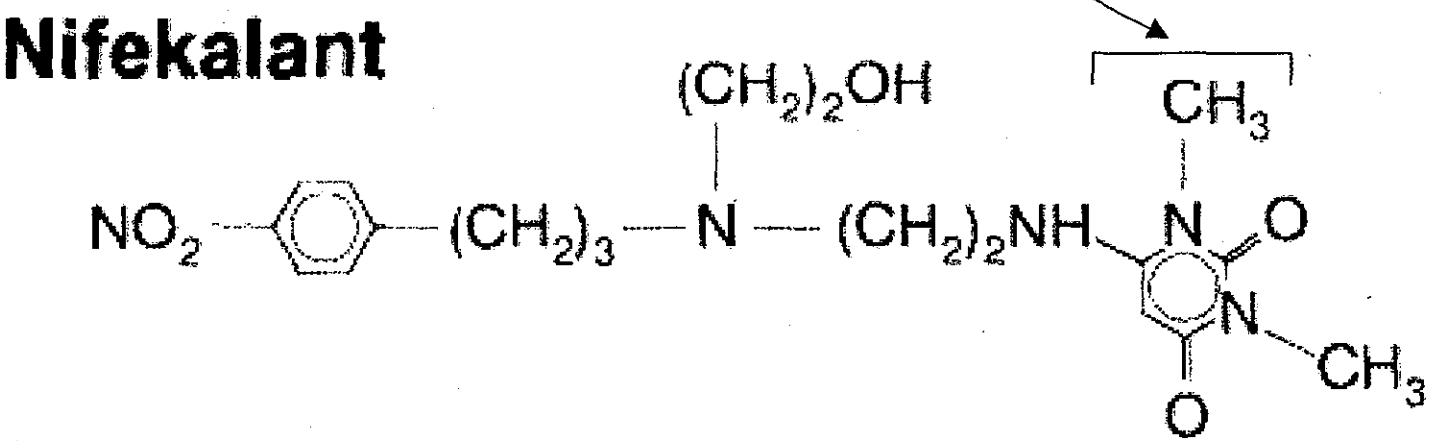
Nifekalant hydrochloride (NIF)

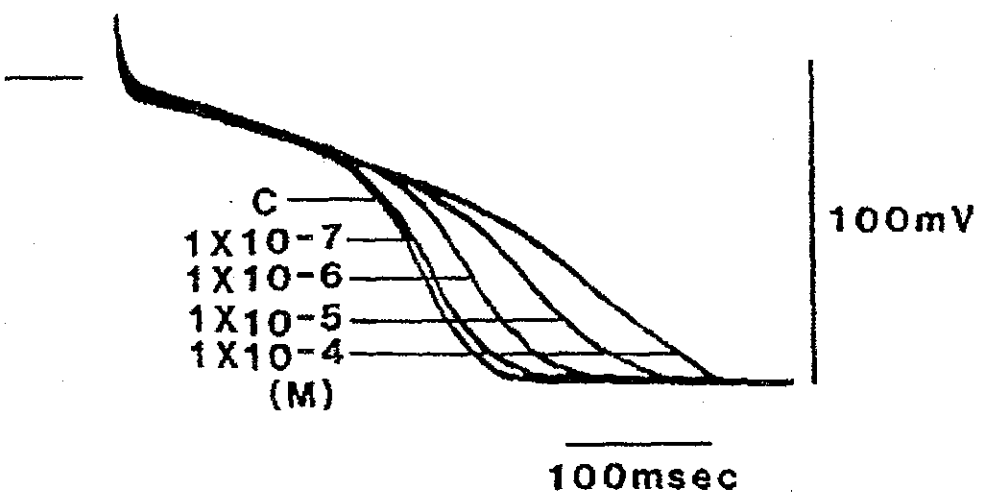
- Nifekalant hydrochloride (NIF), formally known as MS-551, is classified as a class III antiarrhythmic agent having a pirimidinedione structure.



Chemical structure of NIF

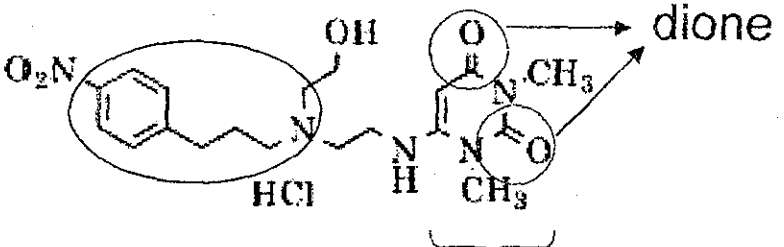
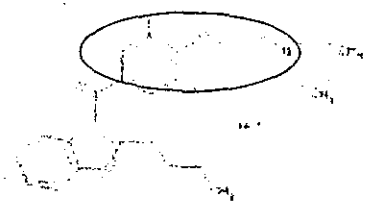
Electrophysiological effects of NIF (MS-551) in canine Purkinje fibers

- 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 (Vmax).



