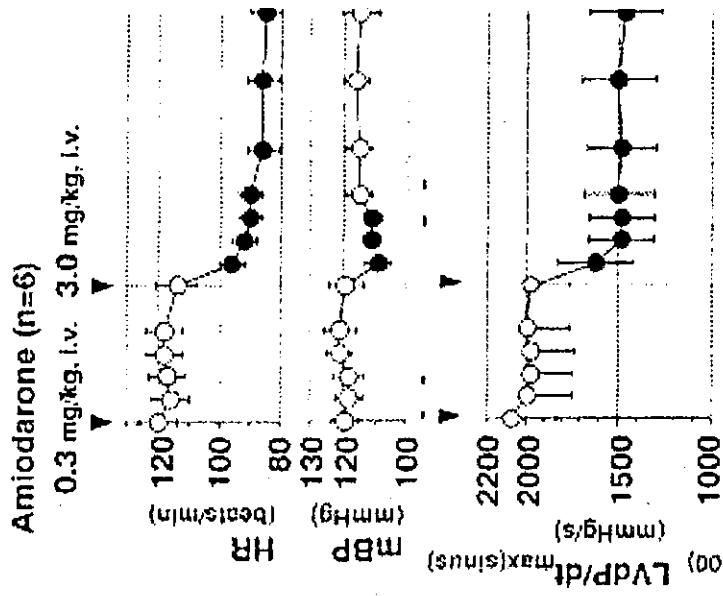
- Pure K channel blocker(selective I_{Kr} blocking agent)
- Reverse use-dependent effect
- Defibrillation threshold improve
- Negative inotropic effect (+/-: may be positive inotropic effect)

Amiodarone

- Multi channel blocker(different action by short and long term)
- Use-dependent effect
- Defibrillation threshold unchanged
- Negative inotropic effect (+)

Amiodarone has negative inotropic effect through its β receptor blocking action

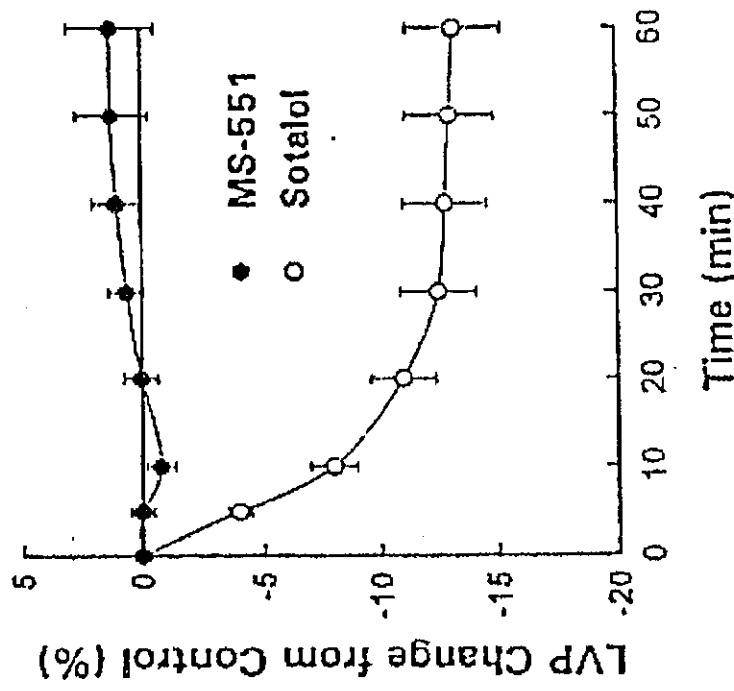
- The intravenous administration of amiodarone (3mg/kg) exerted negative chronotropic and inotropic effects accompanied by a transient hypotensive response in the closed-chest anesthetized canine model.



