Tratamiento de la insuficiencia cardíaca crónica con cronotropicos negativos

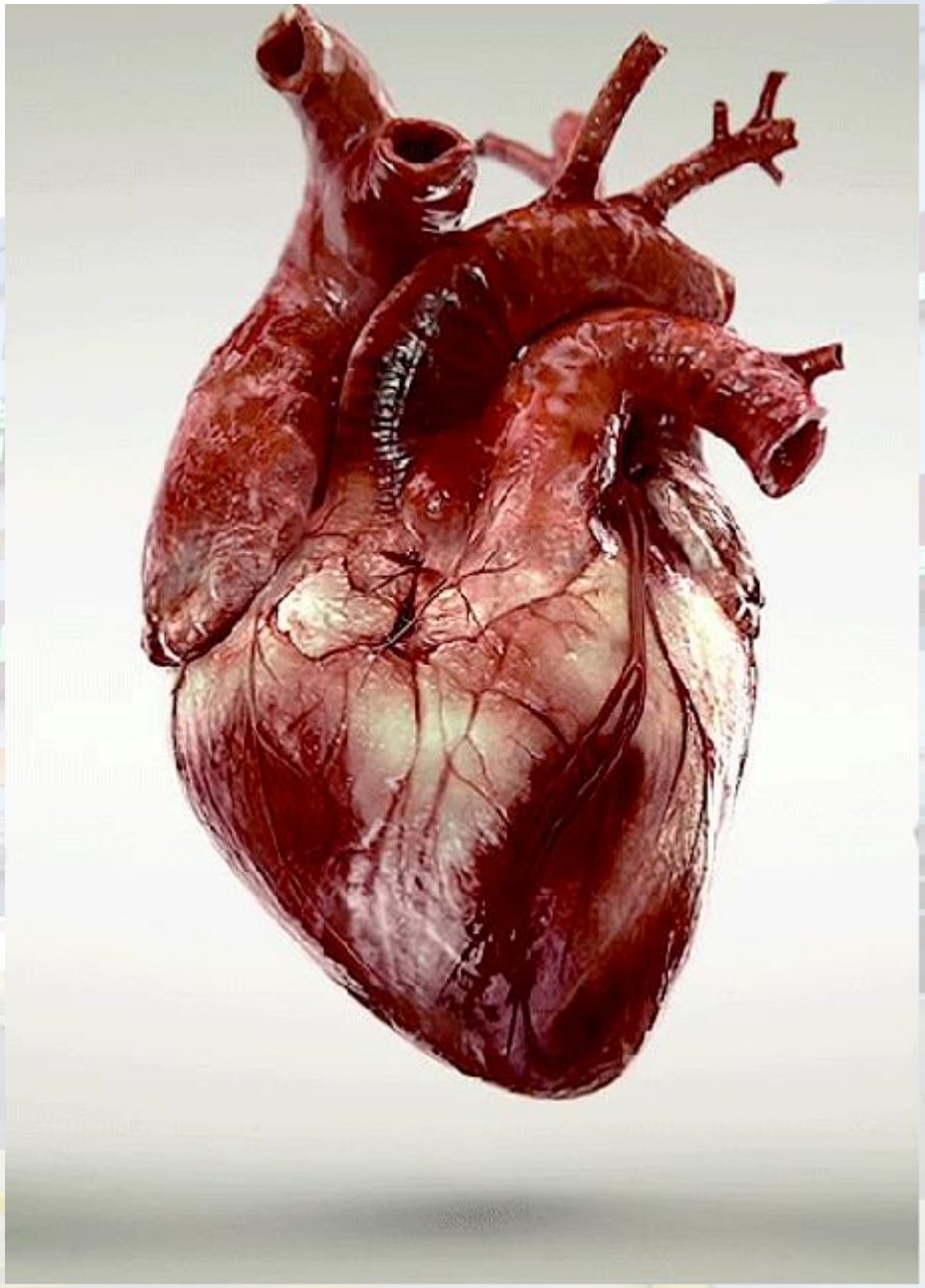
Rafael Porcile

rafael.porcile@vaneduc.edu.ar

DEPARTAMENTO DE CARDIOLOGIA

CATEDRA DE FISIOLOGÍA

Universidad Abierta Interamericana



rafael.porcile@vaneduc.edu.ar

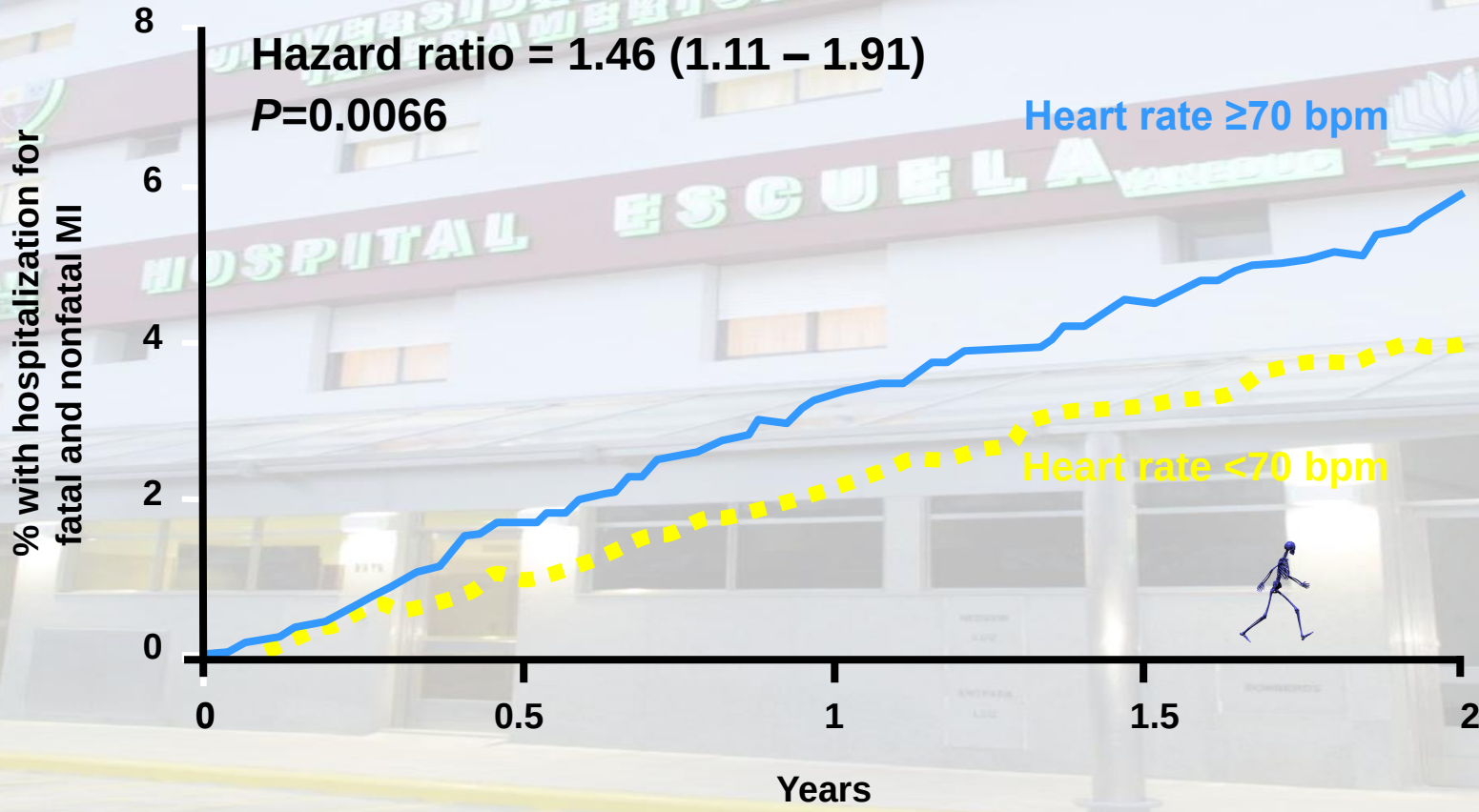
BEAUTIFUL

MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction

rafael.porcile@vaneduc.edu.ar

Heart rate above 70 bpm increases risk of myocardial infarction by 46%

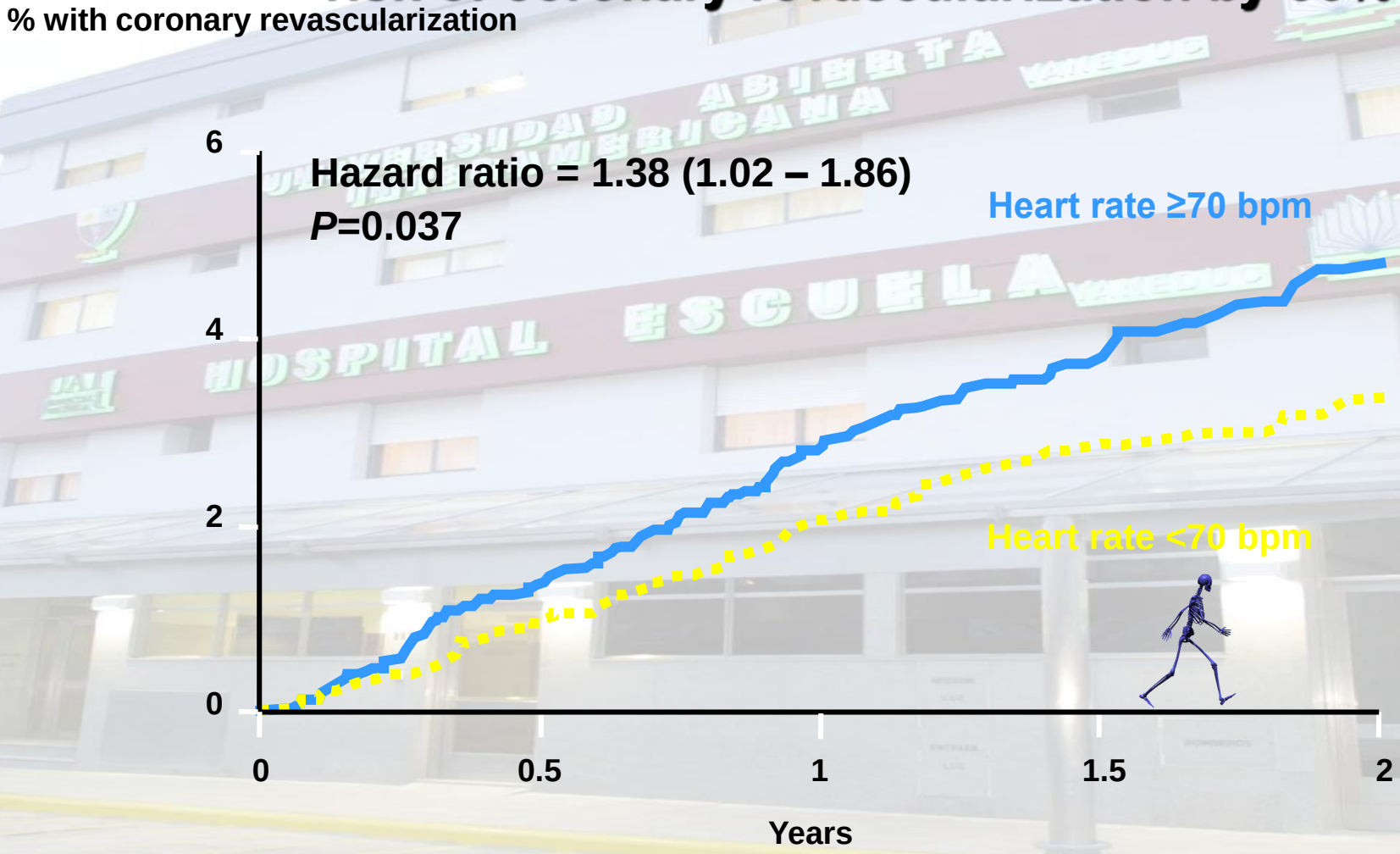
Prospective data from the BEAUTIFUL placebo arm



Fox K et al. *Lancet.* 2008;372:817-821.

rafael.porcile@vaneduc.edu.ar

Heart rate above 70 bpm increases risk of coronary revascularization by 38%



Fox K et al. Lancet. 2008;372:817-821

rafael.porcile@vaneduc.edu.ar

BEAUTIFUL: ivabradina en pacientes con enfermedad coronaria con y sin disfunción sistólica

Pacientes frecuencia cardiaca mayor o igual a 70 lpm, tienen más probabilidades de morir o de sufrir otro evento cardiovascular. El aumento en el riesgo es del 34% para muerte cardiovascular, 46% para el infarto de miocardio, el 56% para la insuficiencia cardíaca y 38% para revascularización coronaria.

6Crdq

Cardiology. 2008;110(4):271-82

rafael.porcile@vaneduc.edu.ar

Am Heart J. 1987 Jun;113(6):1489-94.

Heart rate and cardiovascular mortality: the Framingham Study

rafael.porcile@vaneduc.edu.ar

5070 subjects free of cardiovascular disease at entry into the study.
In both sexes
At all ages, all-cause
cardiovascular, and coronary mortality rates increased progressively in relation to antecedent heart rates determined biennially.
A more impressive association to cardiovascular disease was observed in men than in women, which was independent of associated cardiovascular risk factors.
Case fatality rates following coronary events also increased with antecedent heart rate and the fraction of coronary deaths as sudden death increased strikingly with heart rate in men 35 to 64 years of age.
There was also a substantial excess of noncardiovascular deaths at high heart rates, and the proportion of all deaths resulting from cardiovascular disease did not increase with heart rate.

rafael.porcile@vaneduc.edu.ar

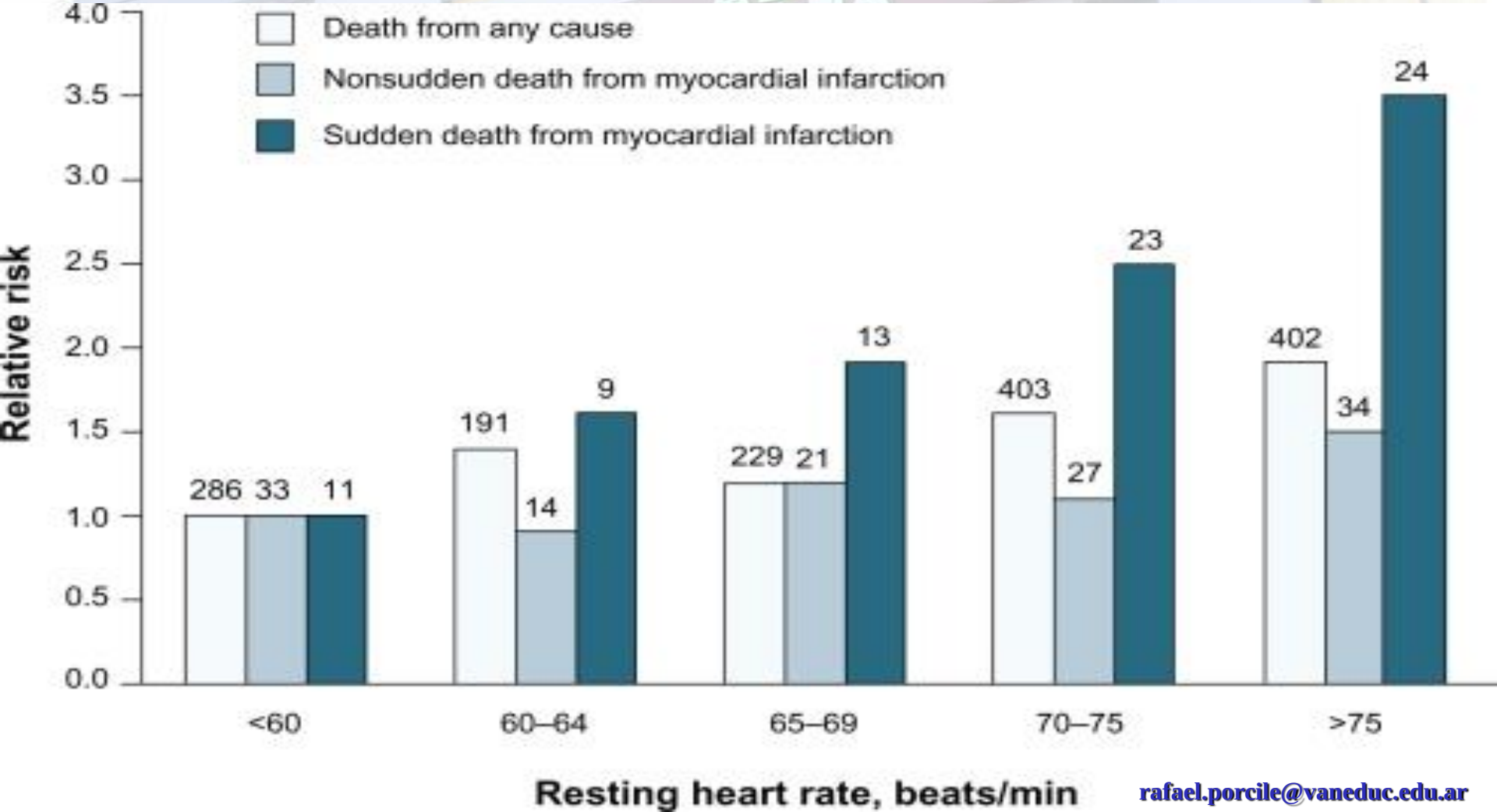
Heart-rate profile during exercise as a predictor of sudden death.

N Engl J Med. 2005;352(19):1951–1958.

Heart rate and mortality in healthy individuals: Relative risk of death from any cause, nonsudden death from myocardial infarction (MI), and sudden death from MI in 5713 people without known or suspected heart disease. Differences among quintiles with respect to risk of death from any cause, $P < 0.001$; nonsudden death from cardiac causes, $P = 0.02$; sudden death from cardiac causes, $P < 0.001$.

rafael.porcile@vaneduc.edu.ar

Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med*. 2005;352(19):1951–1958.