(Drug Dev Res 1995;35:61-68)

NIF vs Amiodarone: structure

	Nifekalant	Amiodarone
Chemical name	6-[2-[(*N*-2-hydroxyethyl)-3-(4-nitrophenyl)propylamino]ethylamino]-1,3-dimethyl-1*H*,3*H*-pyrimidine-2,4-dione monohydrochloride	2-butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride
Structural formula	 dione / pirimidinedione	
Molecular formula	$C_{19}H_{27}N_5O_5 \cdot HCl$	$C_{25}H_{29}I_2NO_3 \cdot HCl$
M.W.	441.91	681.78
m.p	171～175℃	ca. 160℃ (decomposition)
Description	Pale yellow to yellow crystal or crystalline powder	White to slightly yellow crystalline powder
Solubility	Very soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and practically insoluble in ethyl ether	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

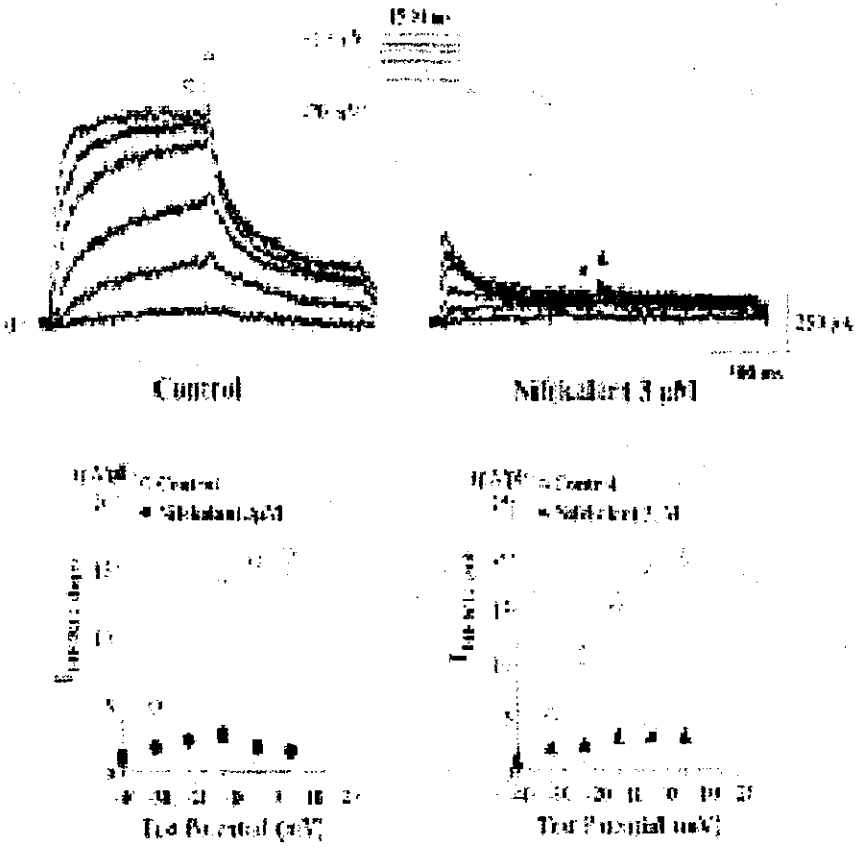
The Sicilian Gambit : A New Approach to the Classification of Antiarrhythmic Drugs

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

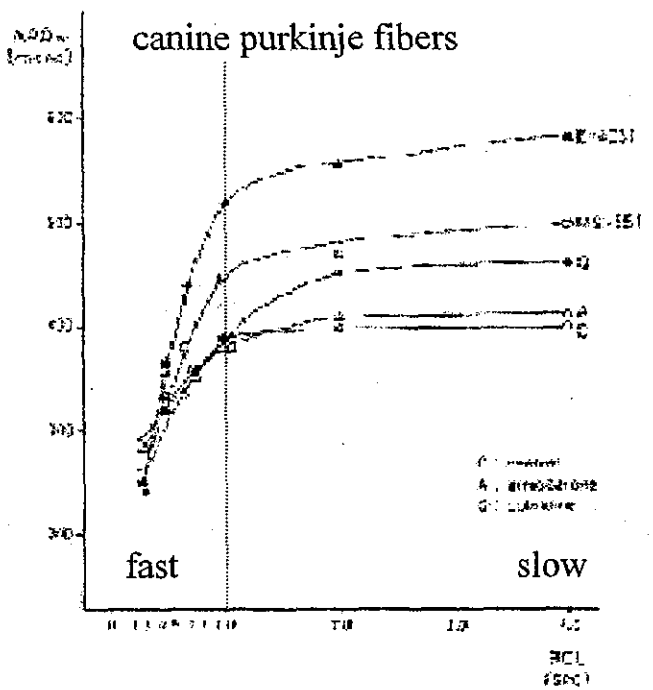
- NIF inhibited HERG channels, suggesting the selective inhibition of the rapid component of the delayed rectifier K^+ current (I_{Kr}).