(Jpn J Pharmacol
2001;87:74-82)

Less depressant effect of NIF on LV pressure in the open-chest dog

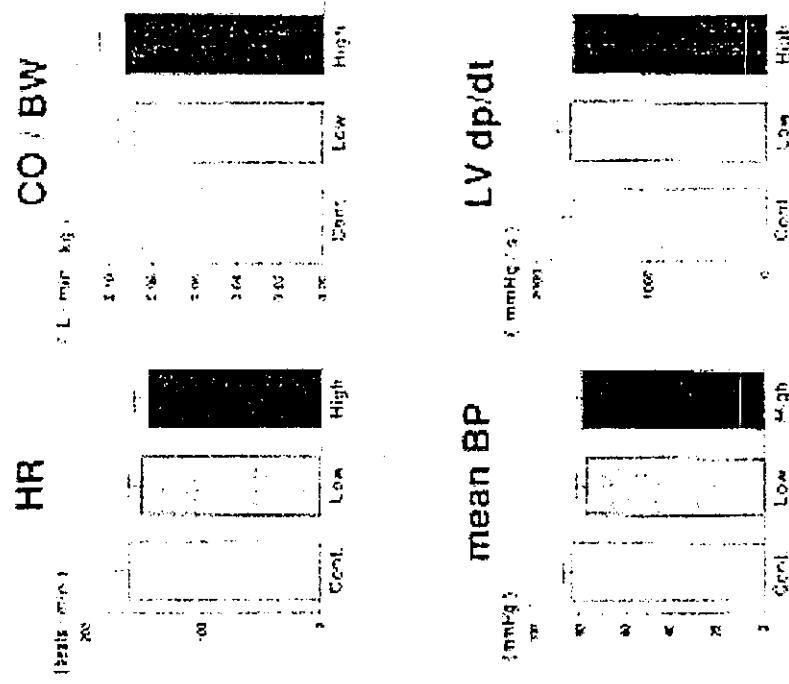
- In the open-chest anesthetized canine model, the LV pressure was significantly decreased by sotalolol (2mg/kg) but not by NIF (MS-551, 1mg/kg)



NIF did not significantly alter cardiac function in the MI model

- In the canine myocardial infarction model, NIF at either a low or high dose did not significantly change the maximum rate of increase in the left ventricular pressure (LV dp/dt).

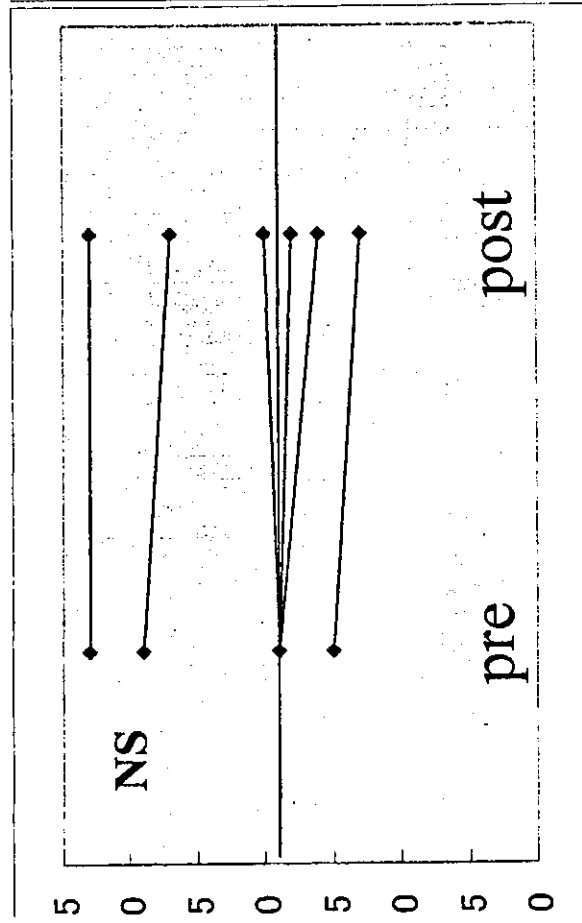
- Low: 0.3mg/kg \Rightarrow 0.05mg/kg/min
- High: 0.3mg/kg \Rightarrow 0.1mg/kg/min