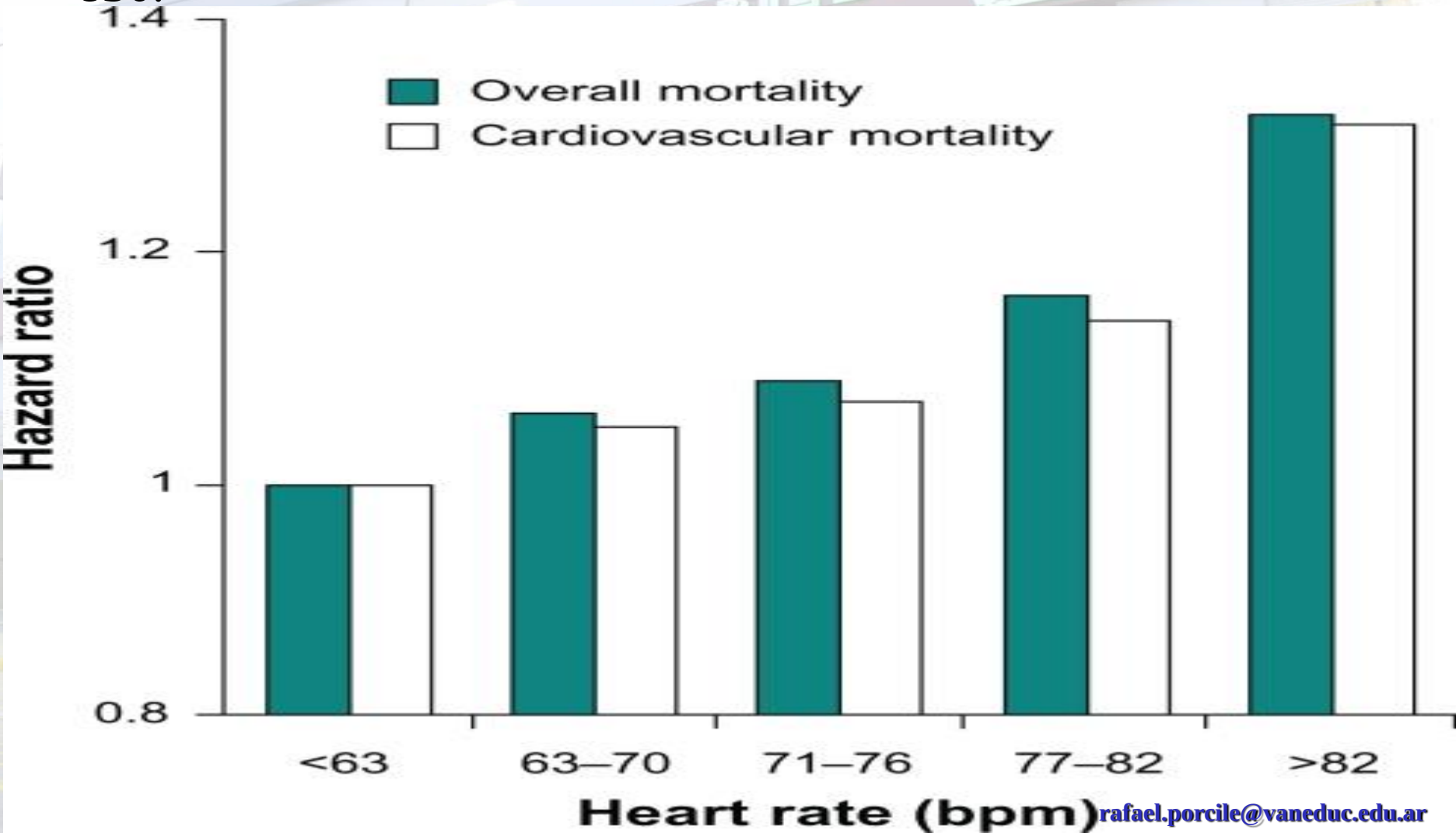
rafael.porcile@vaneduc.edu.ar

Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007;50(9):823–830.

Relationship between resting heart rate and all-cause and cardiovascular mortality in 24,913 patients with suspected or proven coronary artery disease

rafael.porcile@vaneduc.edu.ar

Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007;50(9):823–830.



rafael.porcile@vaneduc.edu.ar

Association Between Resting Heart Rate, Chronotropic Index, and Long-Term Outcomes in Patients With Heart Failure Receiving B-Blocker Therapy: Data from the HF-ACTION Trial

- Eur Heart J (2013) doi: 10.1093/eurheartj/ehs433.

rafael.porcile@vaneduc.edu.ar

Este subanálisis del estudio HF-ACTION incluyó a 1118 pacientes (de los 2331 iniciales) con insuficiencia cardiaca y FEVI <35% bajo tratamiento con betabloqueantes. El objetivo fue analizar la evolución e incidencia de eventos a largo plazo, en función de la frecuencia cardiaca (FC) mantenida en reposo y el índice cronotrópico (CI).

rafael.porcile@vaneduc.edu.ar

Se incluyeron a aquellos pacientes en ritmo sinusal tratados con betabloqueantes (50 mg/dia de la dosis equivalente de carvedilol) con prueba ergométrica máxima. El tiempo medio de seguimiento fue de unos 32 meses. Respecto a la clase funcional, la mayoría estaba en CF II de la NYHA.

Se comprobó que cada incremento en 5 lpm sobre la frecuencia en reposo, se asociaba con un aumento de la probabilidad de muerte u hospitalización por todas las causas de un 4%.

Por otro lado, la disminución en 0,1 del CI se asociaba con un aumento de morbimortalidad (OR: 1,26).

rafael.porcile@vaneduc.edu.ar

Se postula finalmente que obtener una mejor respuesta cronotropica al ejercicio, incluso en aquellos pacientes tratados con dosis óptimas de betabloqueantes, podría ser un objetivo terapéutico en este subgrupo de población.

rafael.porcile@vaneduc.edu.ar

rafael.porcile@vaneduc.edu.ar

rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

PONGAMONOS DE ACUERDO

rafael.porcile@vaneduc.edu.ar

rafael.porcile@vaneduc.edu.ar

CUAL ES LA MOLECULA EN LA QUE CONFLUYE LA REGULACÍON DEL INOTROPISMO Y EL LUSITROPISMO

rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL
UNIVERSITARIO

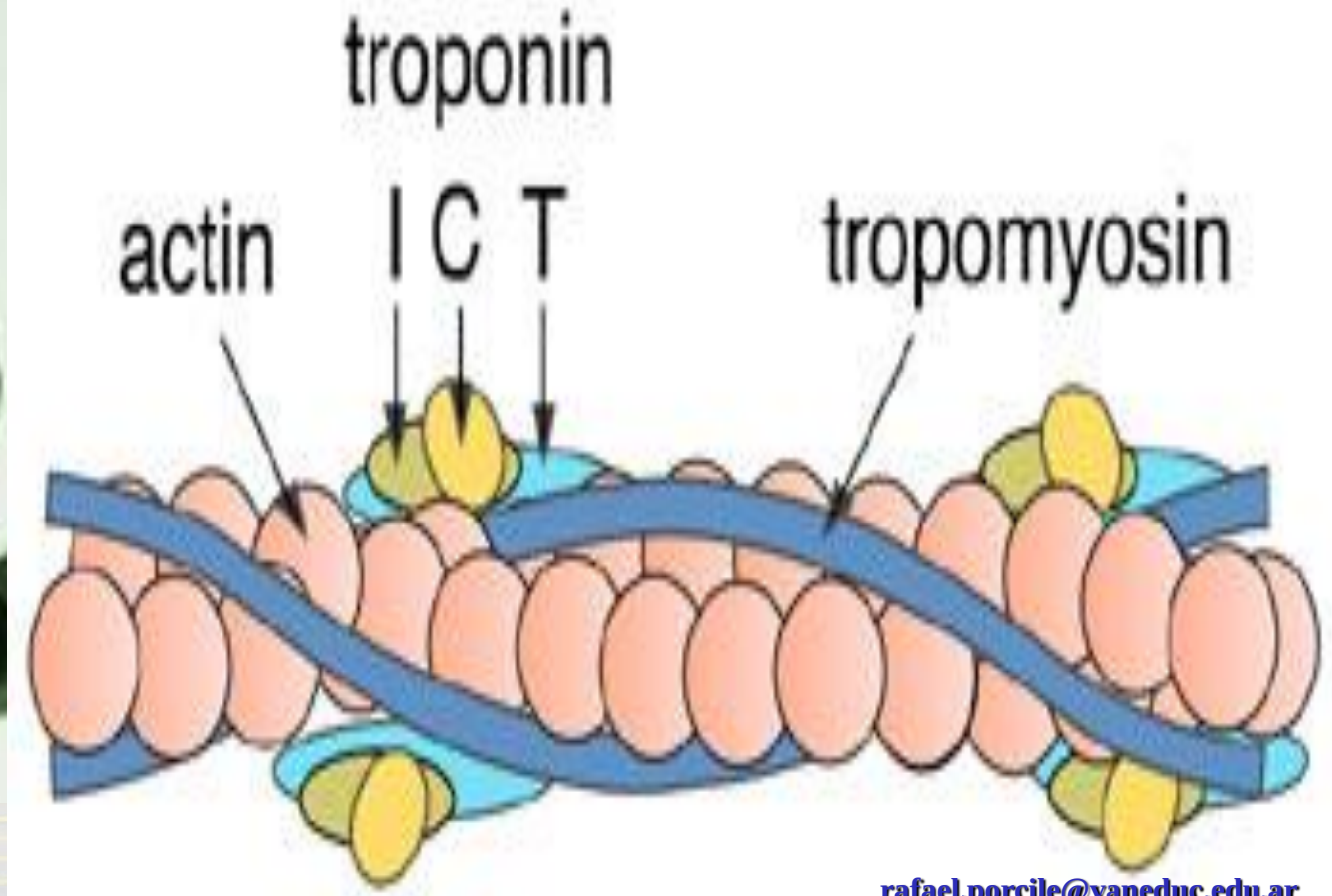
Departamento de Cardiología
U A I
Hospital Universitario