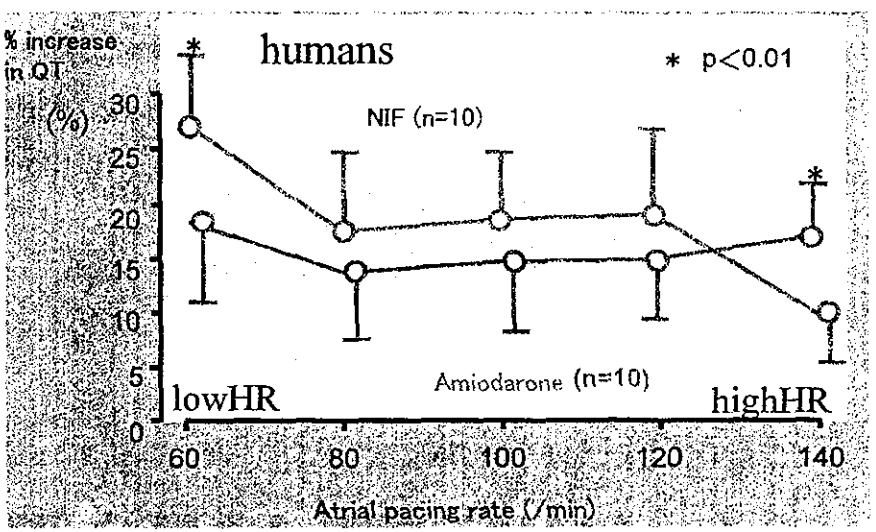
(Jpn J Electrocardiol 2000;20:195-201)

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.



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



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

NIF vs Amiodarone: action

Nifekalant

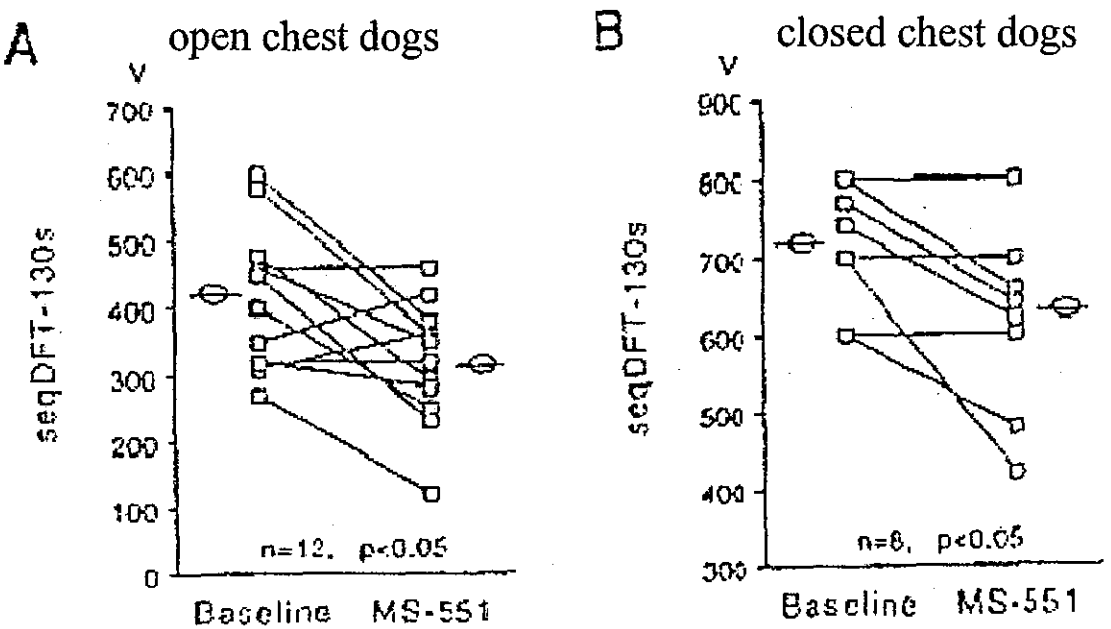
- Pure K channel blocker(selective I_{Kr} blocking agent)
- Reverse use-dependent effect
- Defibrillation threshold improve
- Negative inotropic effect (+/-: may be positive inotropic effect)