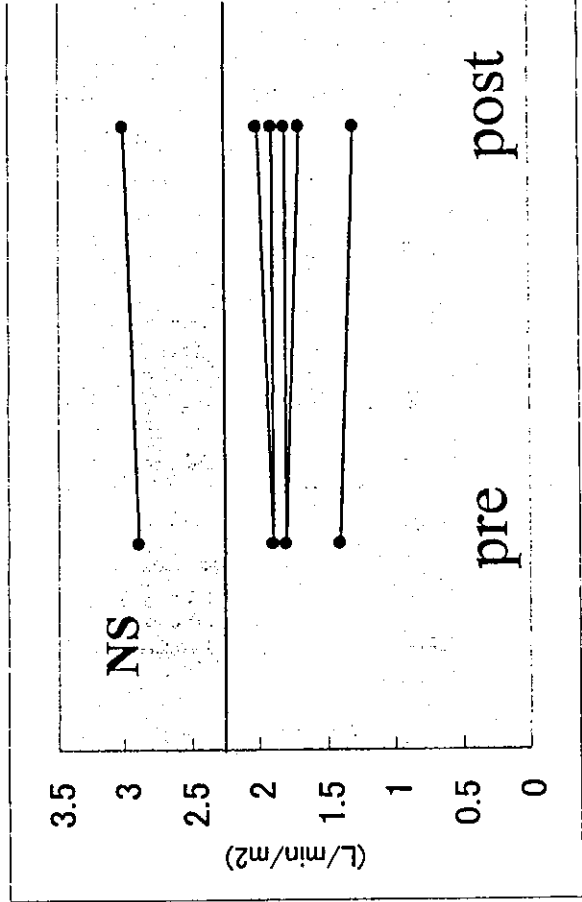
NIF did not deteriorate hemodynamics in AMI patients

- Five patients with anterior AMI (67 ± 8 [mean \pm SD] years)
- Decreased fractional shortening ($16 \pm 3\%$) and refractory VT
- NIF: 0.05-0.20mg/kg/hr

PCm



CI



NIF vs Amiodarone: action

Nifekalant

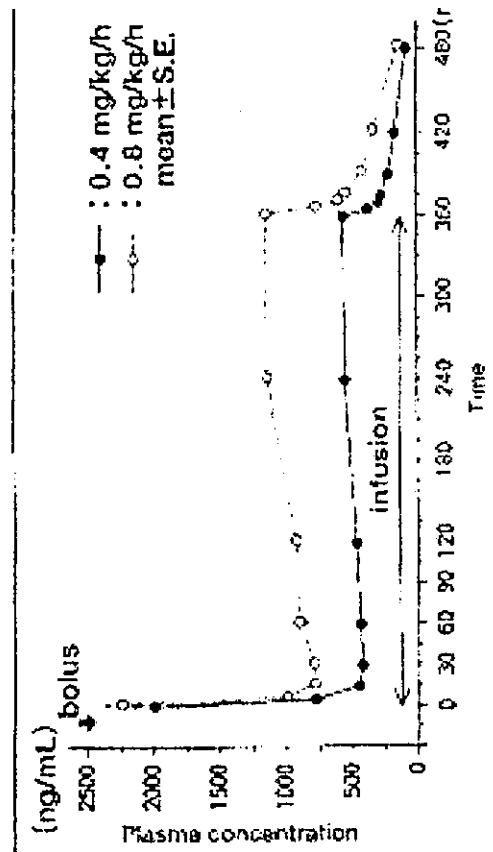
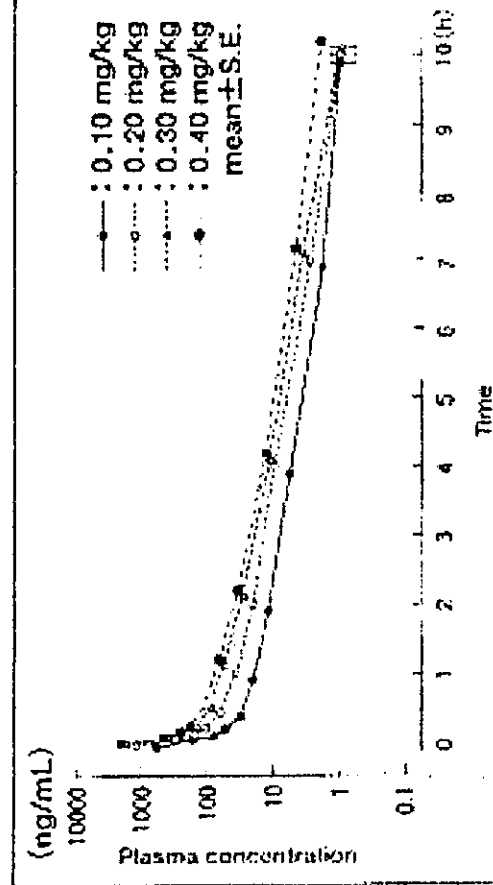
- Pure K channel blocker(selective I_{Kr} blocking agent)
- Reverse use-dependent effect
- Defibrillation threshold improve
- Negative inotropic effect (+/-: may be positive inotropic effect)