TROPONINA C

rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL
UNIVERSITARIO

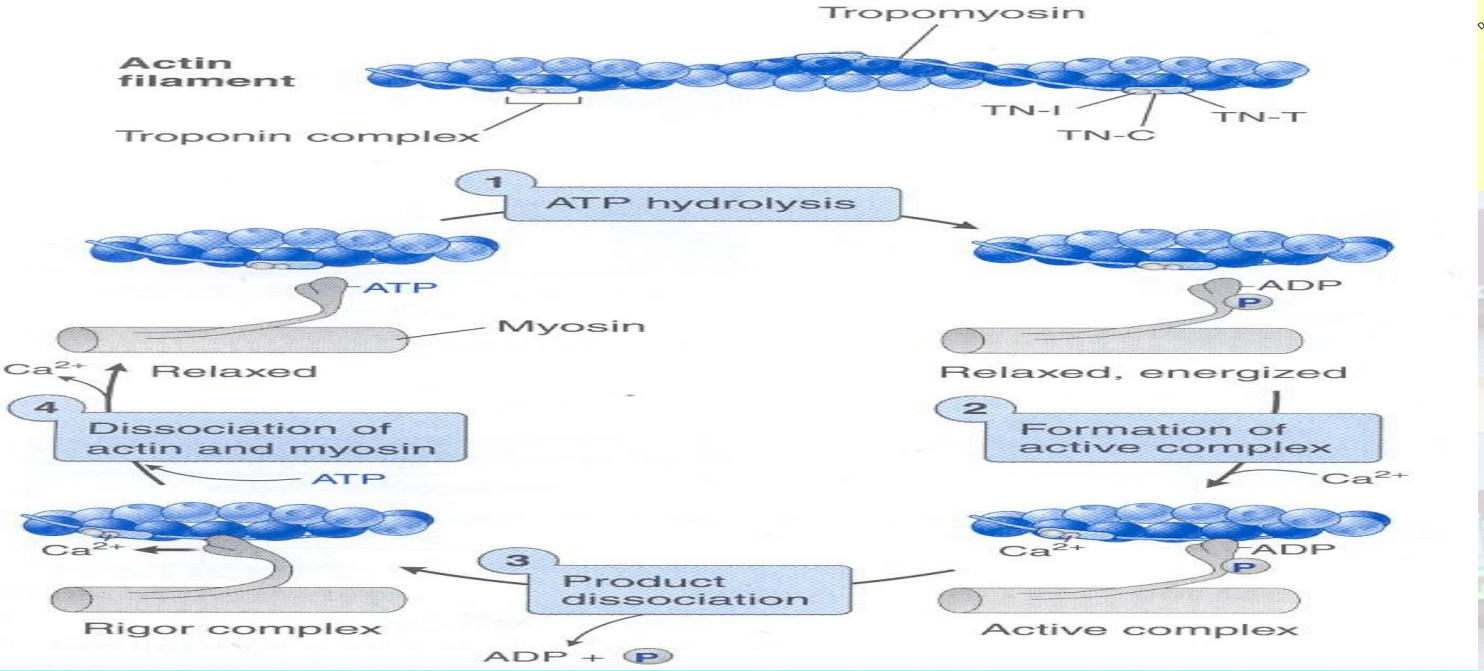
TROPONINA C

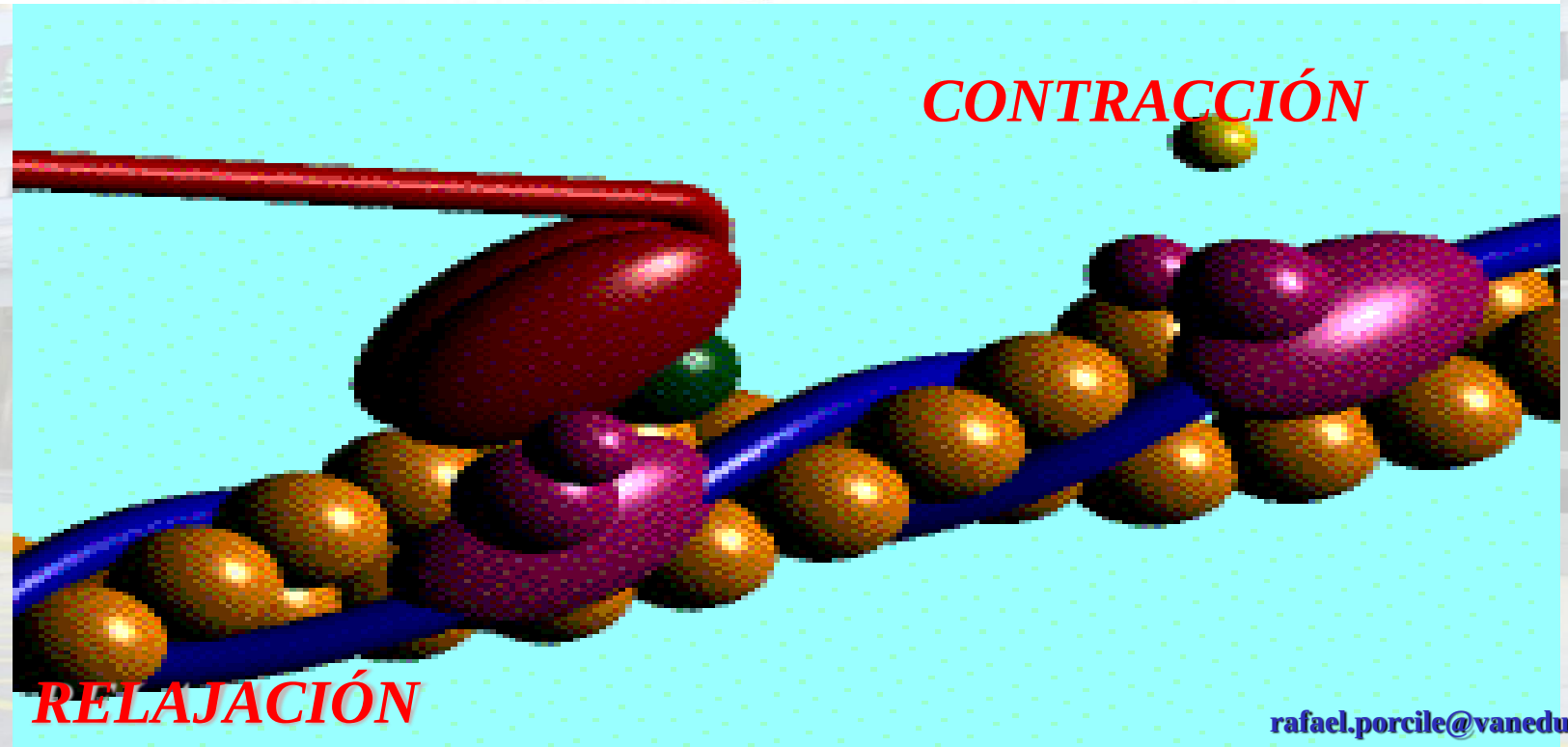


rafael.porcile@vaneduc.edu.ar

rafael.porcile@vaneduc.edu.ar

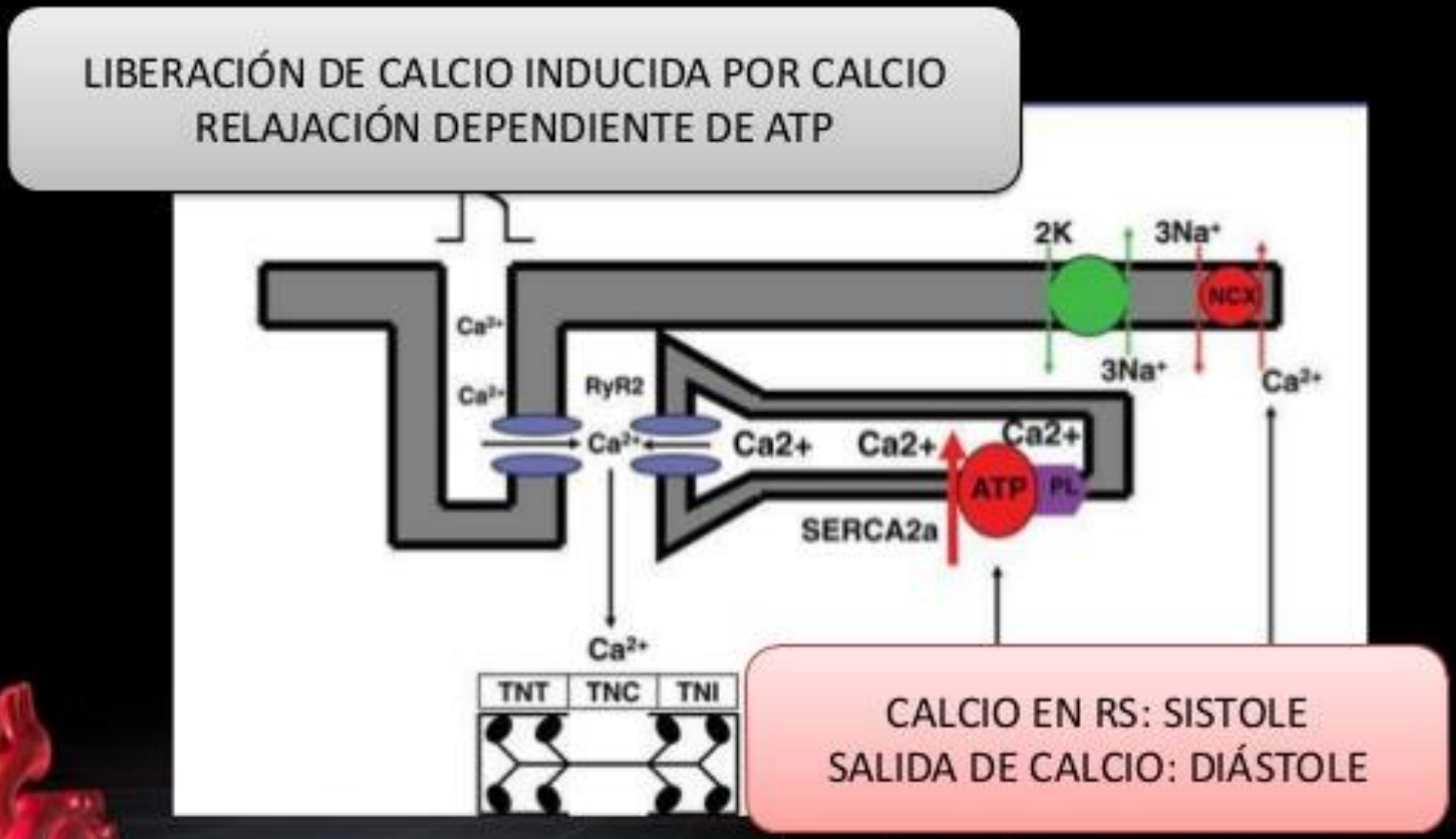
UAI
HOSPITAL UNIVERSITARIO



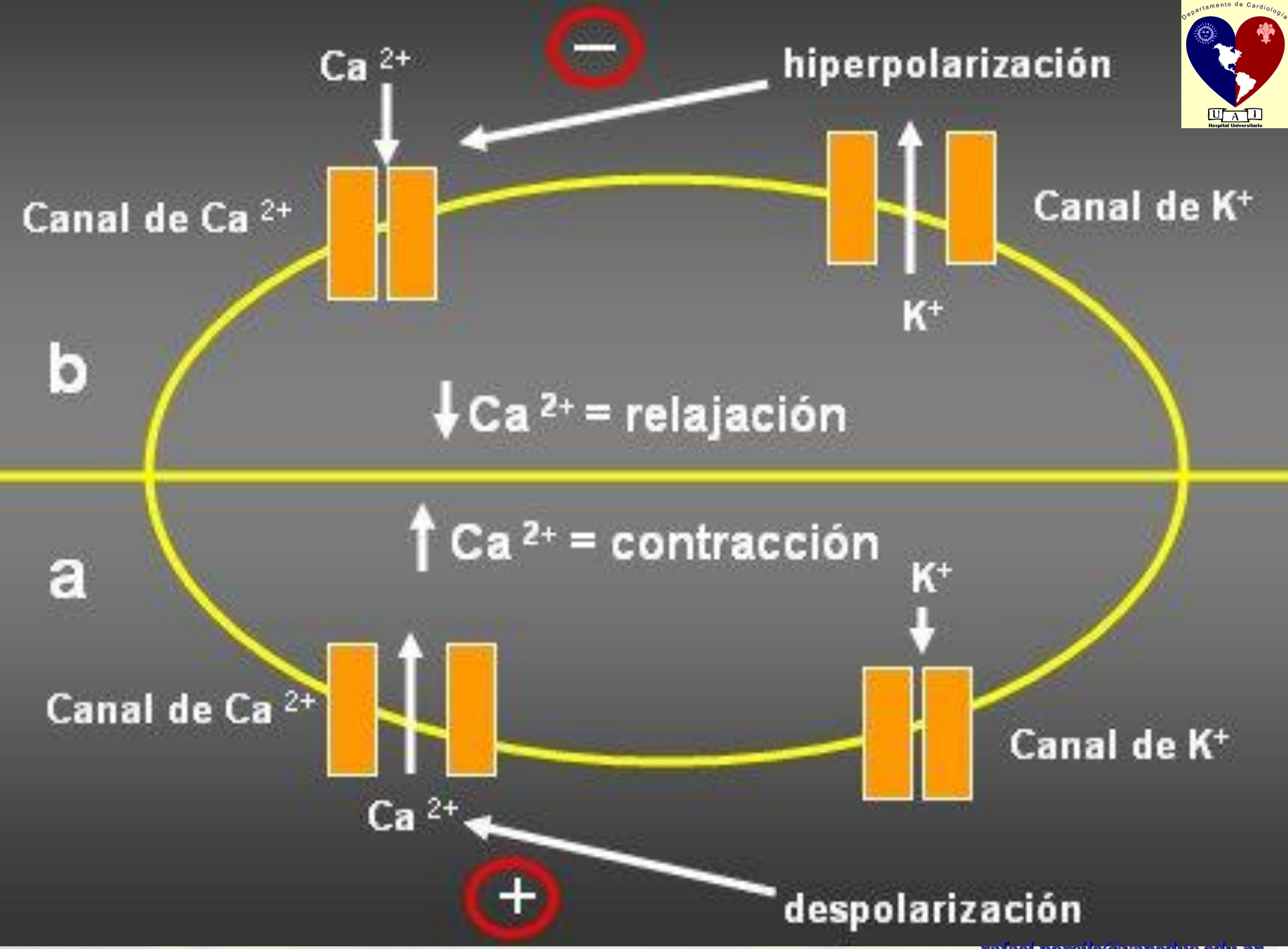


rafael.porcile@vaneduc.edu.ar

Mecanismo de acción de fármacos inotrópicos excepto levosimendan



rafael.porcile@vaneduc.edu.ar



rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL UNIVERSITARIO

LA SATURACIÓN DE LA TROPONINA C DEPENDE DEL GRADIENTE CITOPLASMATICO DE CALCIO

rafael.porcile@vaneduc.edu.ar

rafael.porcile@vaneduc.edu.ar

- Escaso calcio : Falla sistólica
- Calcio excesivo falla Diastólica
- Acortamiento critico del tiempo diastólico Falla sistodiastolica

rafael.porcile@vaneduc.edu.ar

¿DE ACUERDO?

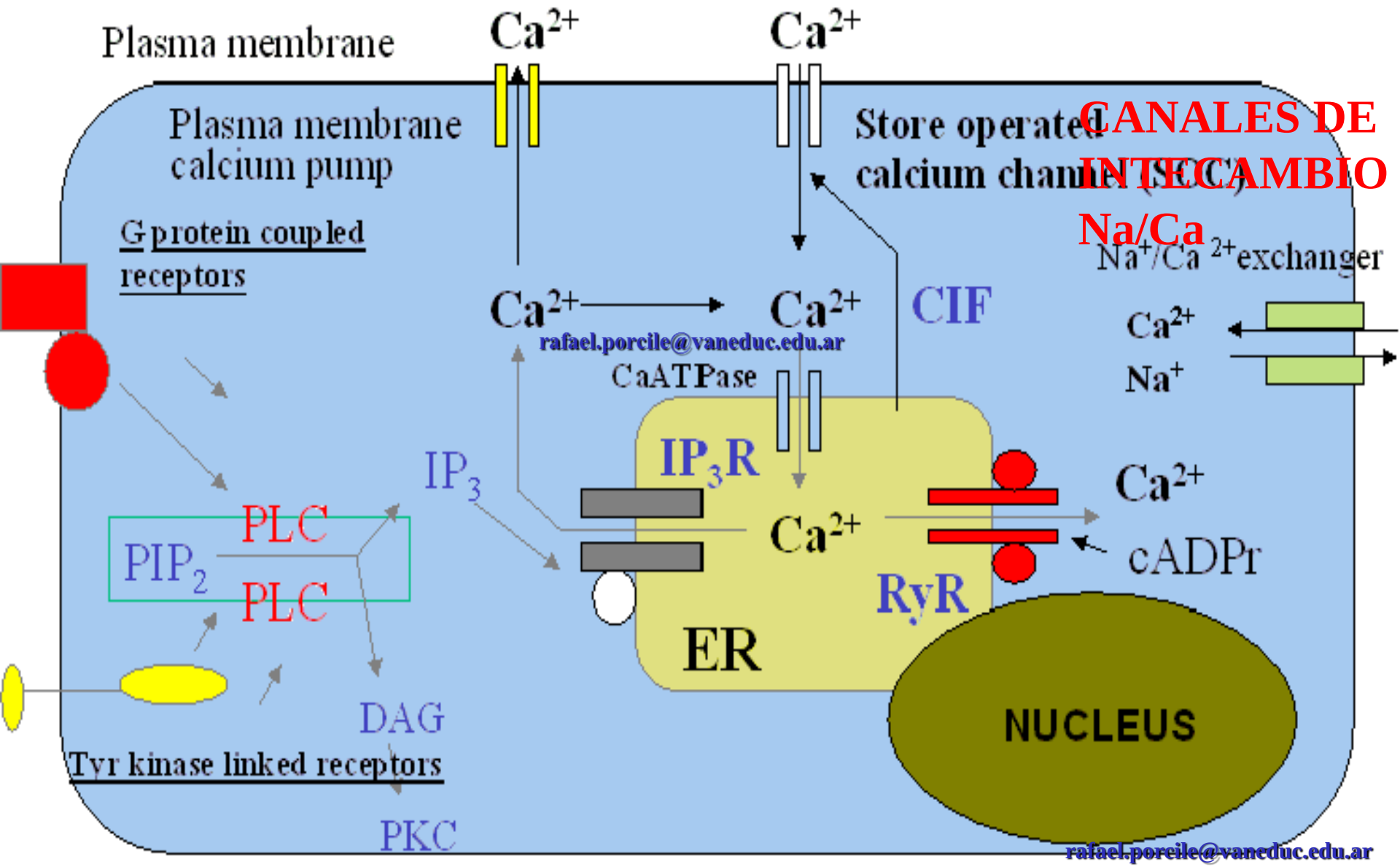
rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL UNIVERSITARIO

COMO SE REGULA LA CONCENTRACIÓN Y EL GRADIENTE CITOPLASMATICA DE CALCIO?