Amiodarone

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

Improvement of defibrillation efficacy

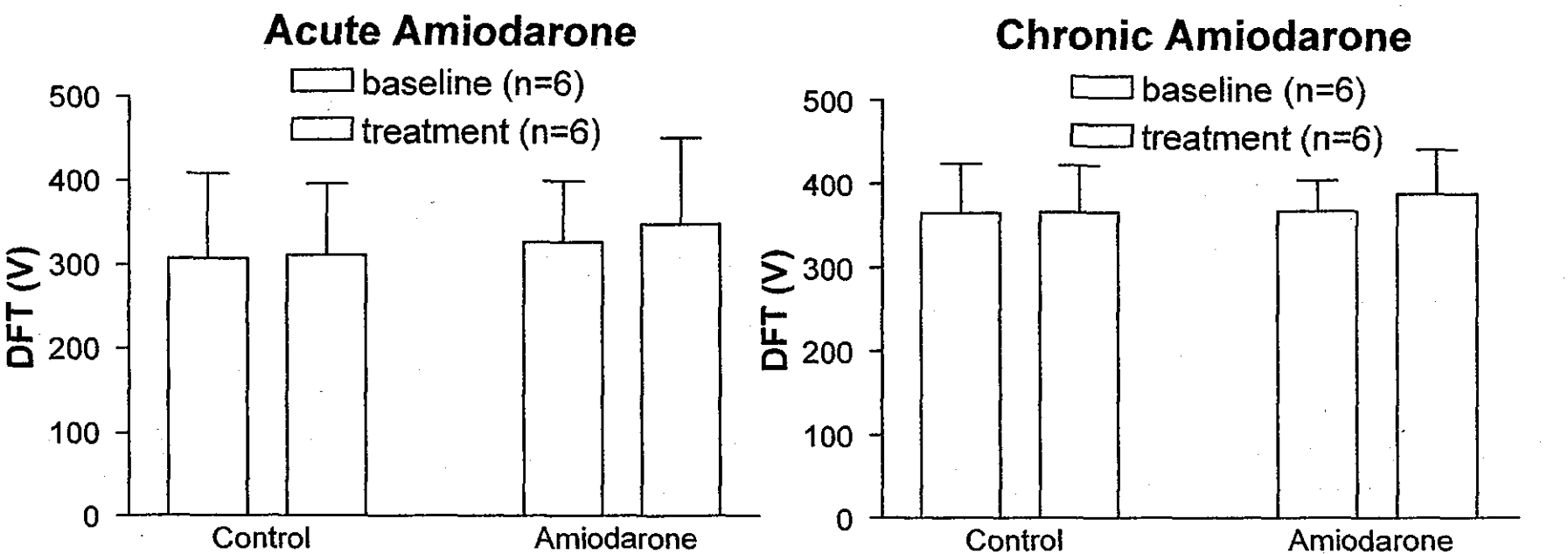
- In the anesthetized dogs, NIF (MS-551) decreased defibrillation threshold (DFT).



(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

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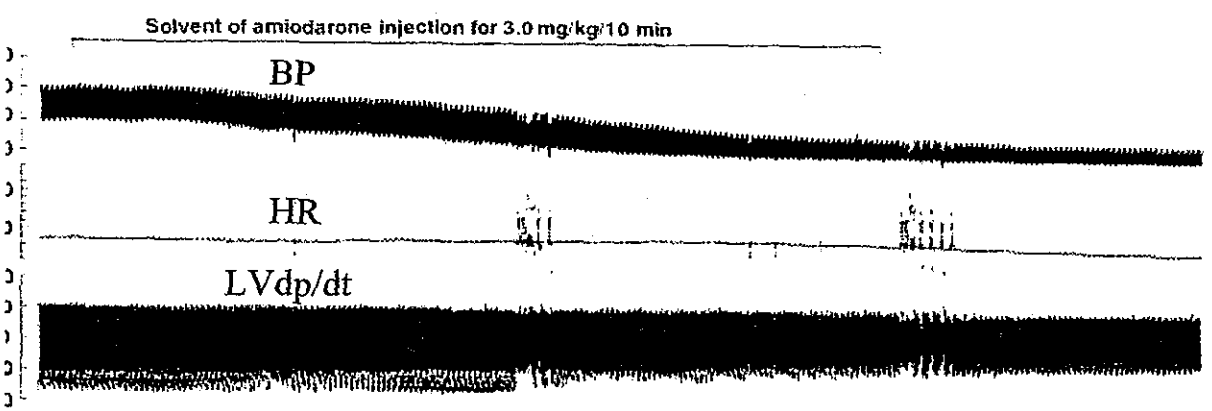
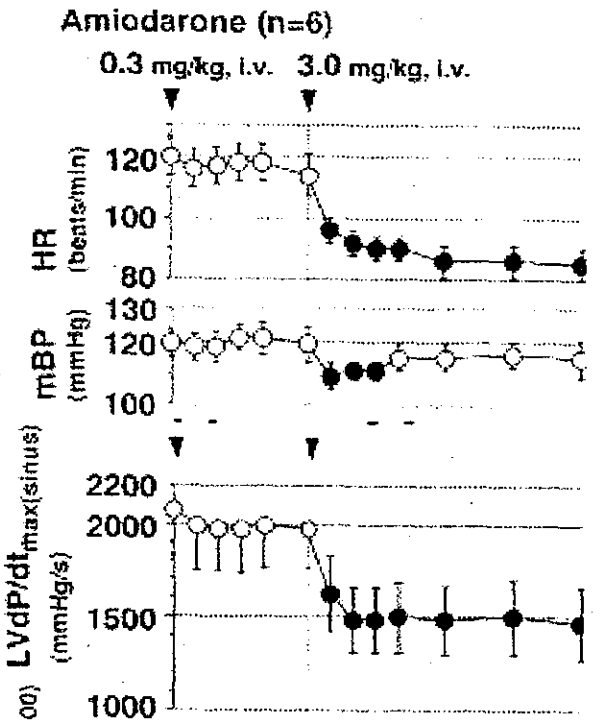
Amiodarone

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

Amiodarone has negative inotropic effect through its βreceptor 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.