Amiodarone

- Multi channel blocker(different action by short and long term)
- Use-dependent effect
- Defibrillation threshold unchange
- Negative inotropic effect (+)

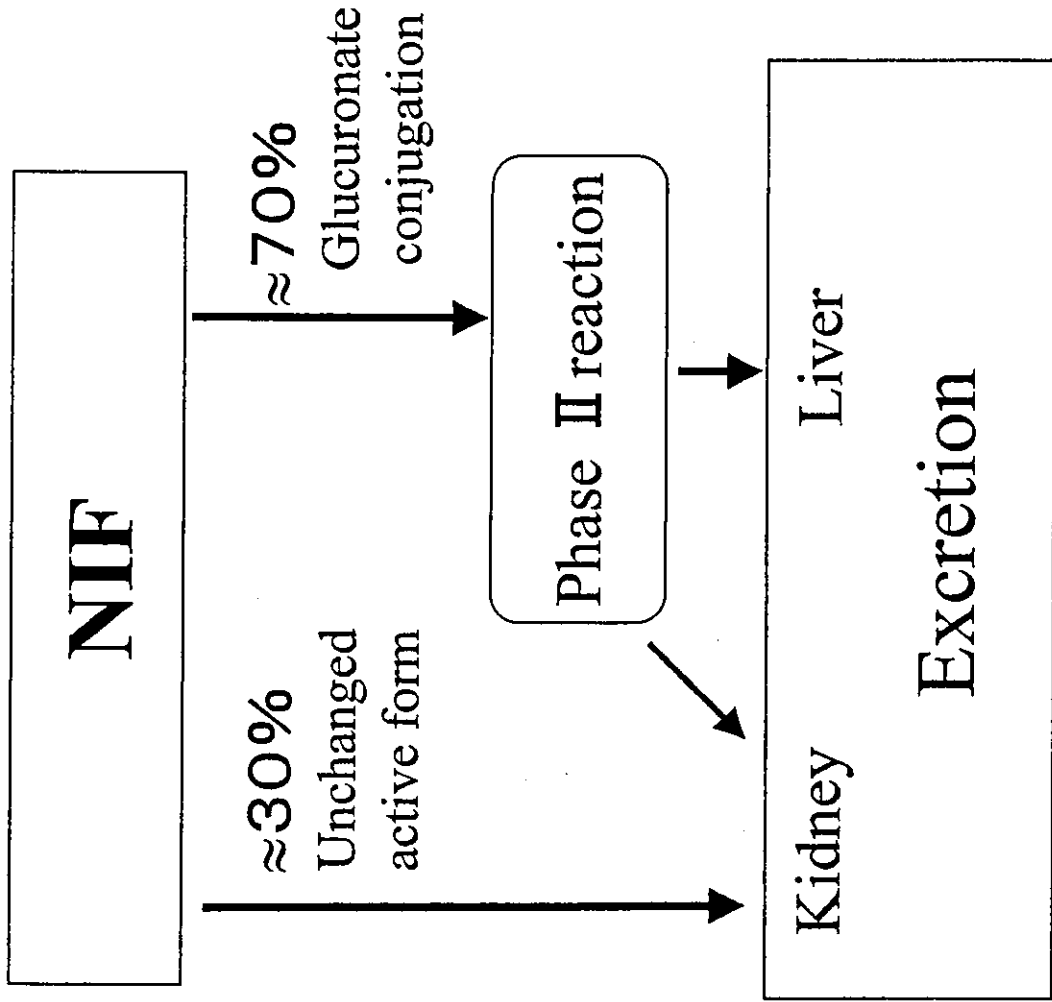
Pharmacokinetics of NIF

	$T_{1/2}\beta$ (hr)	V_c (L/kg)	Cl (L/hr/kg)	$AUC_{0-\infty}$ (ng·hr/mL)
single	1.53 ± 0.23	0.13 ± 0.01	0.85 ± 0.09	321 ± 37
infusion	1.15 ± 0.08	0.14 ± 0.04	0.78 ± 0.05	3766 ± 345