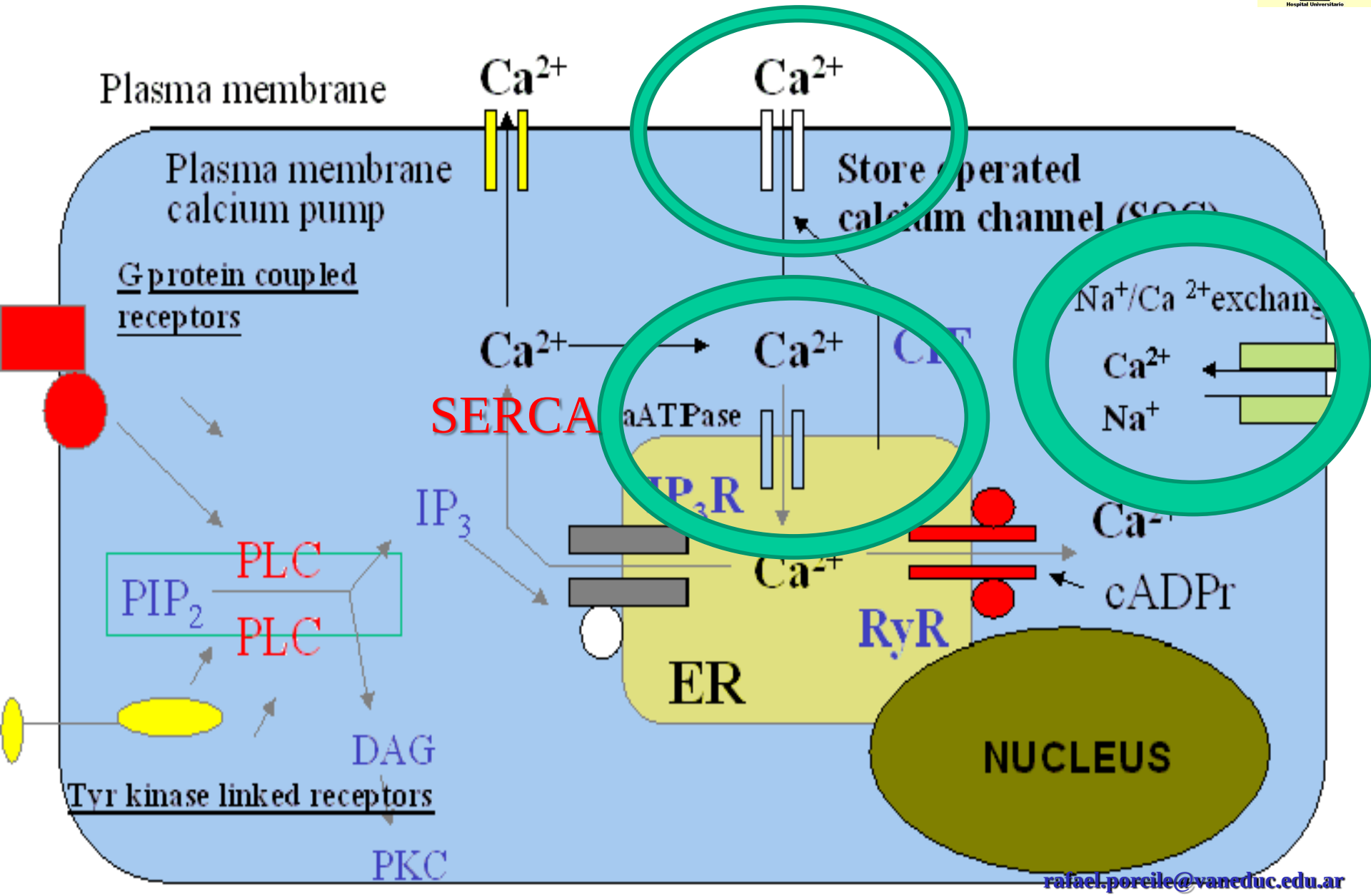
rafael.porcile@vaneduc.edu.ar

Calcium homeostasis



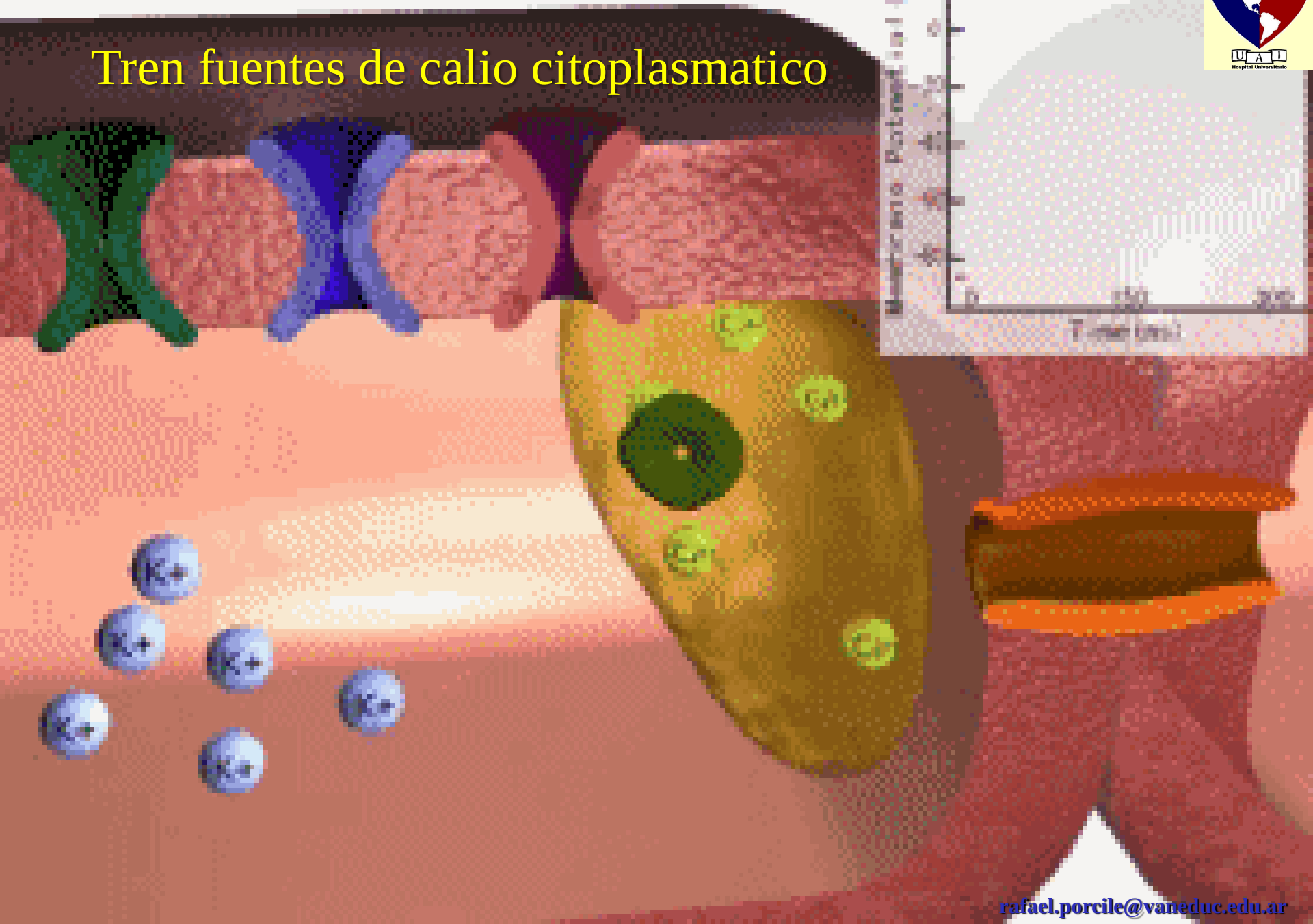
rafael.porcile@vaneduc.edu.ar

Calcium homeostasis



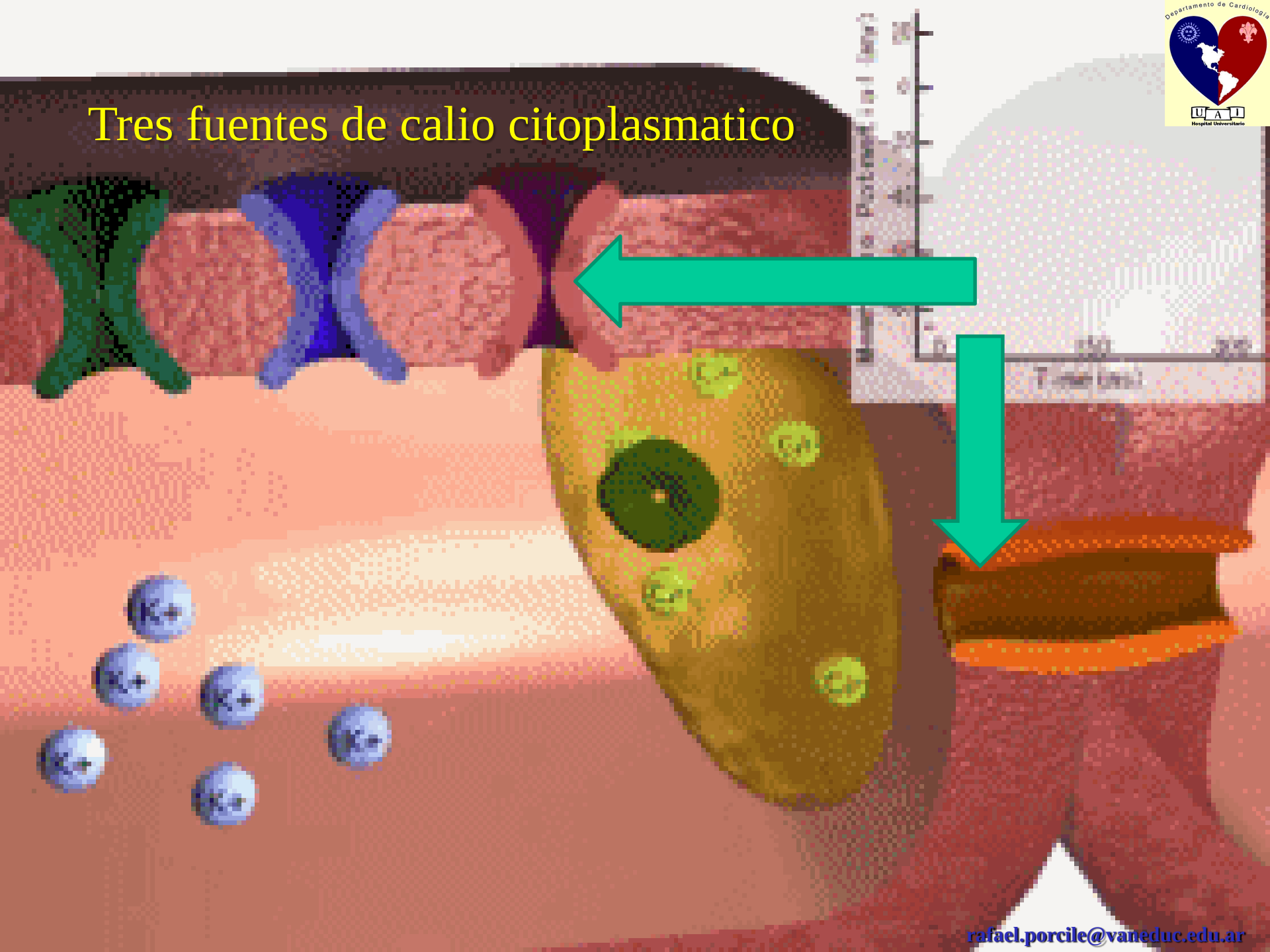
rafael.porcile@vaneduc.edu.ar

Tren fuentes de calio citoplasmatico



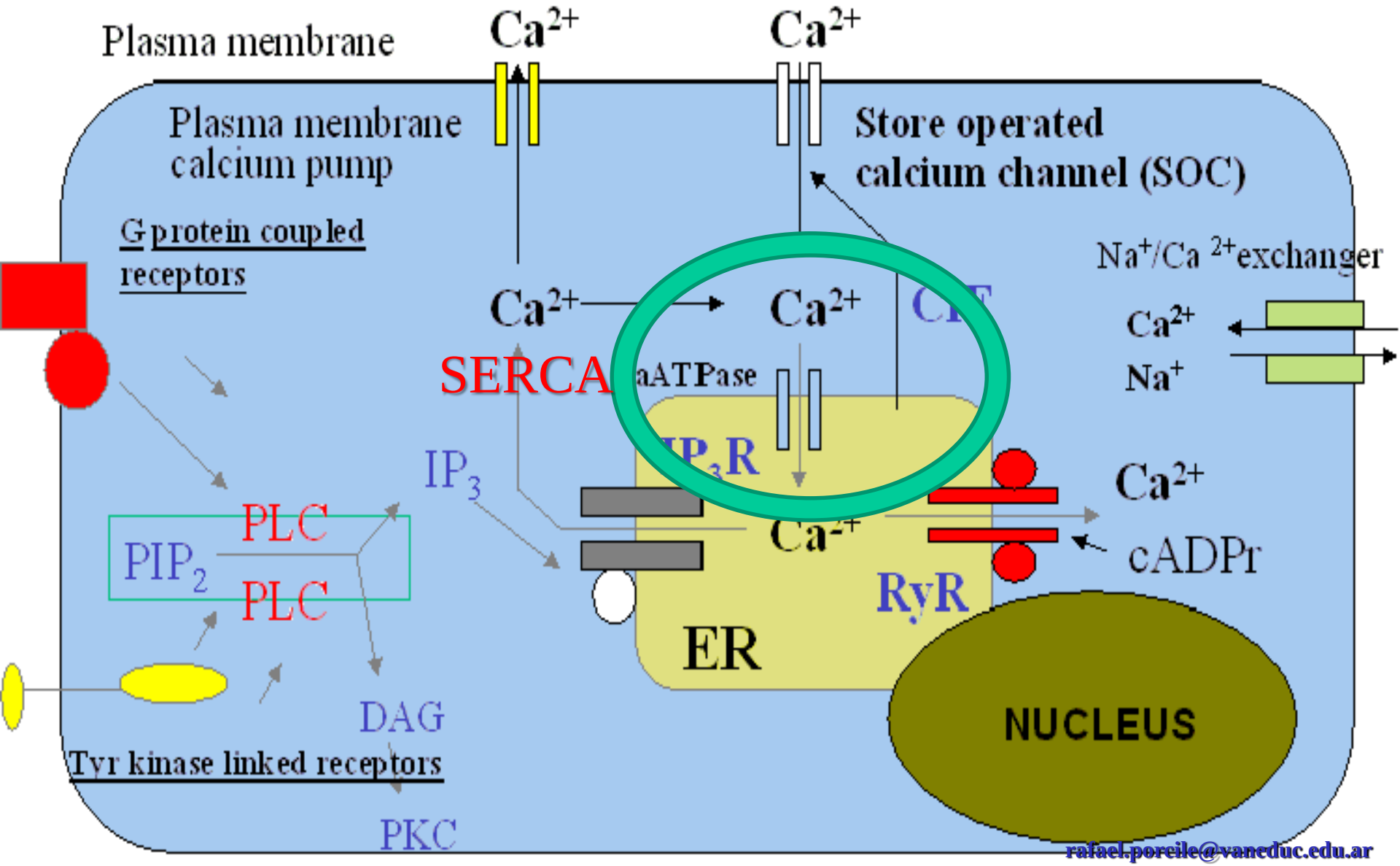
rafael.porcile@vaneduc.edu.ar

Tres fuentes de calio citoplasmatico

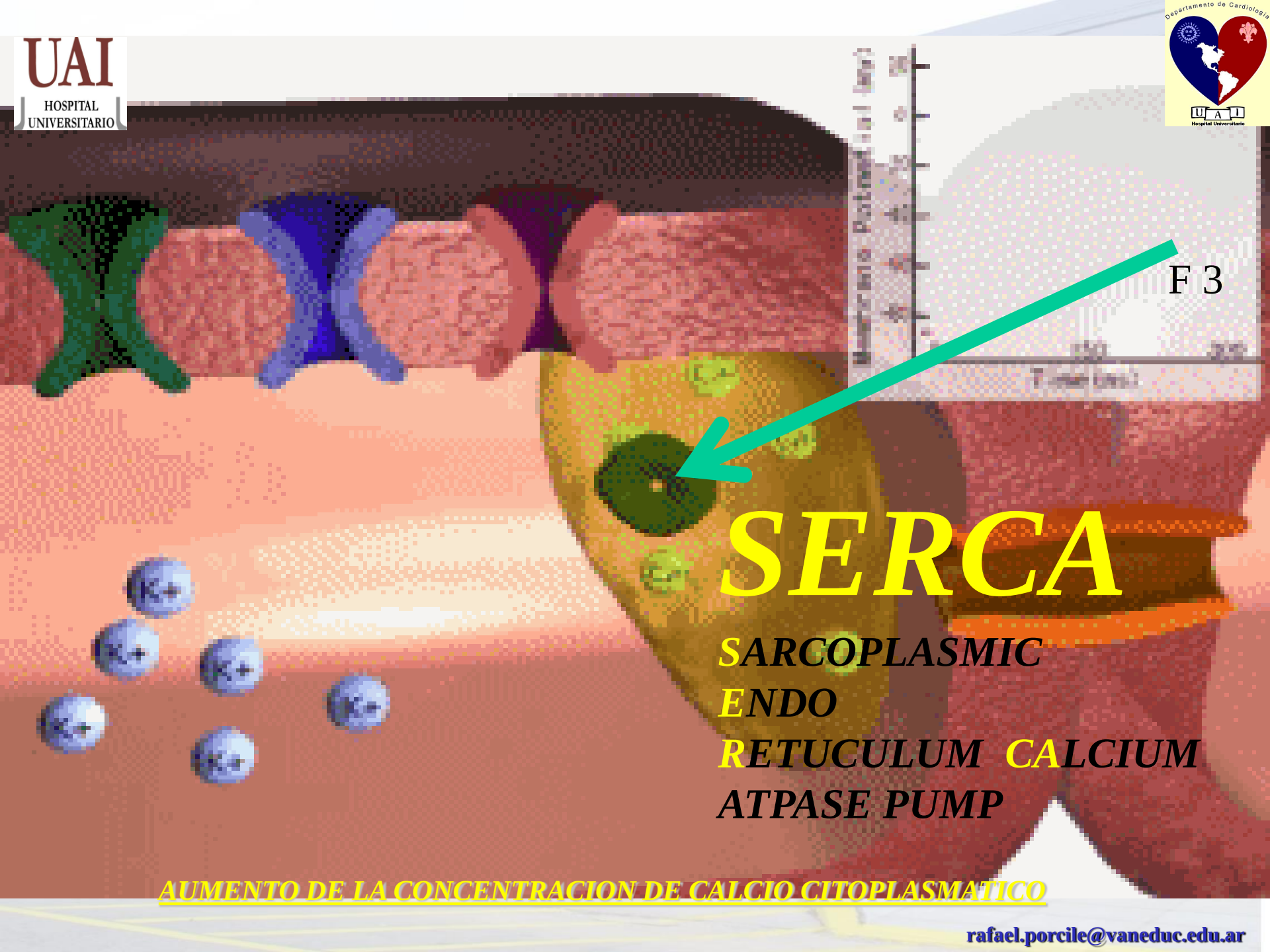


rafael.porcile@vaneduc.edu.ar

Calcium homeostasis

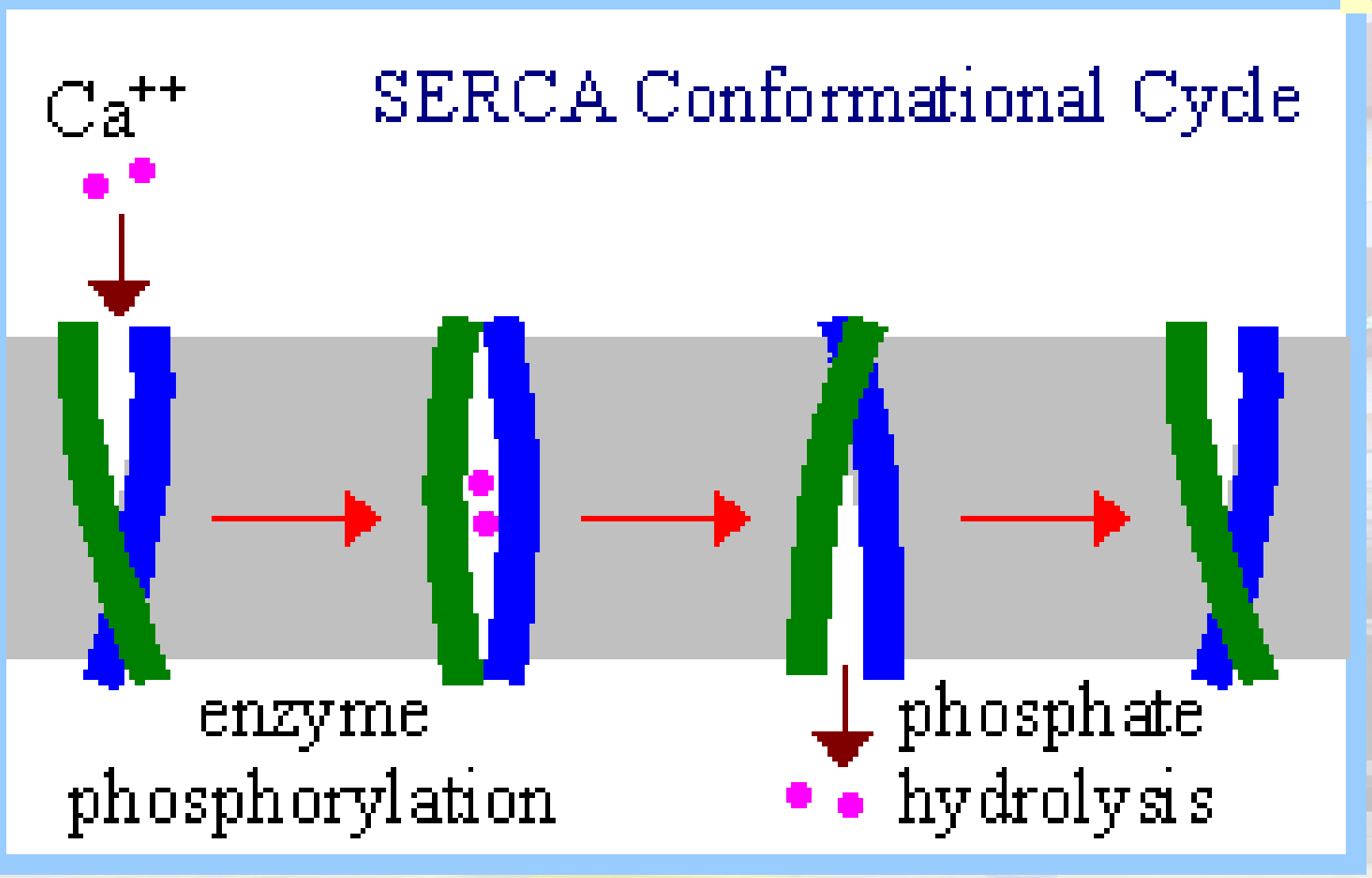


rafael.porcile@vaneduc.edu.ar



rafael.porcile@vaneduc.edu.ar

rafael.porcile@vaneduc.edu.ar



rafael.porcile@vaneduc.edu.ar

¿DE ACUERDO?

rafael.porcile@vaneduc.edu.ar

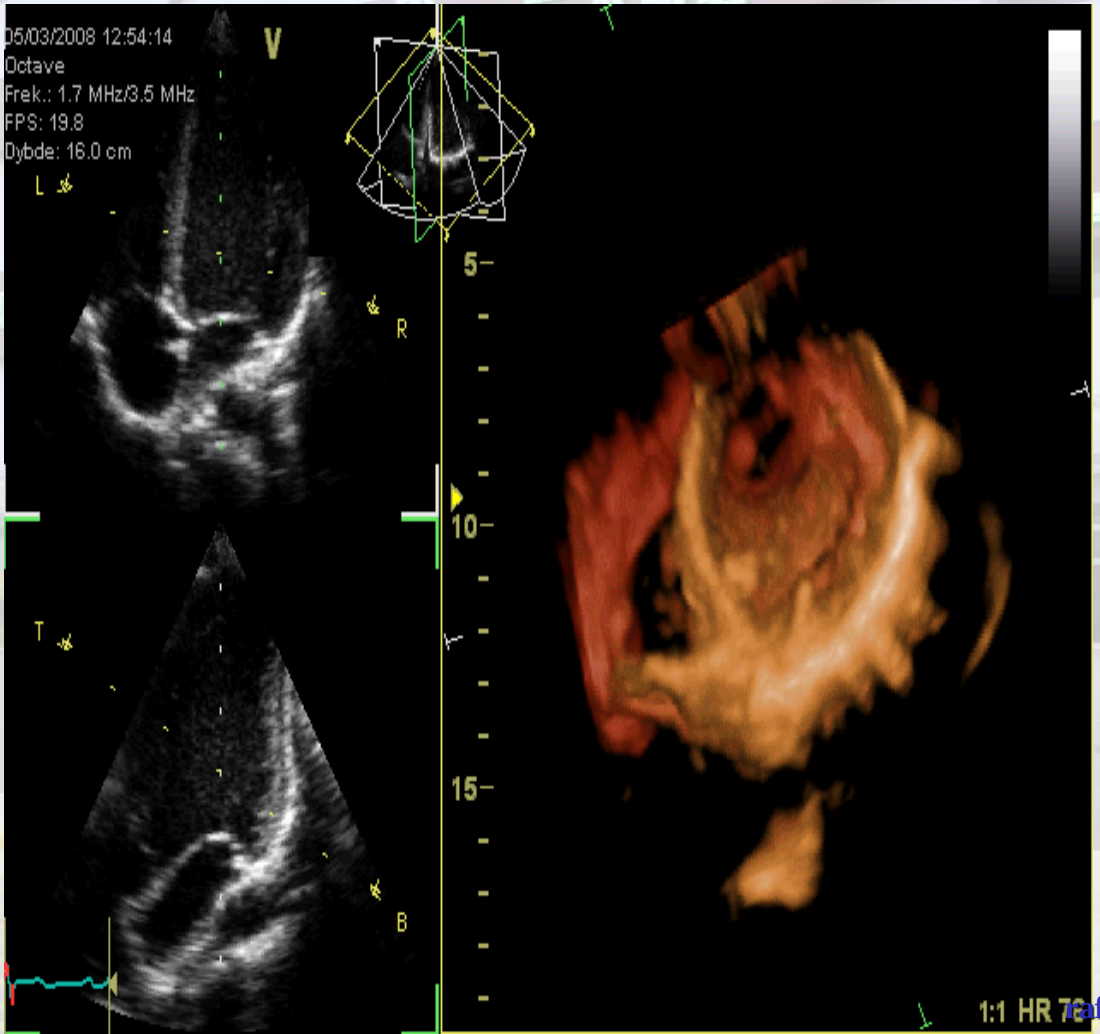
Glucósidos cardiacos: Digitalicos

William Withering 1785
:Diuréticos

En 1920 se descubre su acción inotrópica

rafael.porcile@vaneduc.edu.ar

DIGOXINA



rafael.porcile@vaneduc.edu.ar

Digitalicos

Digoxina

Metildigoxina

Bloquean la bomba ATPasa Na-K

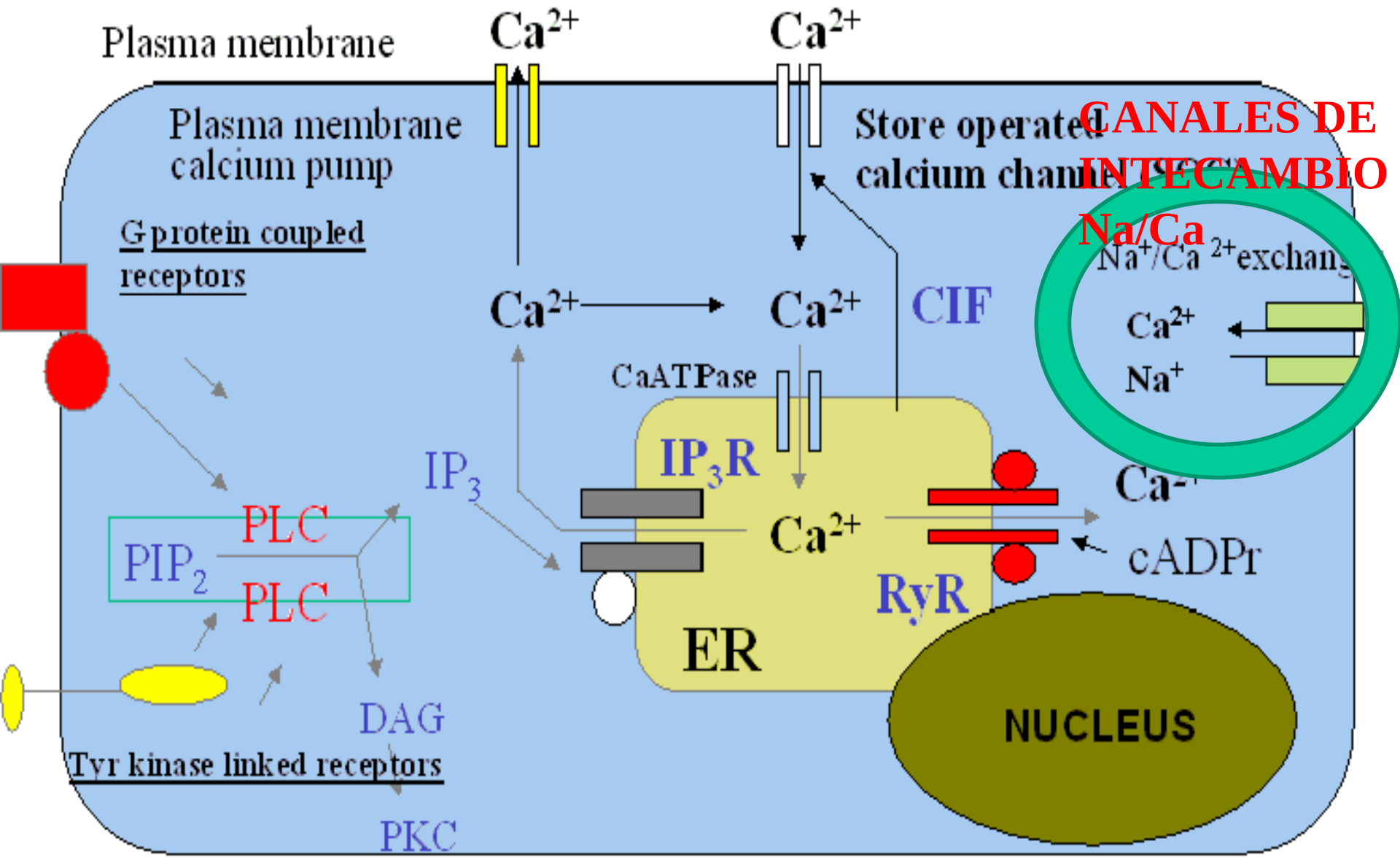
Se incrementa la concentración de sodio intracelular