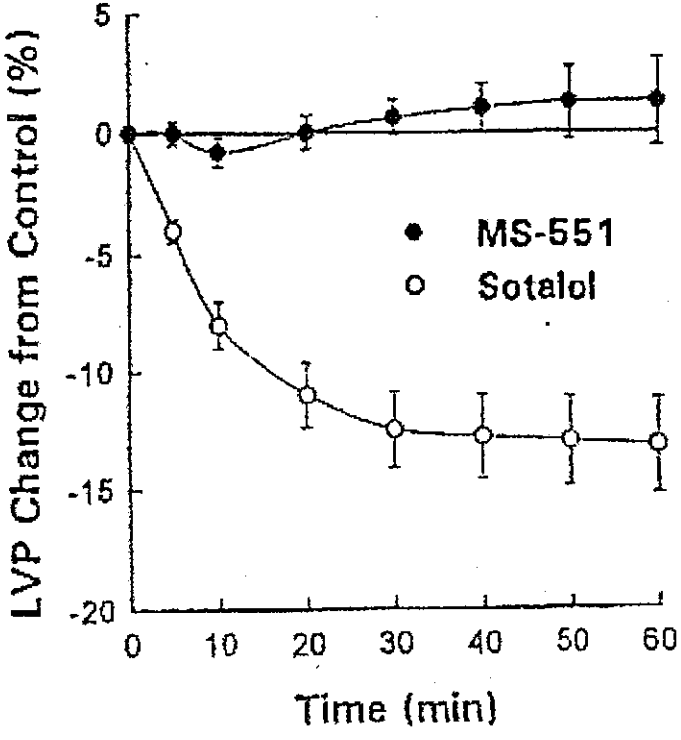




(Jpn J Pharmacol 2001;87:74-82)

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

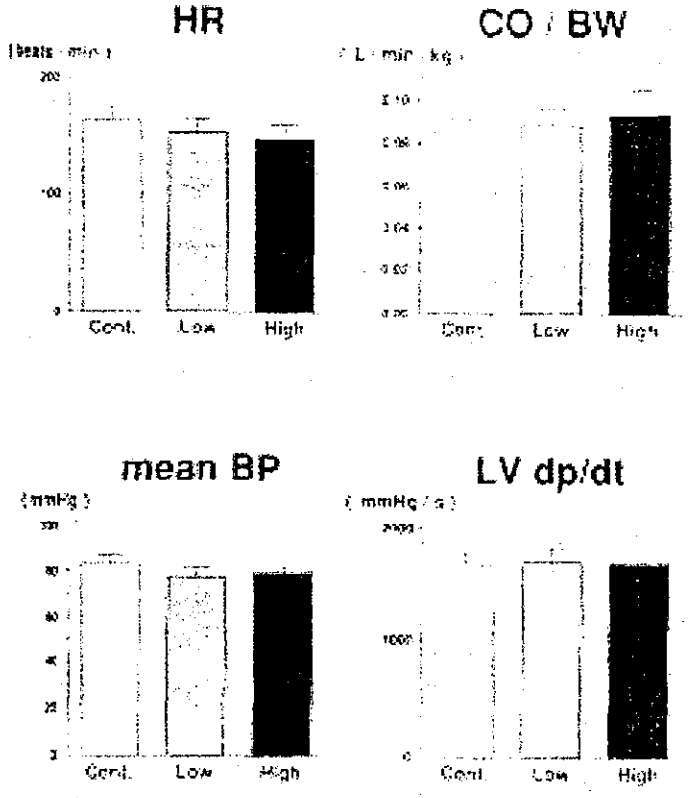
- In the open-chest anesthetized canine model, the LV pressure was significantly decreased by sotalol (2mg/kg) but not by NIF (MS-551, 1mg/kg)