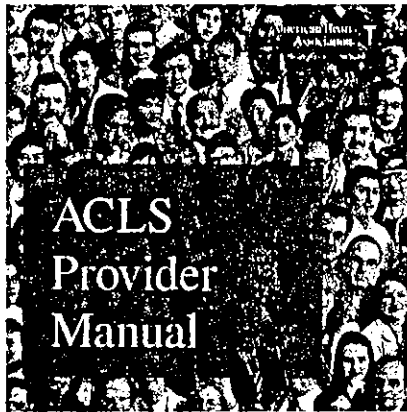
(Folia Pharmacol Jpn 2002;119:103-110)

Pharmacokinetics of NIF

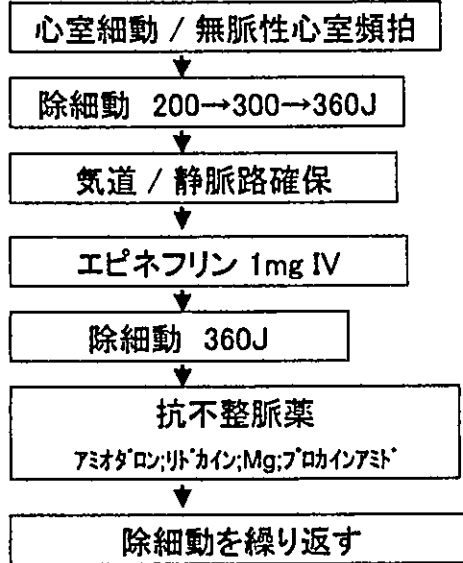


(Circ I 2003・67・898-1)

アルゴリズム: Shock-Shock-Shock-Drug-Shock

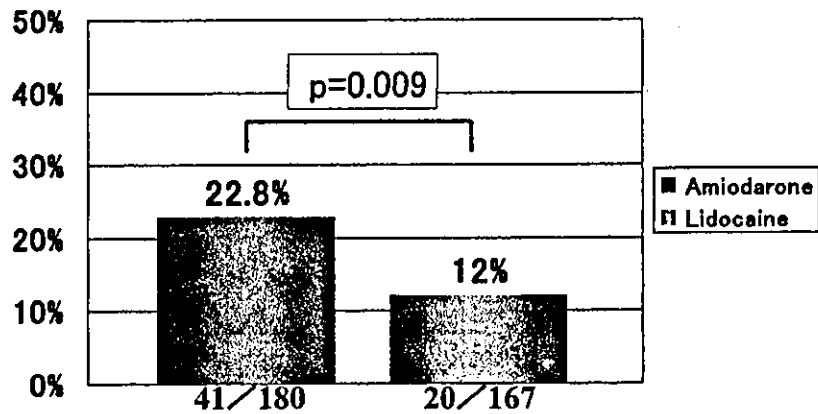


ACLS
Provider
Manual
(Guidelines 2000 for Cardiopulmonary
Resuscitation and Emergency
Cardiovascular Care)