Se activa el intercambiador Na+/Ca++ de la membrana

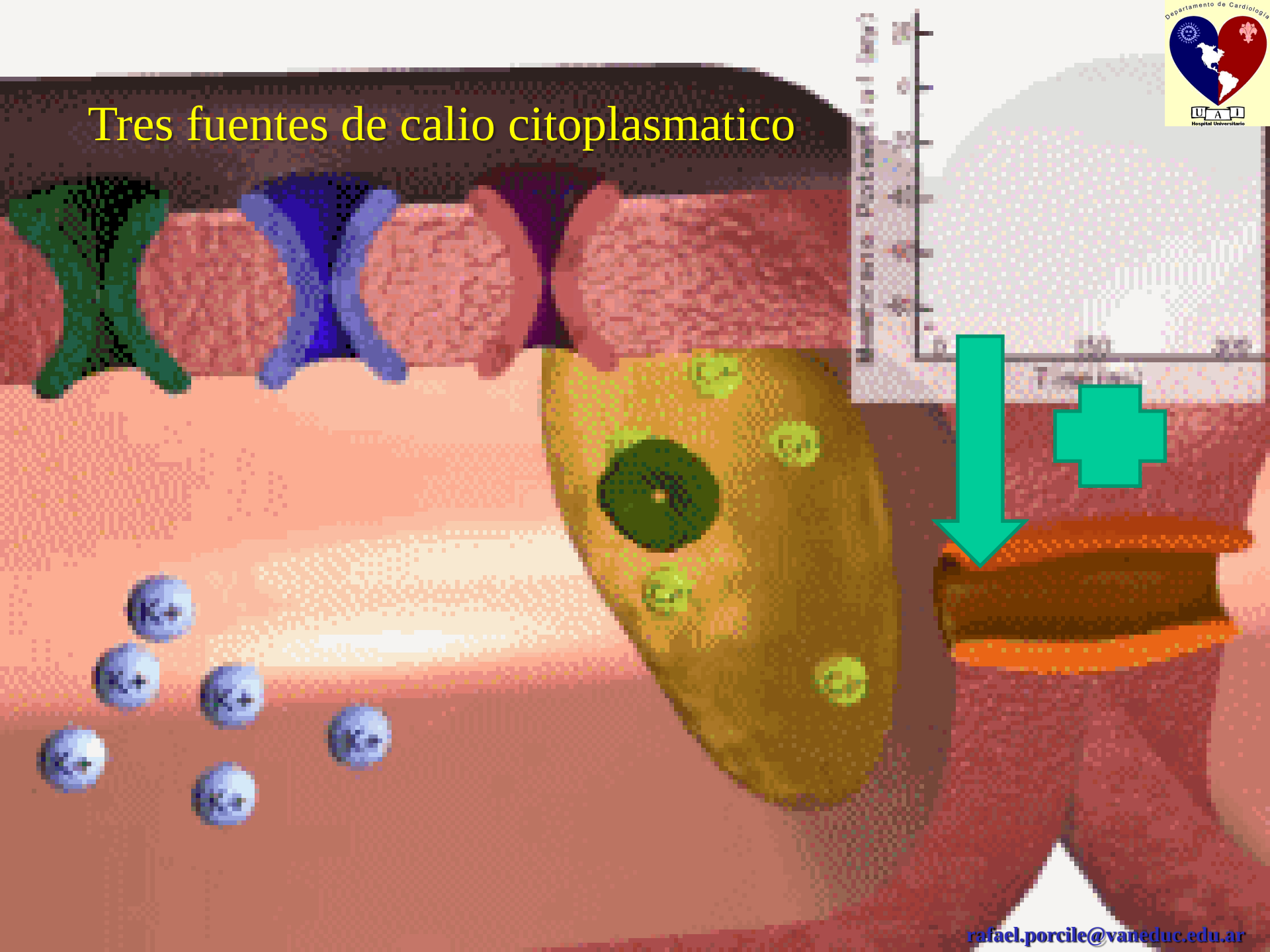
Incrementa la concentración de calcio intracelular

rafael.porcile@vaneduc.edu.ar

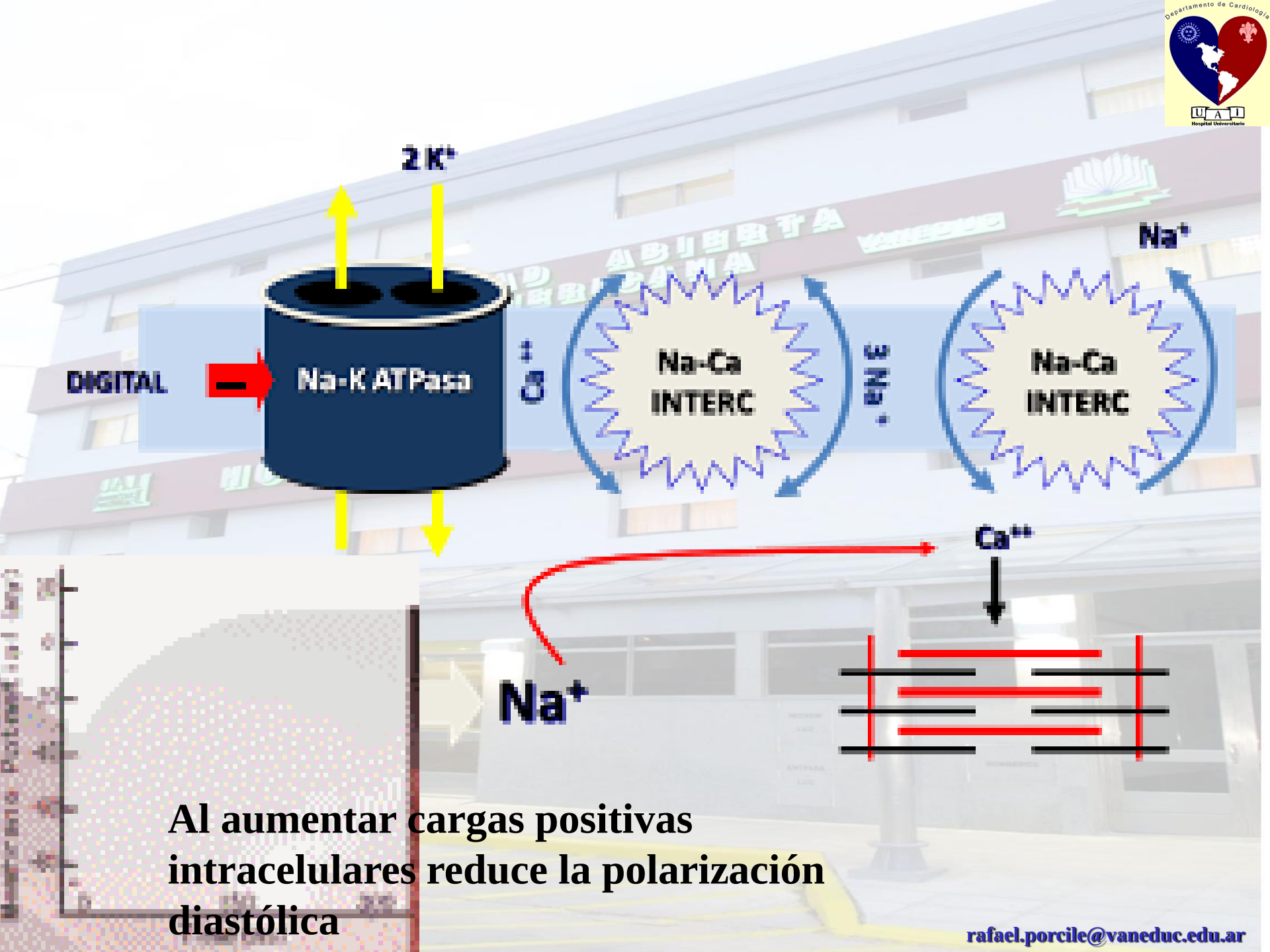
Calcium homeostasis



Tres fuentes de calio citoplasmatico

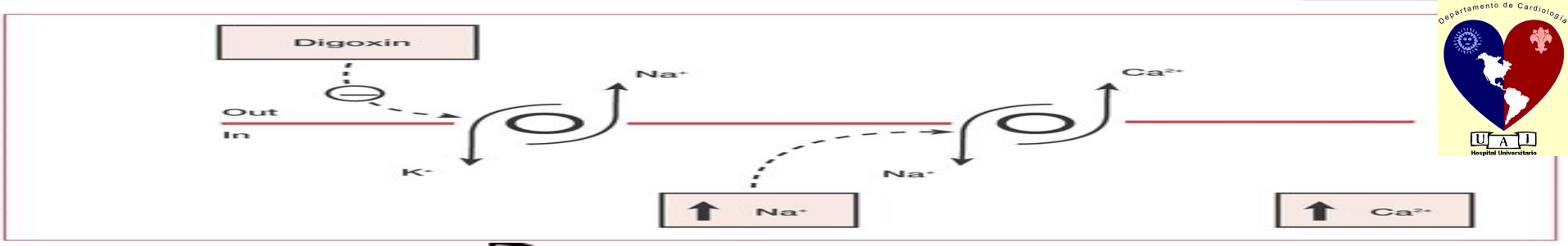


rafael.porcile@vaneduc.edu.ar

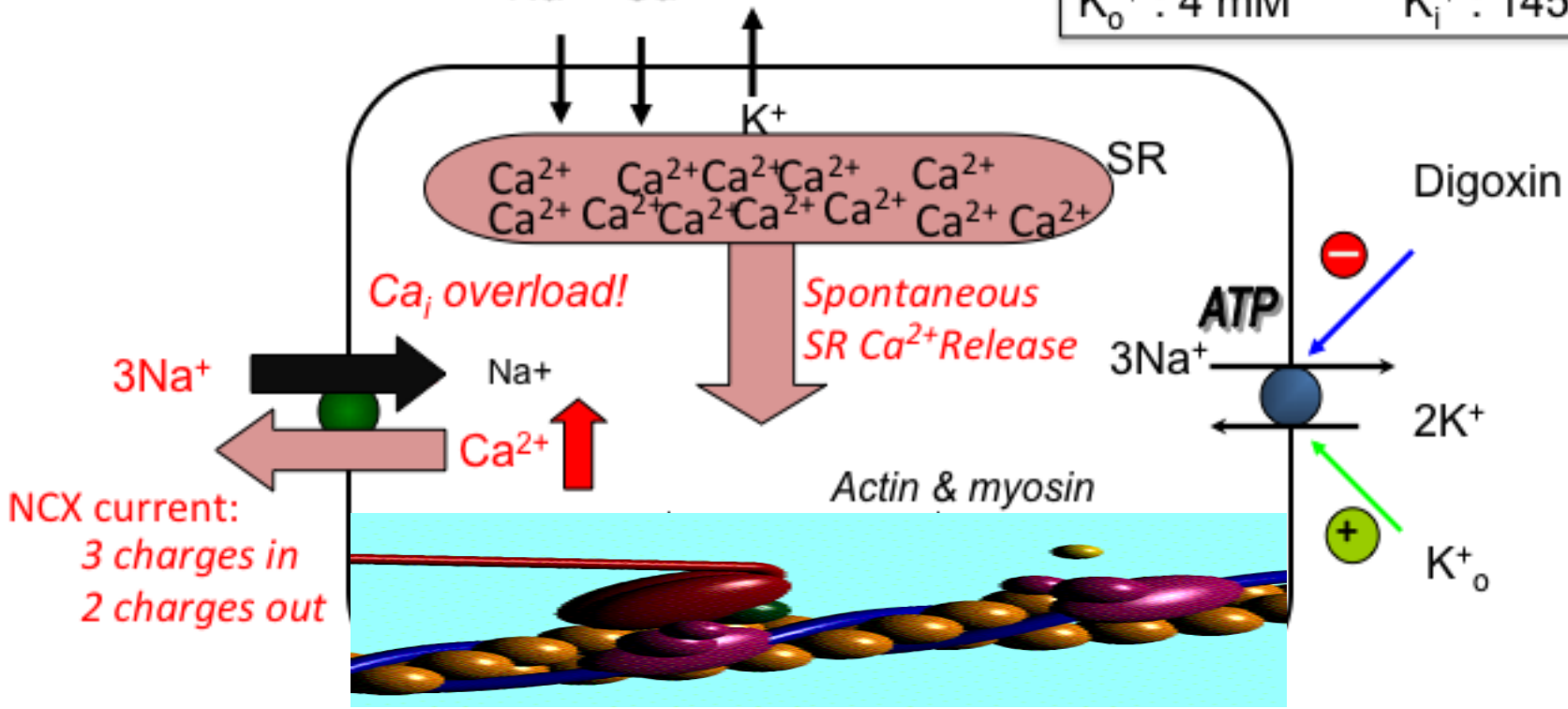


Al aumentar cargas positivas intracelulares reduce la polarización diastólica

rafael.porcile@vaneduc.edu.ar

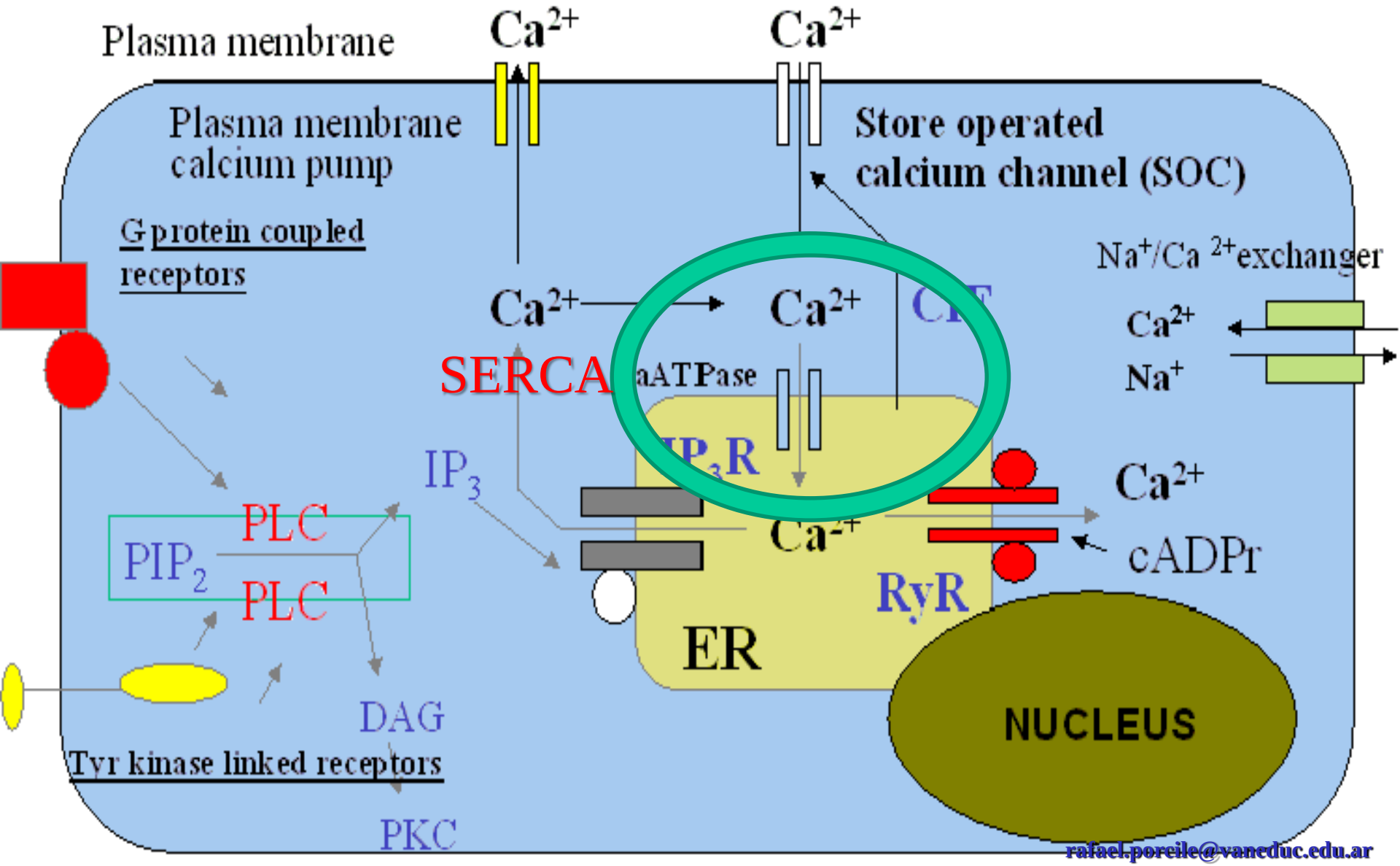


Na_o^+ : 140 mM Na_i^+ : 7 mM
Ca_o^{2+}: 2 mM Ca_i^{2+}: ~100 nM
K_o^+ : 4 mM K_i^+ : 145 mM