(J Pharmacol Exp Ther 1998;285:687-69

NIF did not significantly alter cardiac function in the MI model

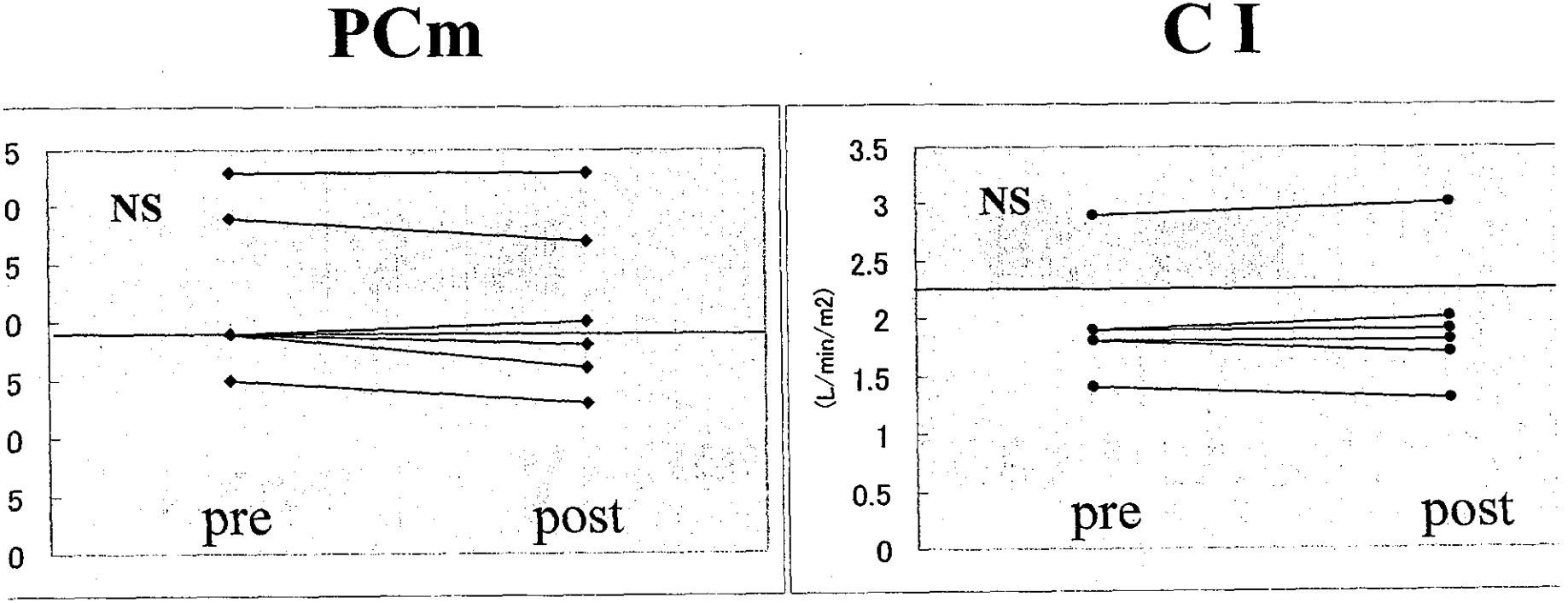
- In the canine myocardial infarction model, NIF at either a low or high dose did not significantly change the maximum rate of increase in the left ventricular pressure (LV dp/dt).
  - Low: 0.3mg/kg⇒0.05mg/kg/min
  - High: 0.3mg/kg⇒0.1mg/kg/min



(J Cardiovasc Pharmacol 1994;23:674-8

NIF did not deteriorate hemodynamics in AMI patients

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



(Jpn Circ J 2001:65:60-

NIF vs Amiodarone: action

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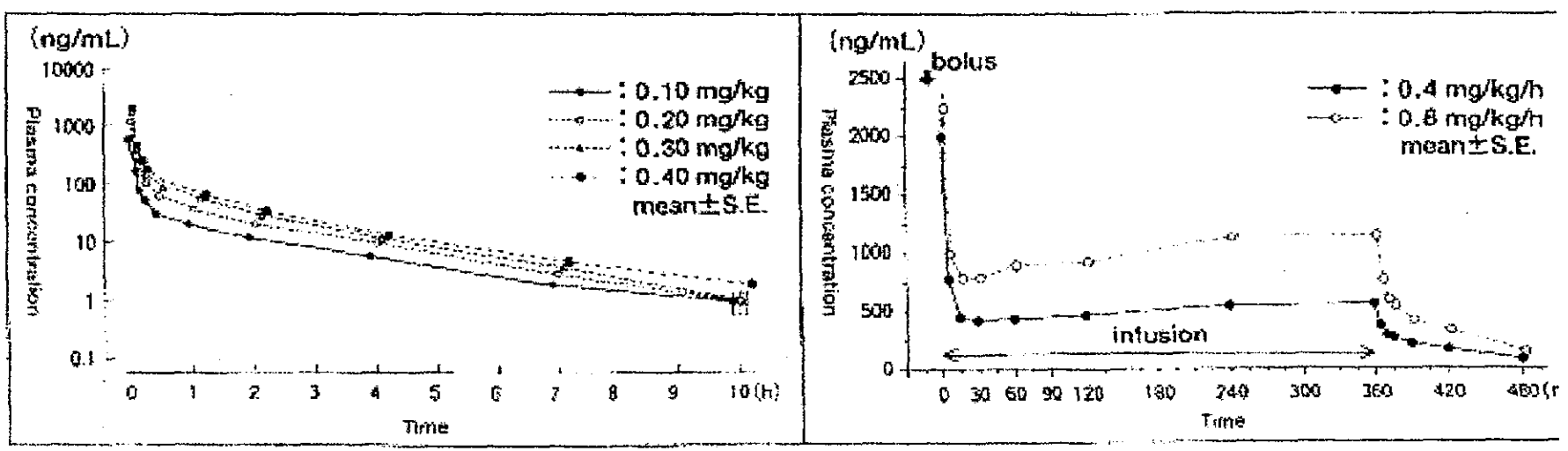
- Negative inotropic effect (+/-: may be positive inotropic effect)