アミオダロン vs リドカイン ショック抵抗性心室細動: ALIVE 試験

生存入院率



(N Eng J Med 2002;346:884-90)

III群抗不整脈薬:ニフェカレント vs アミオダロン

	ニフェカレント	アミオダロン
チャンネル・リセプター遮断	K	K,Na,Ca,β-R
心抑制	なし	あり
除細動閾値	改善	不変

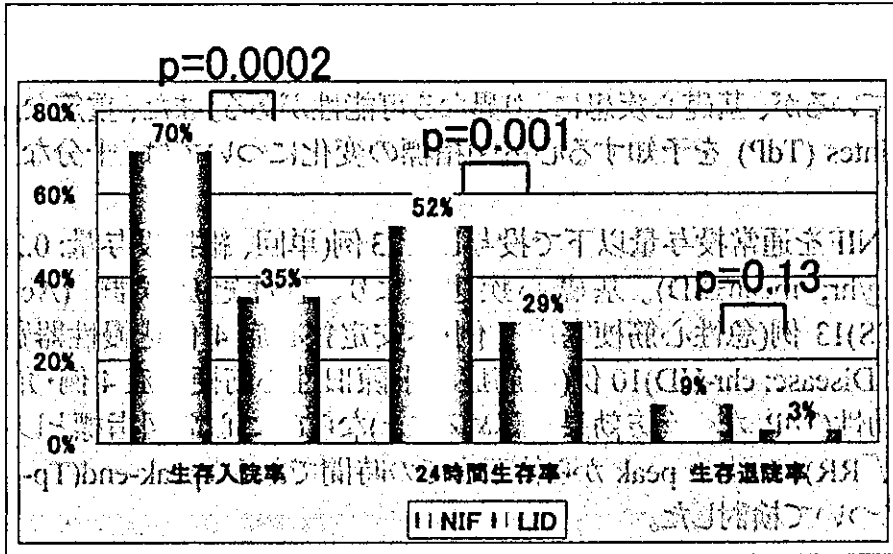
DRUG	CHANNELS					RECEPTORS				PUMPS	
	Na			Ca	K	If	α	β	M ₂	A ₁	Na-K ATPase
	Fast	Mod	Slow								
Nifekalant					●						
Amlodarone(Short-term)	△			△	●		○	○			○
Amlodarone(Long-term)				○	●		△	△			○

Relative potency of block: ○=low, △=moderate, ●=high

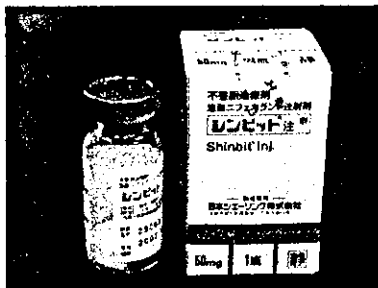
横浜市大救命センター: ショック抵抗性心室細動 ニフェカレント (2000-2003) vs リドカイン (1994-1999)

	ニフェカレント (0.3mg/kg)	リドカイン (1.5mg/kg)	p
症例数	46	77	
年齢(歳)	64	61	0.3
男性(%)	87%	77%	0.16
冠動脈疾患(%)	72%	64%	0.36
目撃のある心停止(%)	54%	40%	0.13
バイスタンダー CPR(%)	37%	23%	0.11
病院搬入までの時間(分)	24	27	0.59
DC回数	7	8	0.31
エピネフリン投与量(mg)	5	8	0.005

ニフェカントによる生存入院率の向上



日本では?: Shock-Shock-Shock-Drug-Shock



ニフェカント: 15-20mg IV
適応: VF・VT