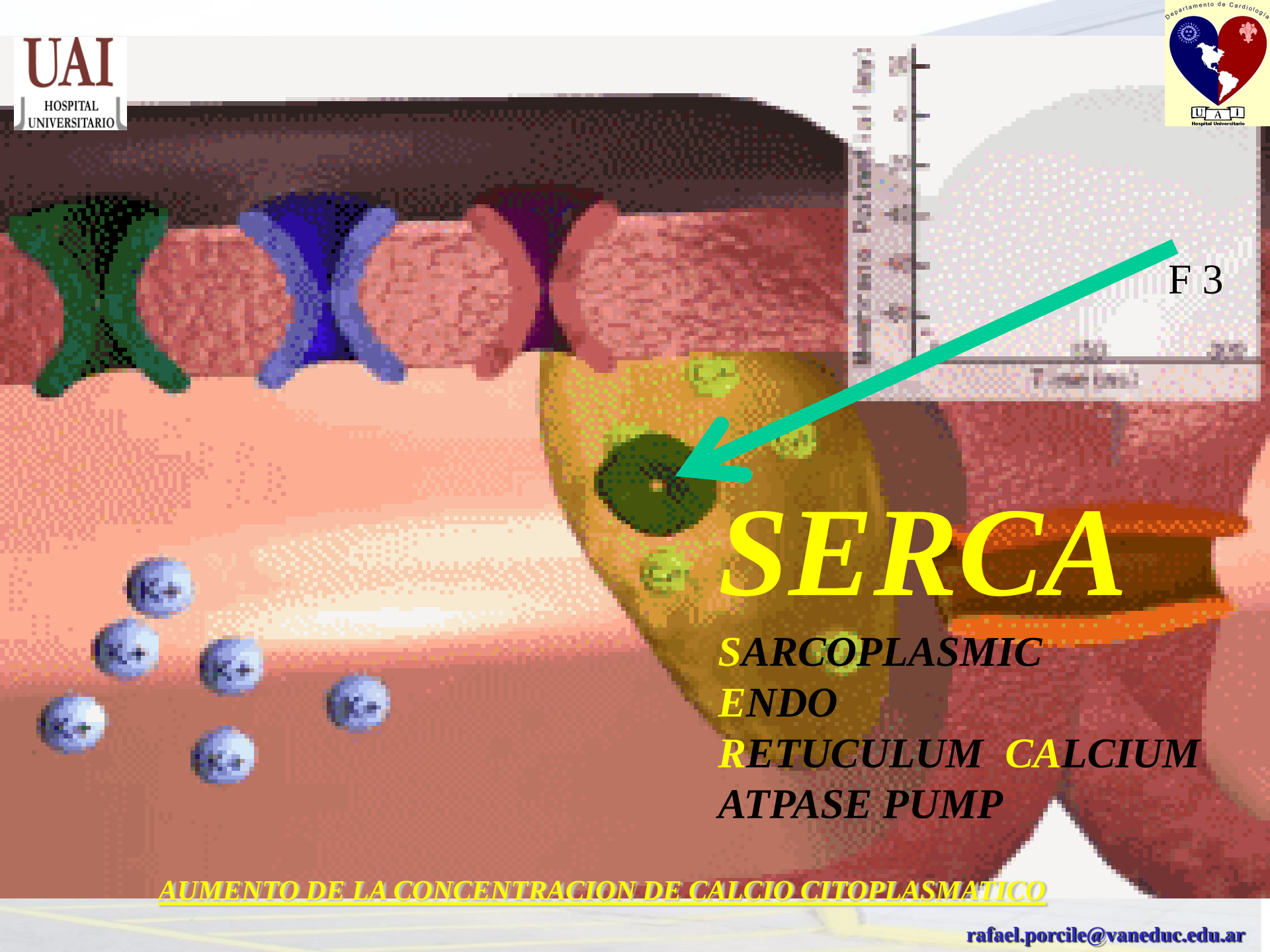


rafael.porcile@vaneduc.edu.ar

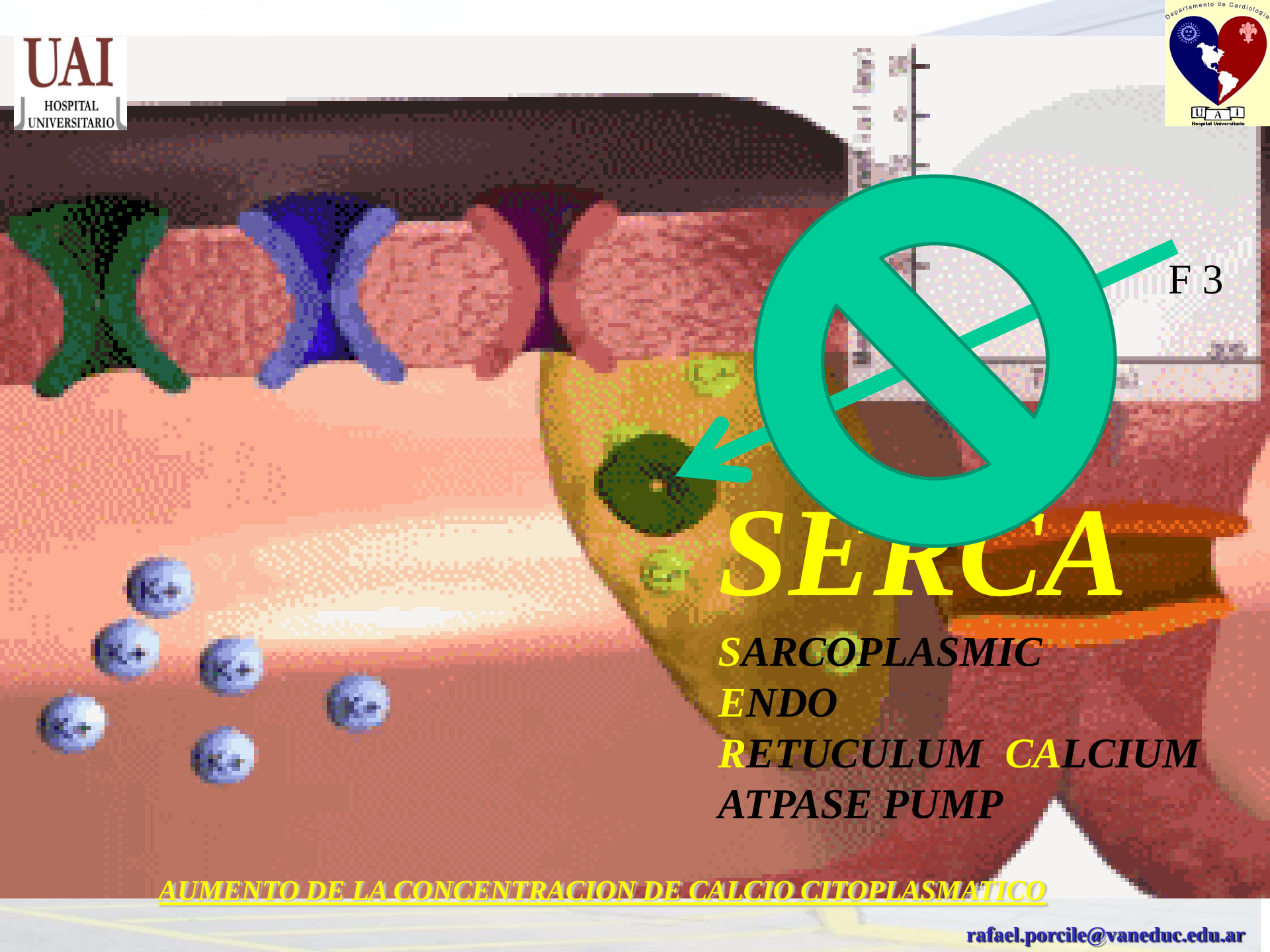
Calcium homeostasis



rafael.porcile@vaneduc.edu.ar



rafael.porcile@vaneduc.edu.ar



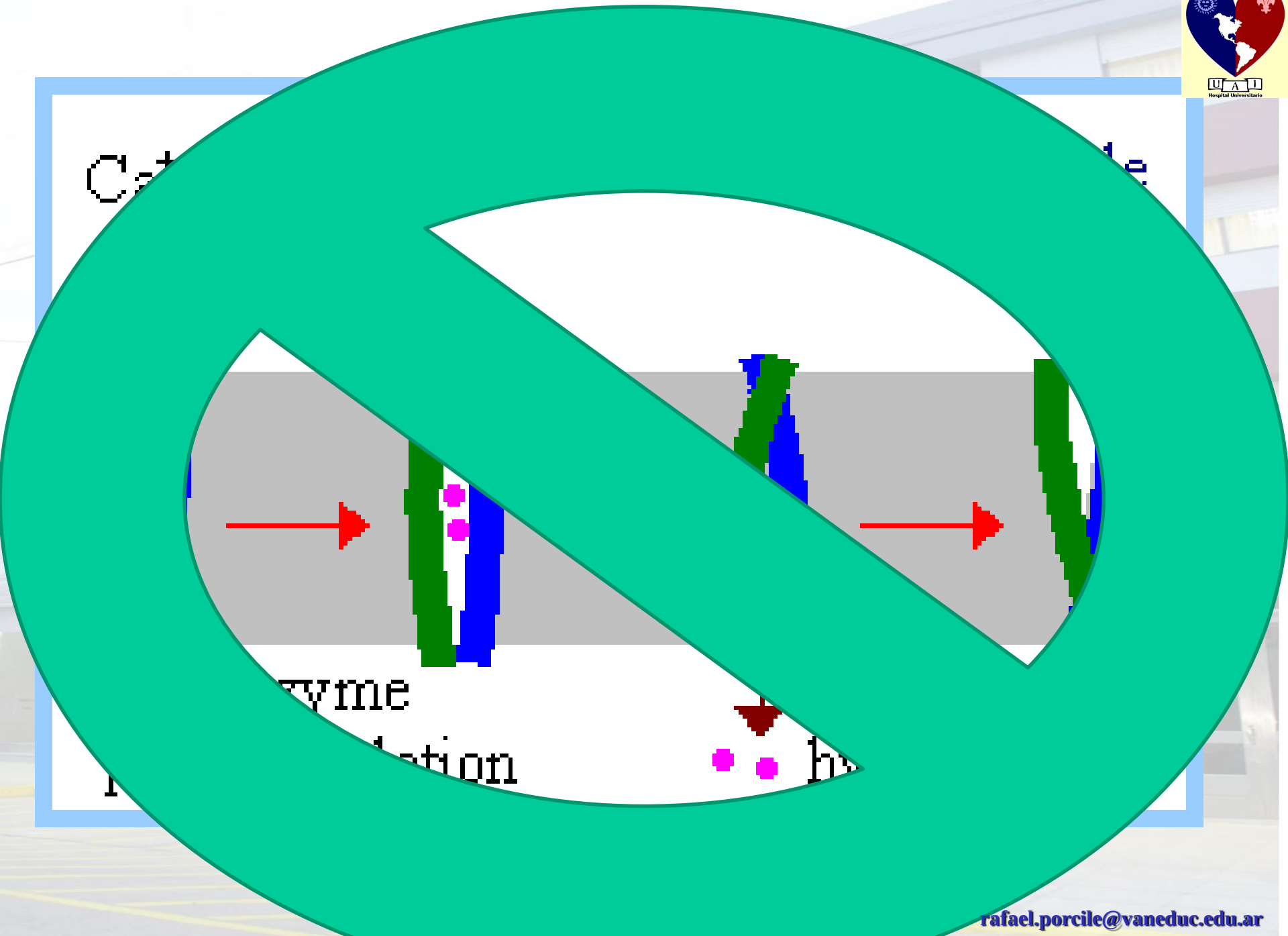
rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL
UNIVERSITARIO

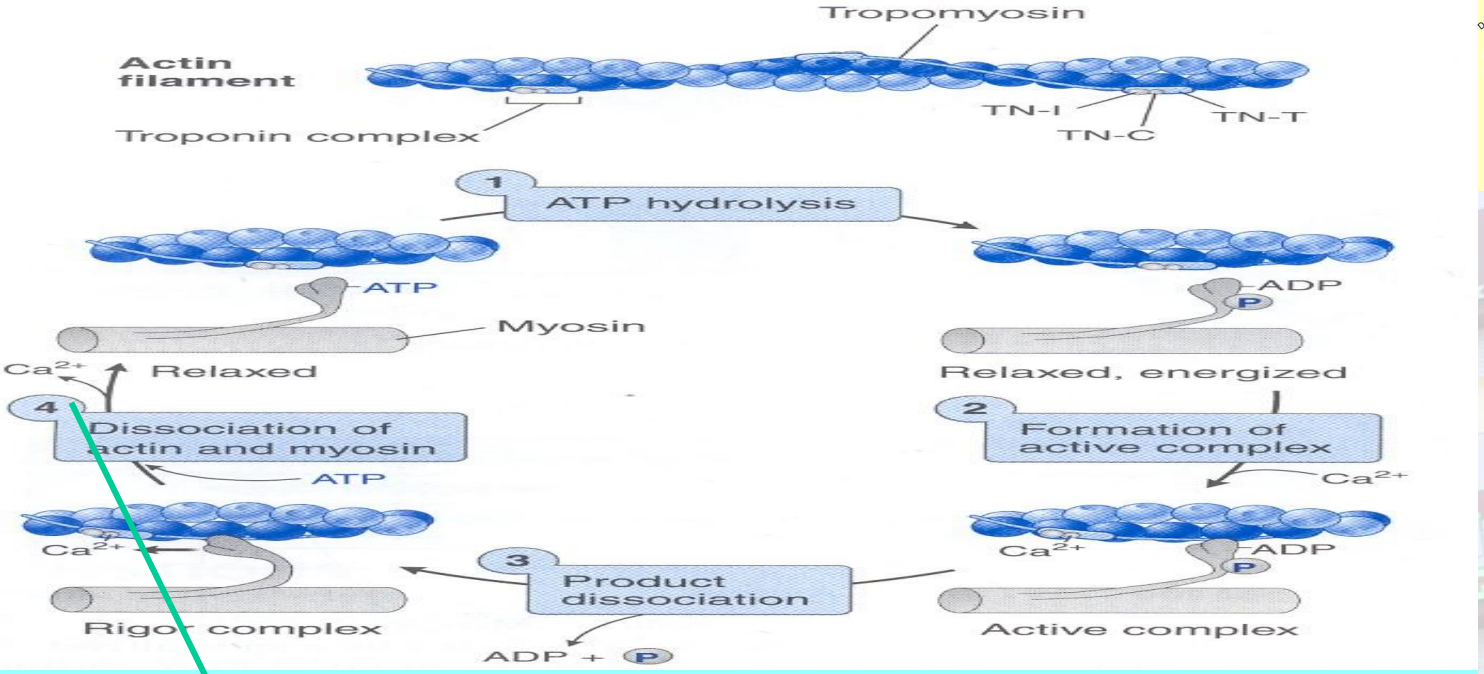
Departamento de Cardiología
UAI
Hospital Universitario

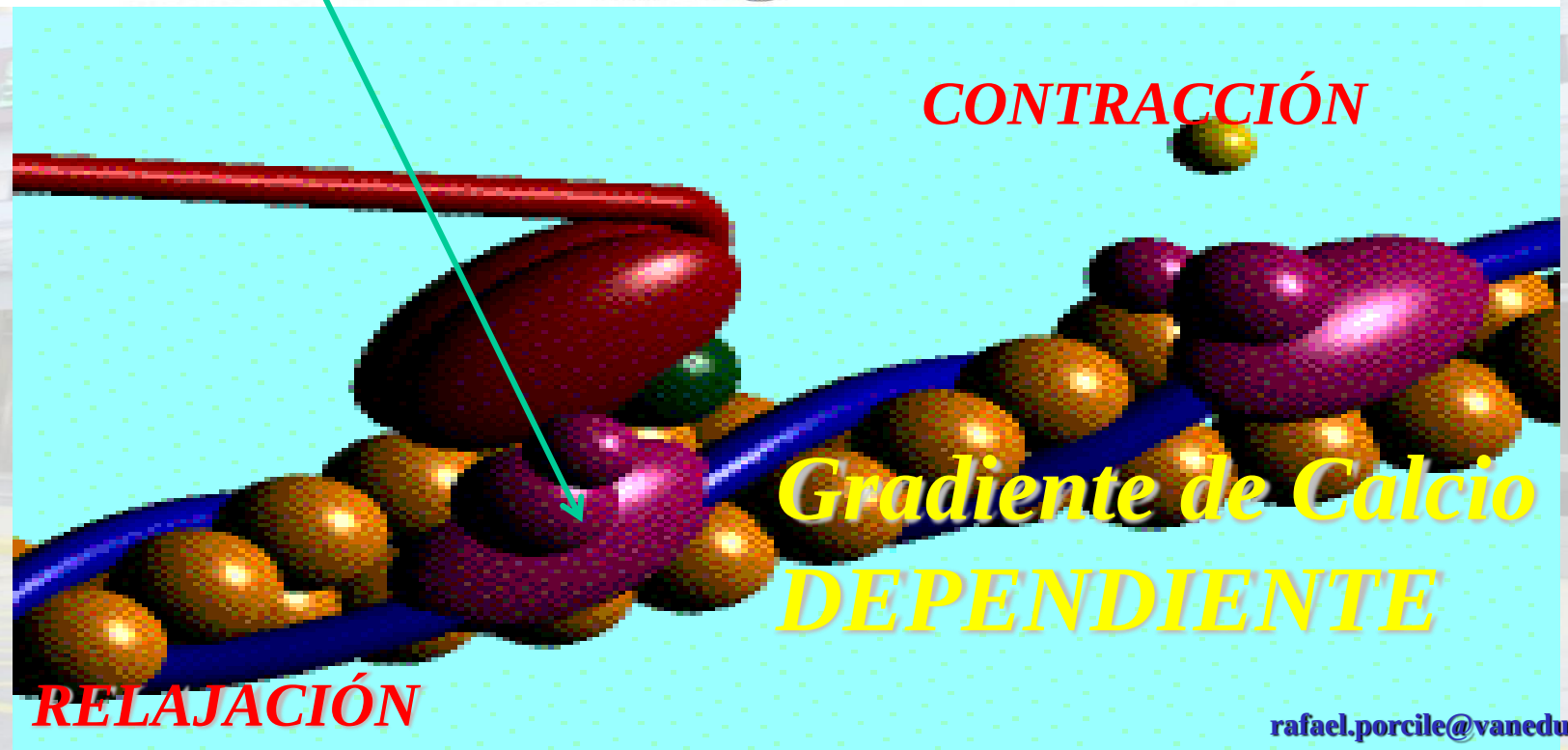
DEUDA DE OXIGENO

rafael.porcile@vaneduc.edu.ar



rafael.porcile@vaneduc.edu.ar

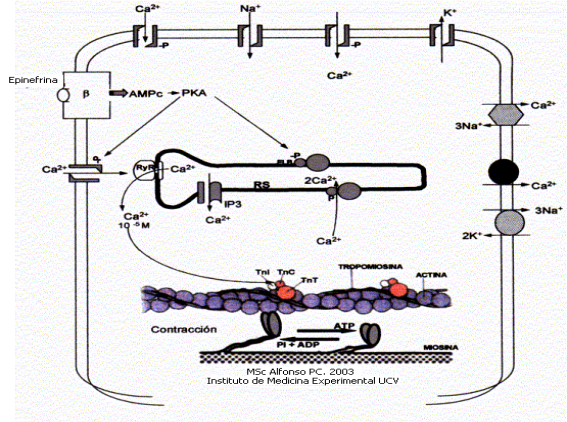


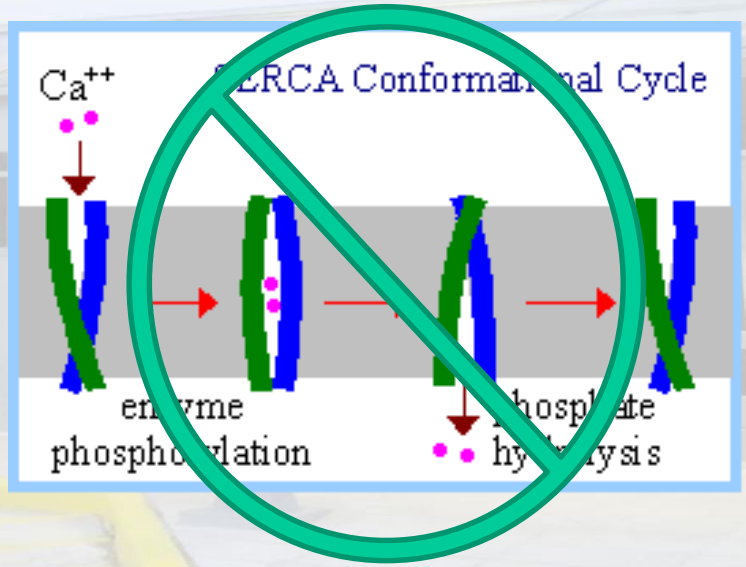


rafael.porcile@vaneduc.edu.ar

Digitalicos Aumentan el Calcio citoplasmatico

- Aumentan de su ingreso extra celular
- Raducen su bombeo al circuito sarcoplasmico