Amiodarone

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

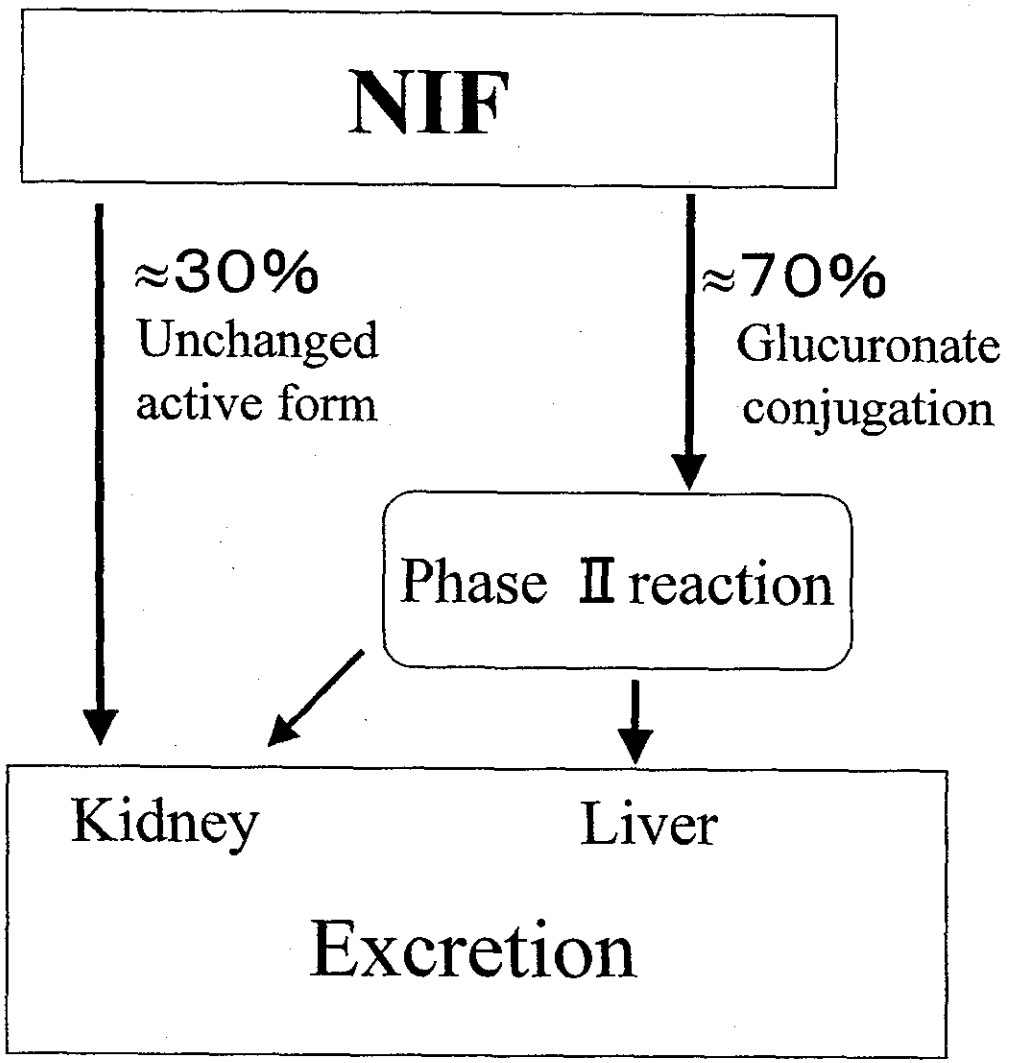
Pharamacokinetics of NIF

	$T_{1/2}\beta$(hr)	Vc (L/kg)	Cl (L/hr/kg)	AUC $_{0\sim\infty}$ (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