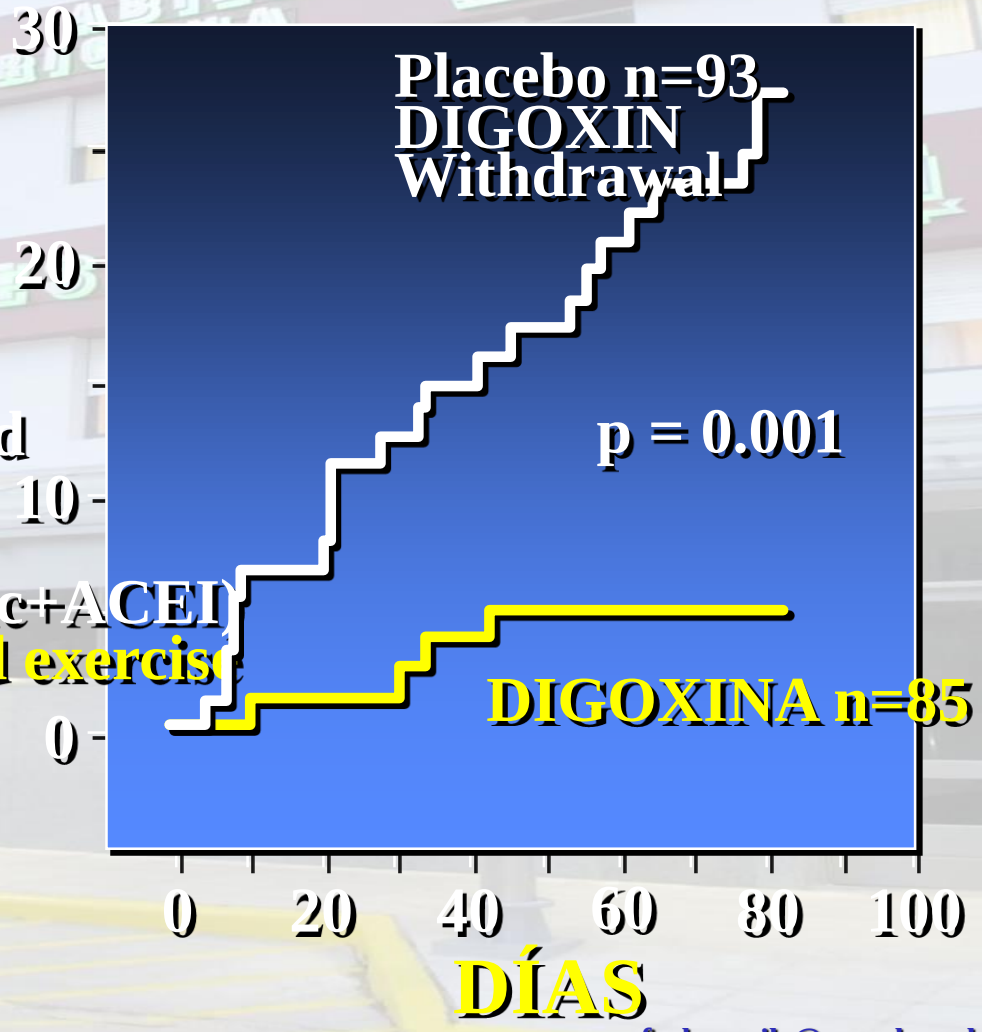




rafael.porcile@vaneduc.edu.ar

DIGOXINA
EFECTO SOBRE EVOLUCIÓN DE LA ICC

% PROGRESIÓN



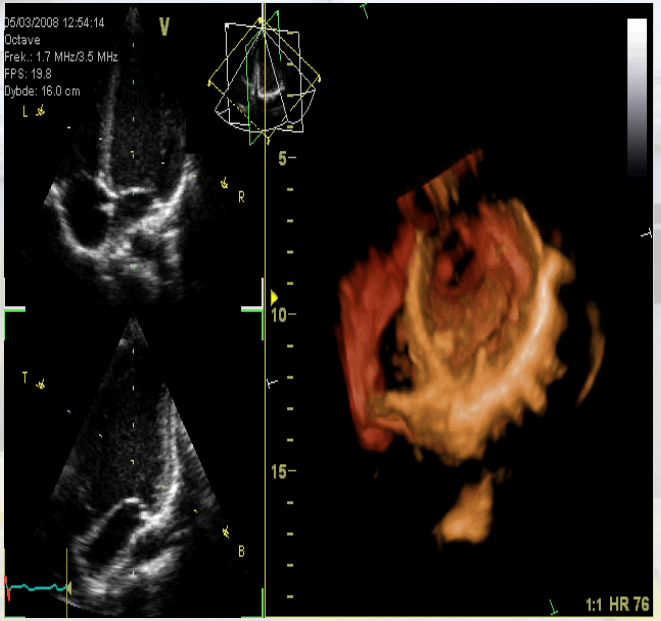
DIGOXIN: 0.125 - 0.5 mg /d
(0.7 - 2.0 ng/ml)
EF < 35%
Class I-III (digoxin+diuretic+ACEI)
Also significantly decreased exercise time and LVEF.