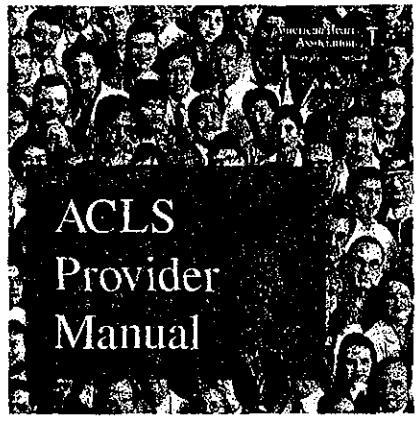
(Folia Pharmacol Jpn 2002;119:103-1(

Pharamacokinetics of NIF



(Circ J 2003;67:898-

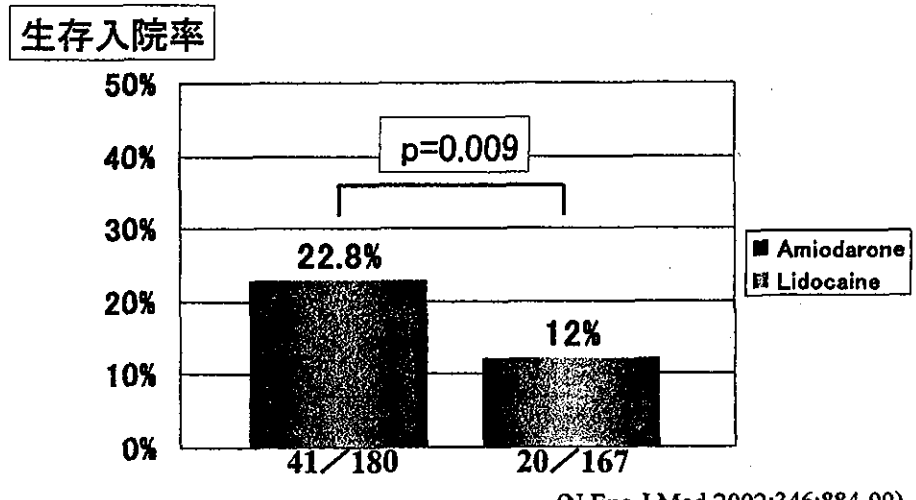
アルゴリズム: Shock-Shock-Shock-Drug-Shock



(Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care)

心室細動 / 無脈性心室頻拍
↓
除細動 200→300→360J
↓
気道 / 静脈路確保
↓
エピネフリン 1mg IV
↓
除細動 360J
↓
抗不整脈薬
ｱﾐｵﾀﾞﾛﾝ;ﾘﾄﾞｶｲﾝ;Mg;ﾌﾟﾛｶｲﾝｱﾐﾄﾞ
↓
除細動を繰り返す

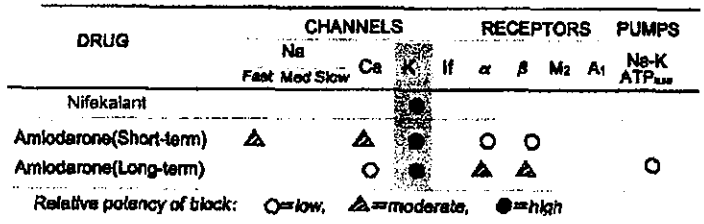
アミオダロン vs リドカイン
ショック抵抗性心室細動: ALIVE 試験



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

III群抗不整脈薬:ニフェカラント vs アミオダロン

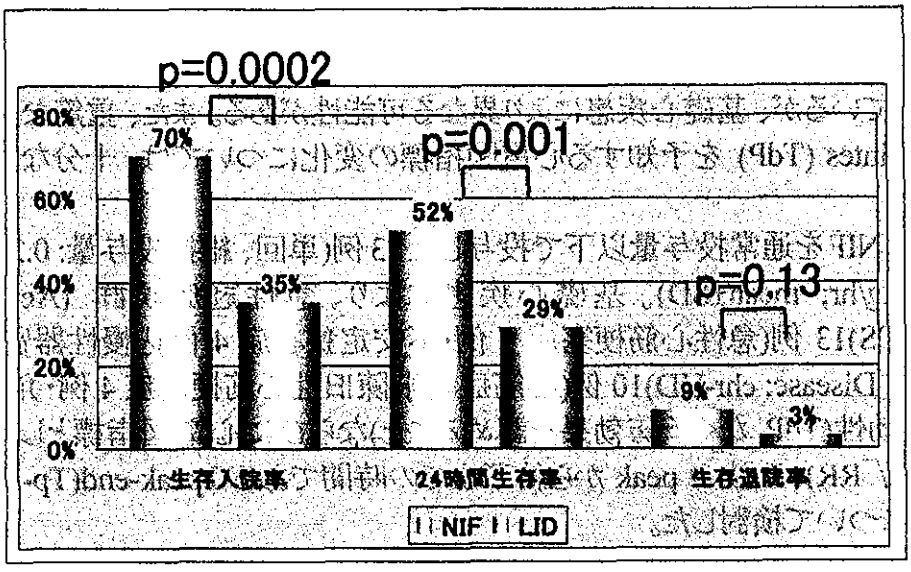
	ニフェカラント	アミオダロン
チャンネル・リセプター遮断	K	K,Na,Ca, β -R
心抑制	なし	あり
除細動閾値	改善	不変



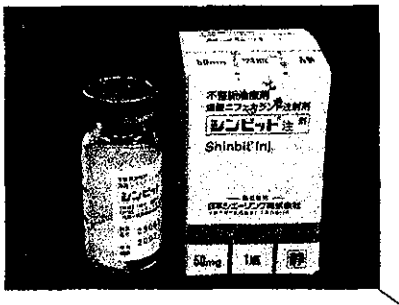
横浜市大救命センター: ショック抵抗性心室細動
ニフェカラント (2000-2003) vs リドカイン (1994-1999)

	ニフェカラント (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

ニフェカラントによる生存入院率の向上



日本では？: Shock-Shock-Shock-Drug-Shock



ニフェカラント:15-20mg IV
適応:VF・VT

心室細動 / 無脈性心室頻拍
↓
除細動 200→300→360J
↓
気道 / 静脈路確保
↓
エピネフリン 1mg IV
↓
除細動 360J
↓
抗不整脈薬
(アミオダロン;リドカイン;Mg;プロカインアミド)
↓
除細動を繰り返す