RADIANCE
N Engl J Med 1993;329:1

rafael.porcile@vaneduc.edu.ar

DIGOXINA

AUMENTA LA CONCENTRACIÓN DE CALCIO INTRACELULAR

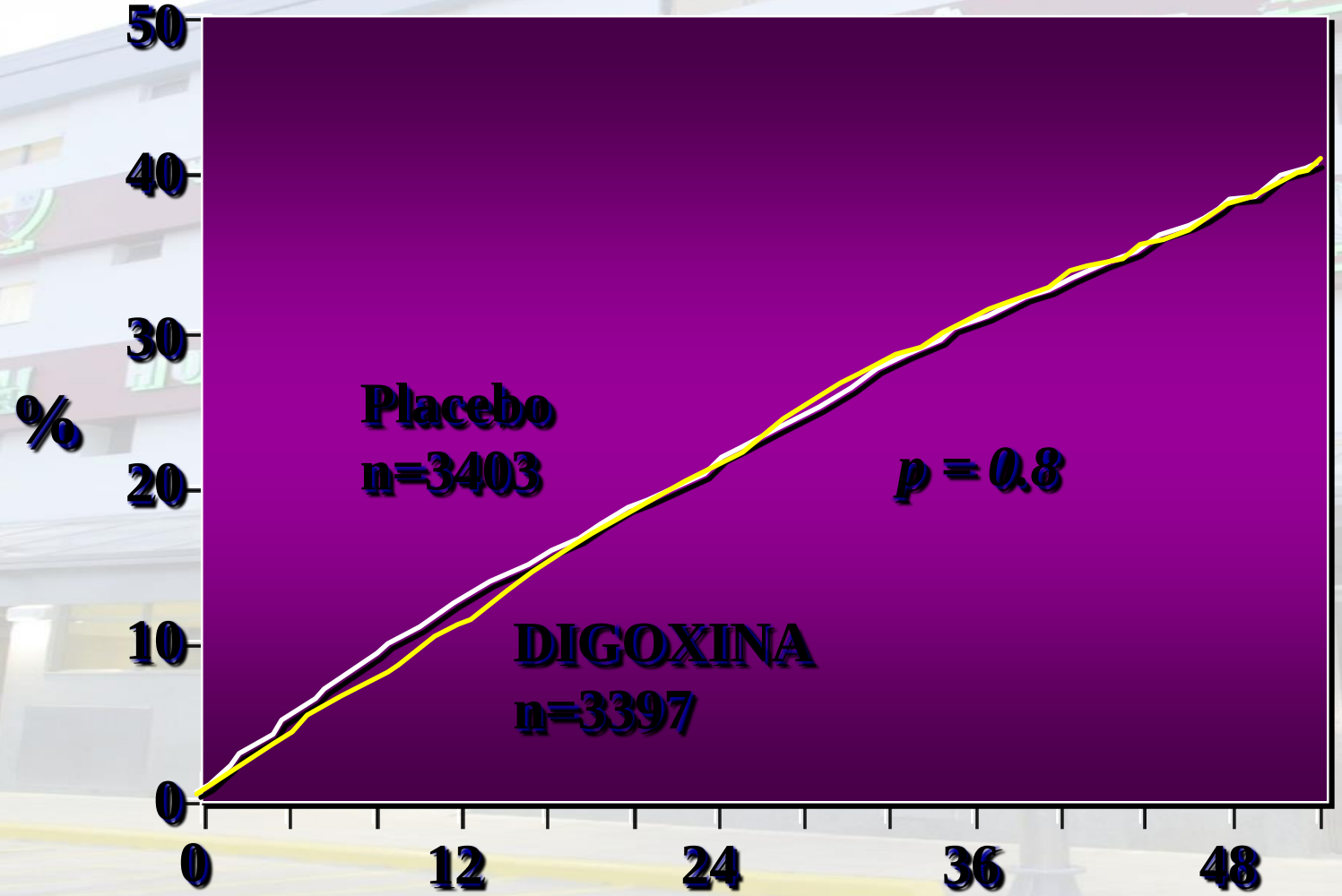


rafael.porcile@vaneduc.edu.ar

ISQUEMIA

rafael.porcile@vaneduc.edu.ar

DIGOXINA Y MORTALIDAD EN ICC



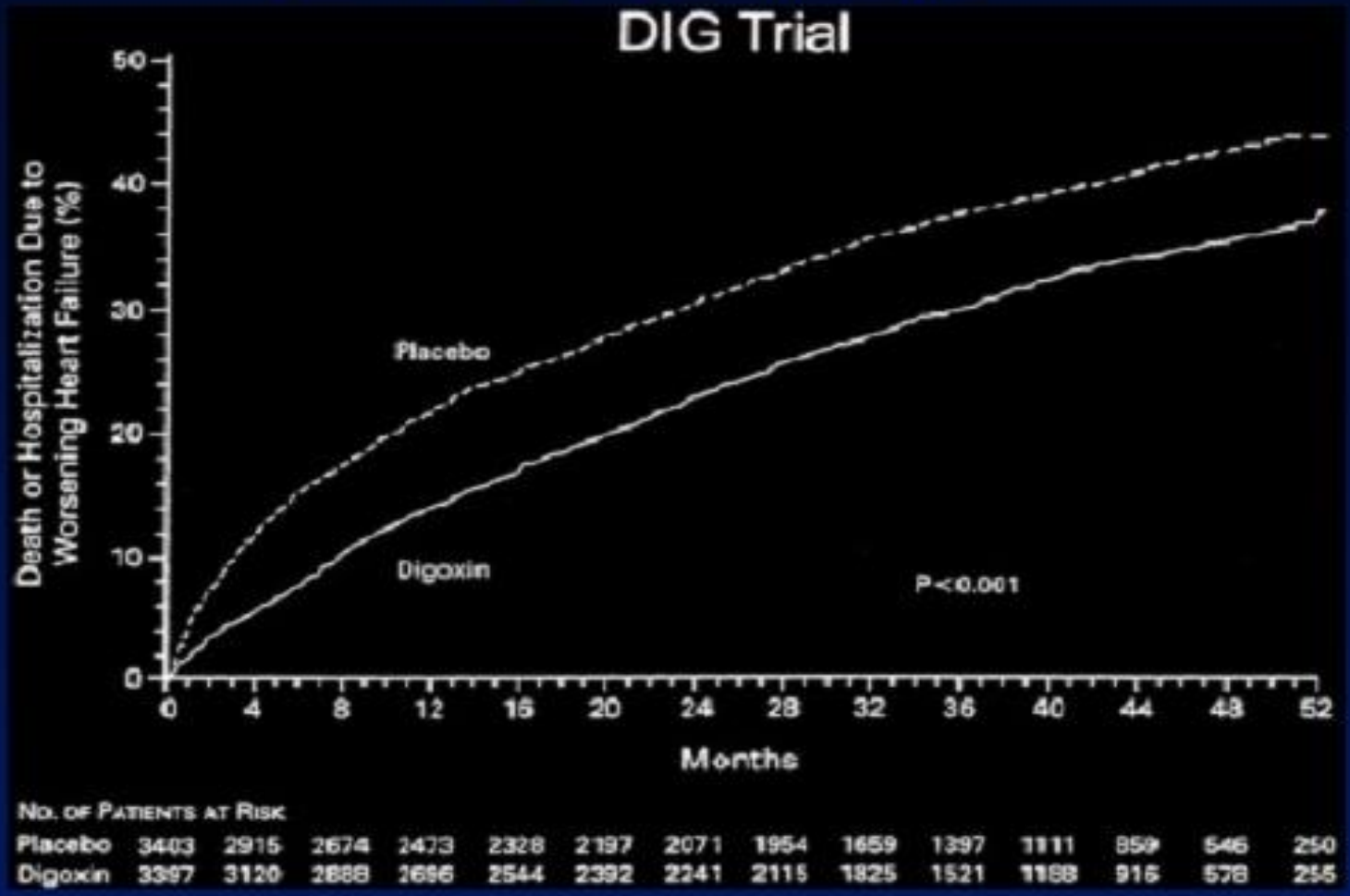
DIG

N Engl J Med 1997;336:525

rafael.porcile@vaneduc.edu.ar

Pero Disminuye los Internamientos y Síntomas

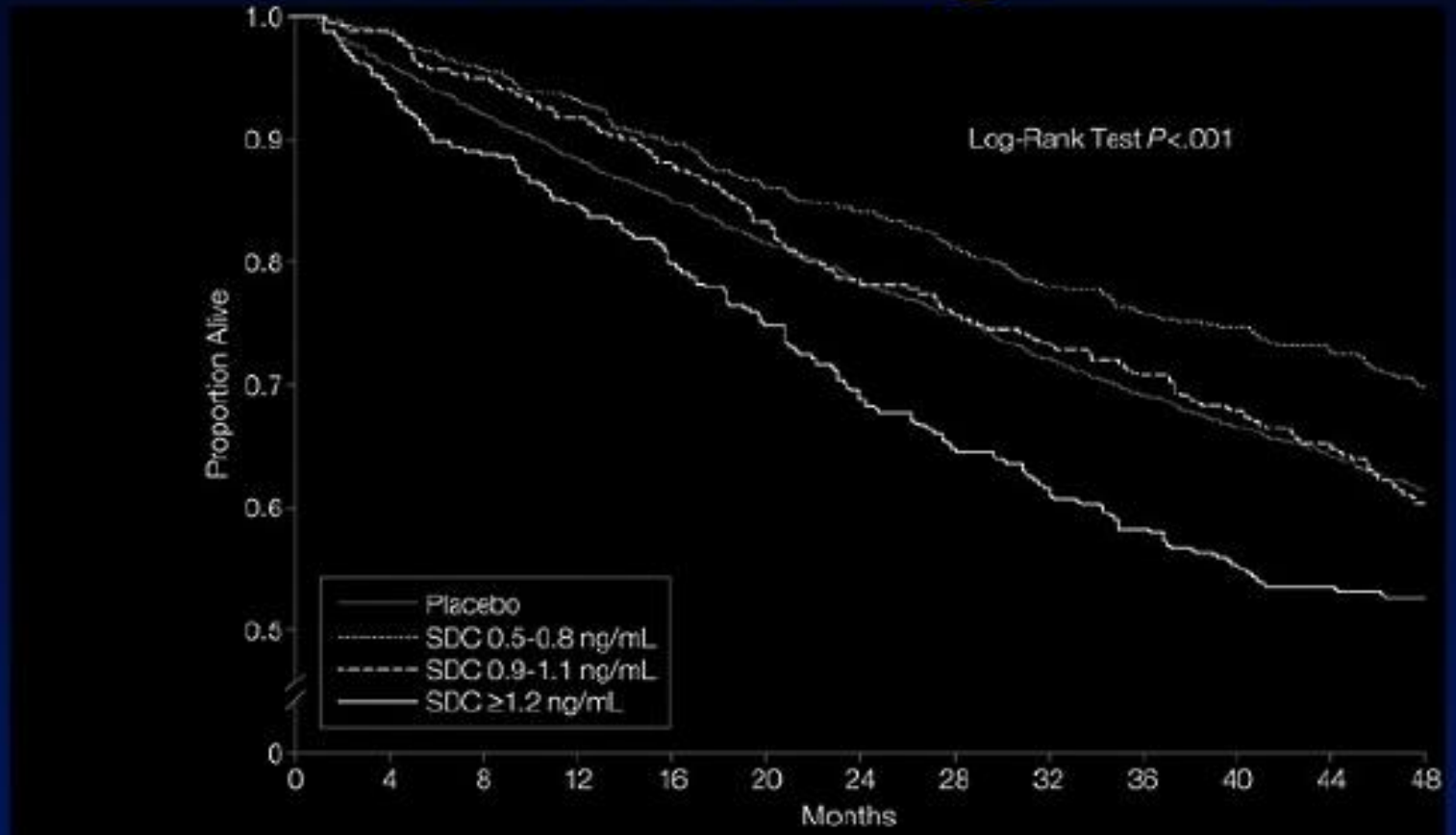
Mortalidad y hospitalizaciones



DIG investigator group. *NEJM*. 1997; 336:525-533

rafael.porcile@vaneduc.edu.ar

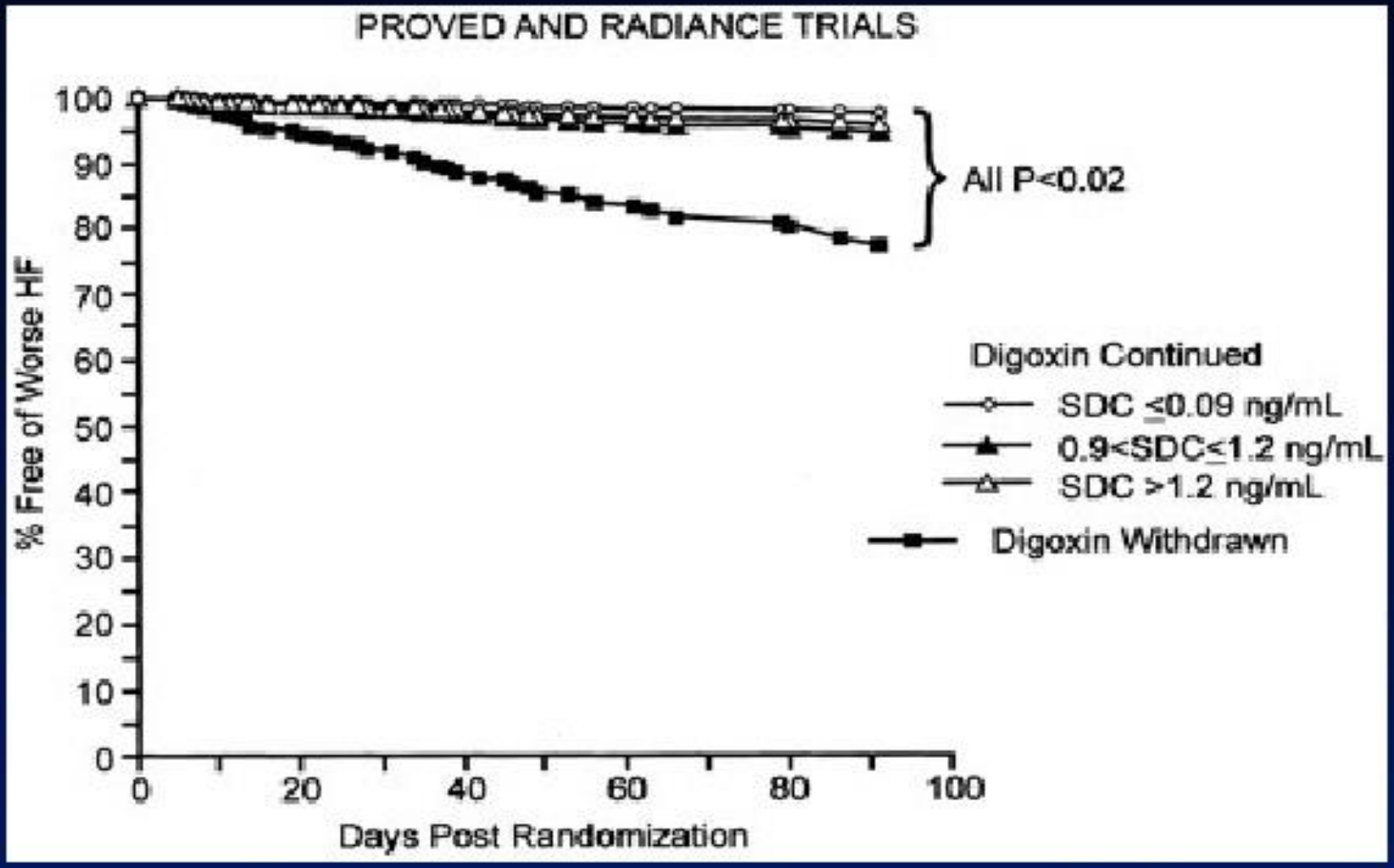
Mortalidad Depende de los Niveles de Digoxina



No. at Risk													
Placebo	2611	2514	2405	2302	2213	2117	2024	1948	1858	1625	1385	1111	852
SDC 0.5-0.8 ng/mL	572	566	549	533	512	490	477	459	441	427	419	361	290
SDC 0.9-1.1 ng/mL	322	319	306	295	282	267	250	240	232	225	211	180	138
SDC ≥1.2 ng/mL	277	262	246	234	221	206	187	177	166	159	150	133	116

S S Rathore. *JAMA*. 2003;289:871-878

Digoxin Withdrawal Worsens HF, Independent of Dig Level



Adams K et al. *JACC*. 2002;39:946 –53

Metanalysis using RADIANCE and PROVED

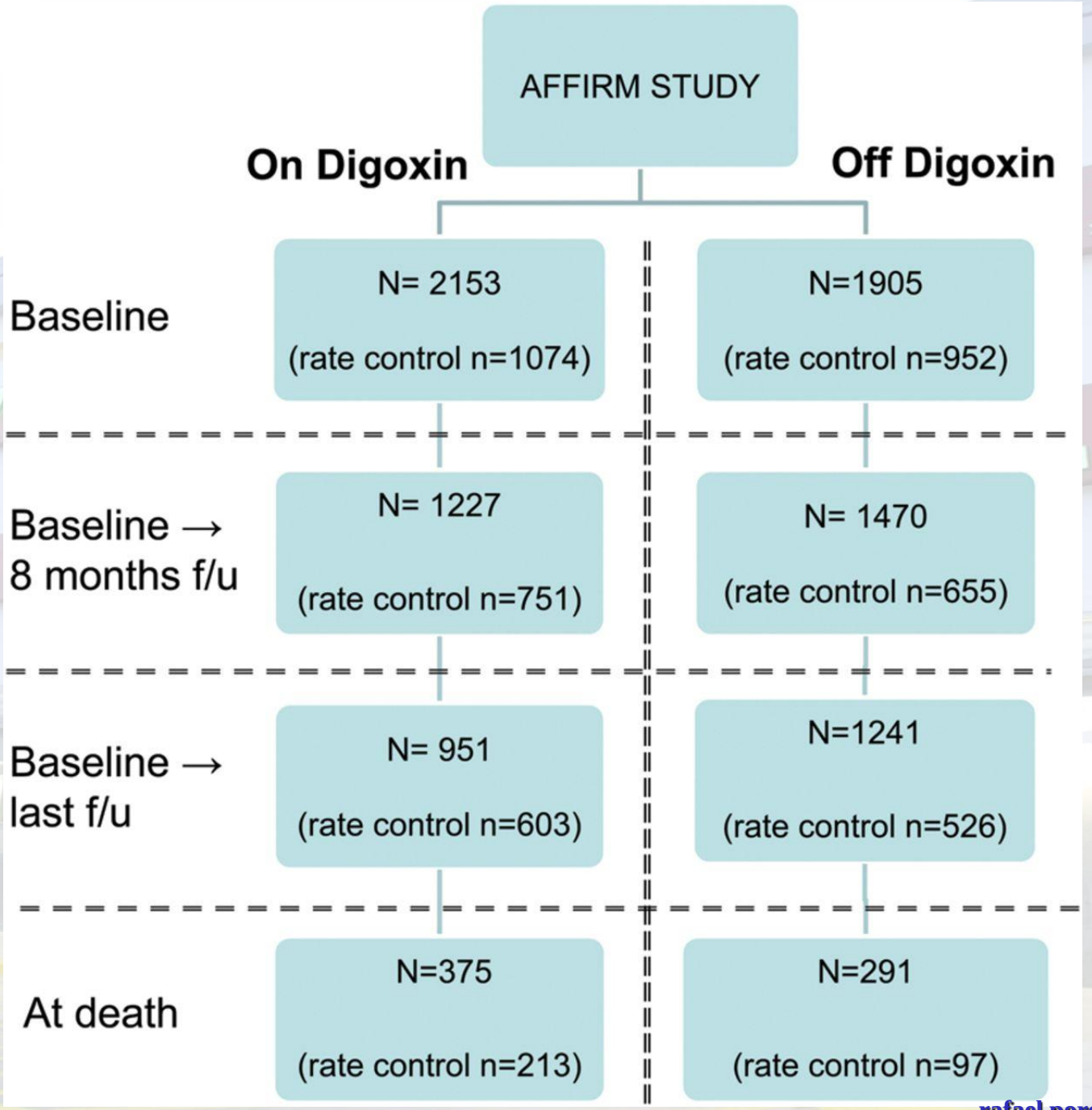
rafael.porcile@vaneduc.edu.ar

Increased mortality among patients taking digoxin—analysis from the AFFIRM study

European Heart Journal (2013) 34, 1481–1488
doi:10.1093/eurheartj/ehs348

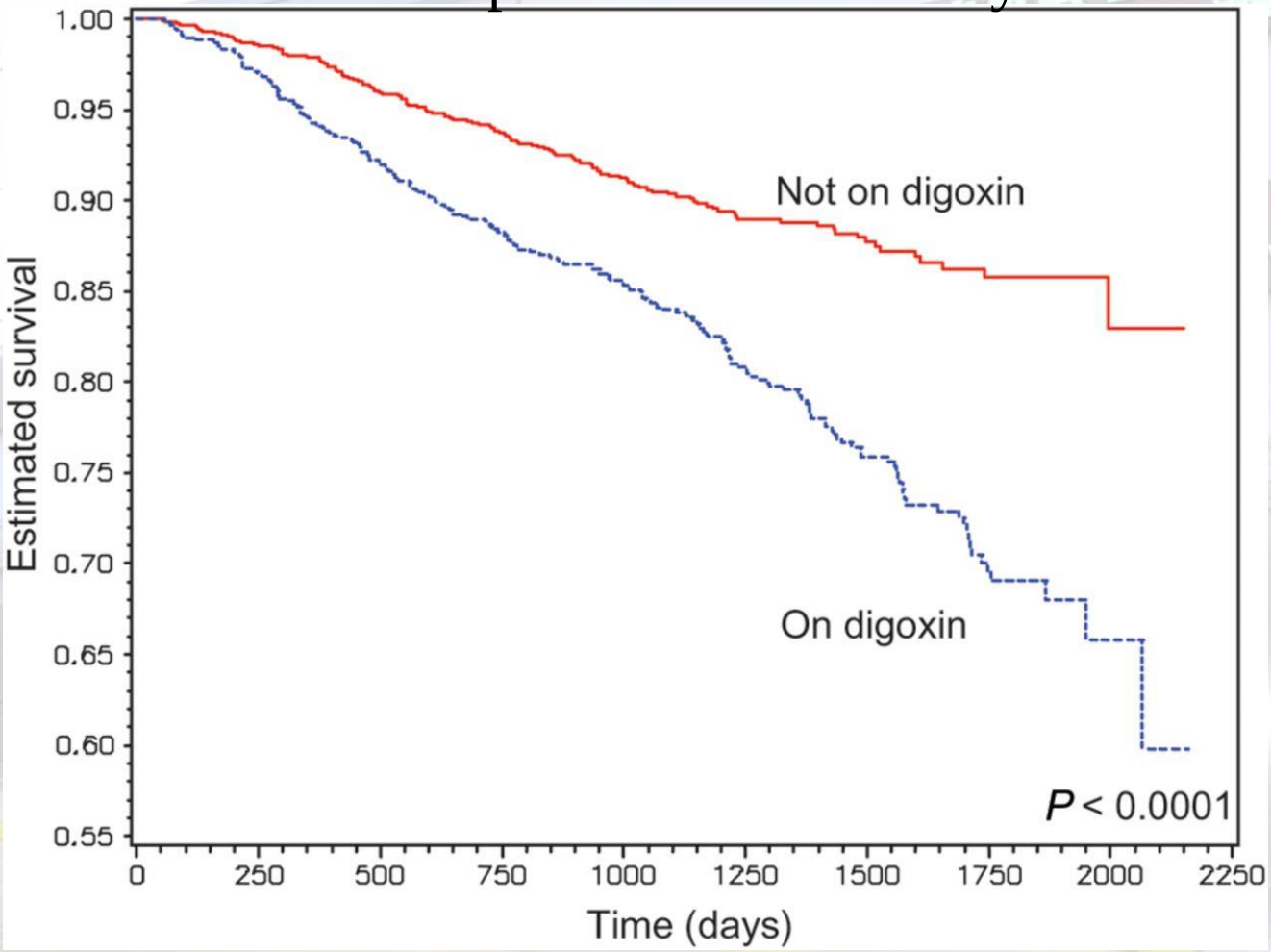
The AFFIRM trial randomized 4060 patients to rhythm control (2033 patients) vs. rate control (2027 patients).
The study included 1594 females representing 39.3% of the study cohort. Overall, 2816 patients (69.4%) received digoxin within 6 months of randomization and/or during the study.

rafael.porcile@vaneduc.edu.ar



rafael.porcile@vaneduc.edu.ar

Kaplan–Meier curves for all-cause mortality based on digoxin use during the study. Shown are Kaplan–Meier curves for all-cause mortality in patients always or never on digoxin during the study. *P*-value for this comparison is <0.0001 by the likelihood ratio test.



European Heart Journal (2013) 34, 1481–1488
doi:10.1093/eurheartj/ehs348

rafael.porcile@vaneduc.edu.ar

Increased mortality among patients taking digoxin—analysis from the AFFIRM study

European Heart Journal (2013) 34, 1481–1488
doi:10.1093/eurheartj/ehs348

Digoxin was associated with a significant increase in all-cause mortality in patients with AF after correcting for clinical characteristics and comorbidities, regardless of gender or of the presence or absence of HF. These findings call into question the widespread use of digoxin in patients with AF

rafael.porcile@vaneduc.edu.ar

¿Cuales pacientes son los que tienen mas probabilidad de morir bajo digoxina?

rafael.porcile@vaneduc.edu.ar

Patients with no congestive heart failure and ejection fraction ≥40%

In patients with AF and no HF, digoxin was associated with a 37% increase in mortality.

This group represented more than half of all patients enrolled in AFFIRM.

These findings are consistent with previously published results from the **Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) study.**[1,2]

The RIKS-HIA study examined 1-year outcomes of patients with AF, CHF, or both on digoxin by comparing them to a matched group of patients not receiving digoxin.

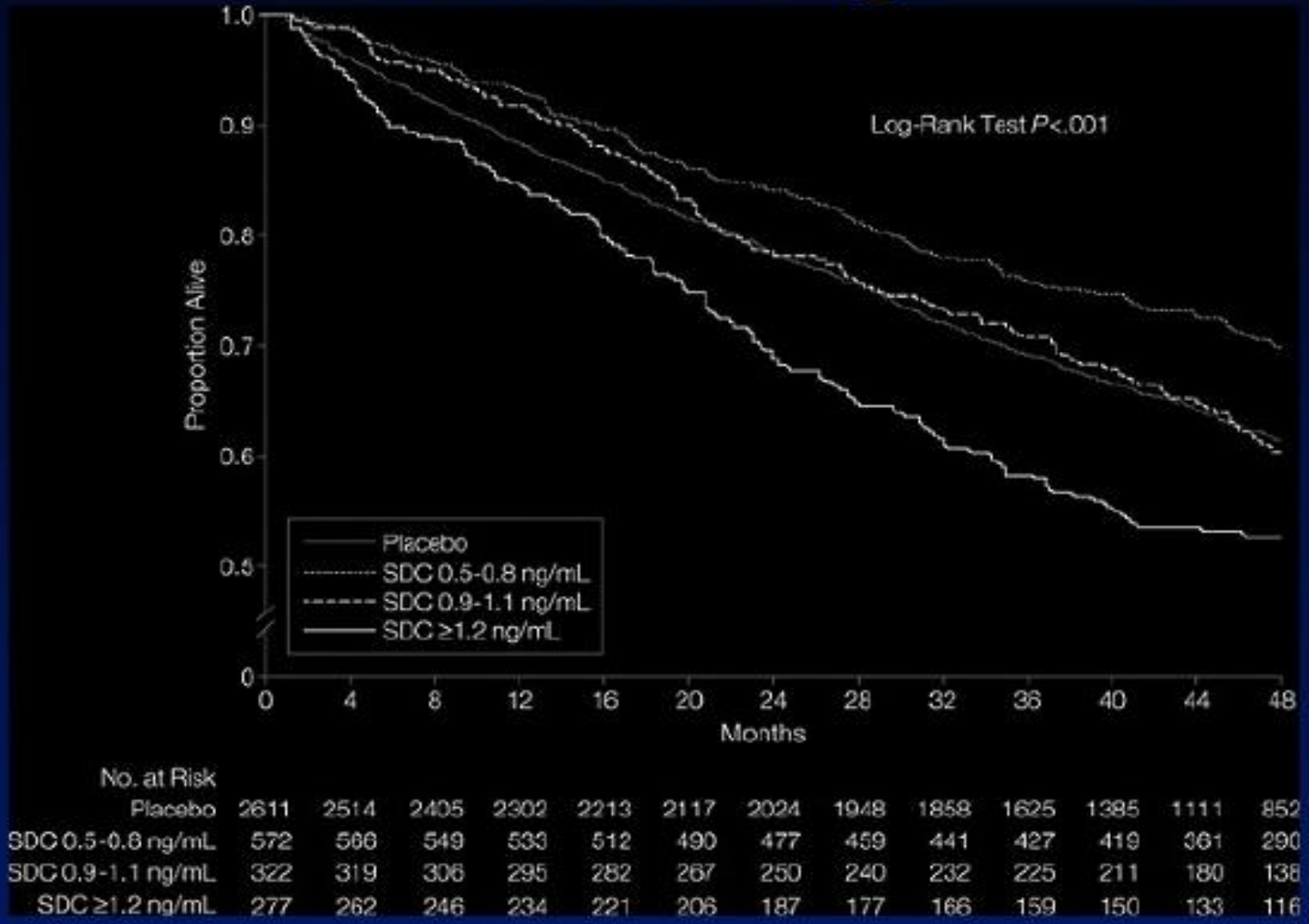
The 4426 patients with AF and no history of CHF taking digoxin had a significant increase in overall mortality (estimated relative risk 1.42, 95% CI 1.29–1.56) compared with 16 587 controls at discharge.

rafael.porcile@vaneduc.edu.ar

Among the 666 patients who died during the study, 375 (56.3%) received digoxin and 291 (43.7%) had no digoxin at the last follow-up visit before death. When comparing those two groups, **cardiac death with no evidence of ischaemia was a significantly more frequent cause of death among patients on digoxin** at the last follow-up visit (*n* = 139, 37.1% vs. *n* = 79, 27.1%, *P* = 0.007). There were no statistical differences for the following causes of death: cancer; pulmonary; and non-cardiovascular

rafael.porcile@vaneduc.edu.ar

Mortalidad Depende de los Niveles de Digoxina



No. at Risk													
Placebo	2611	2514	2405	2302	2213	2117	2024	1948	1858	1625	1385	1111	852
SDC 0.5-0.8 ng/mL	572	566	549	533	512	490	477	459	441	427	419	361	290
SDC 0.9-1.1 ng/mL	322	319	306	295	282	267	250	240	232	225	211	180	138
SDC ≥1.2 ng/mL	277	262	246	234	221	206	187	177	166	159	150	133	116

S S Rathore. *JAMA*. 2003;289:871-878

rafael.porcile@vaneduc.edu.ar

Digoxin-associated mortality: a systematic review and meta-analysis of the literature

European Heart Journal
doi:10.1093/eurheartj/ehv143
2015

rafael.porcile@vaneduc.edu.ar

Class IIa Digoxin can be beneficial in patients with HF*rEF*, *unless contraindicated, to decrease* hospitalizations for HF (484-491). (*Level of Evidence: B*)

May be used only in patients who remain symptomatic despite therapy with the neurohormonalantagonists.

2013 ACCF/AHA Guideline for the Management of Heart Failure

rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

¿DE ACUERDO?

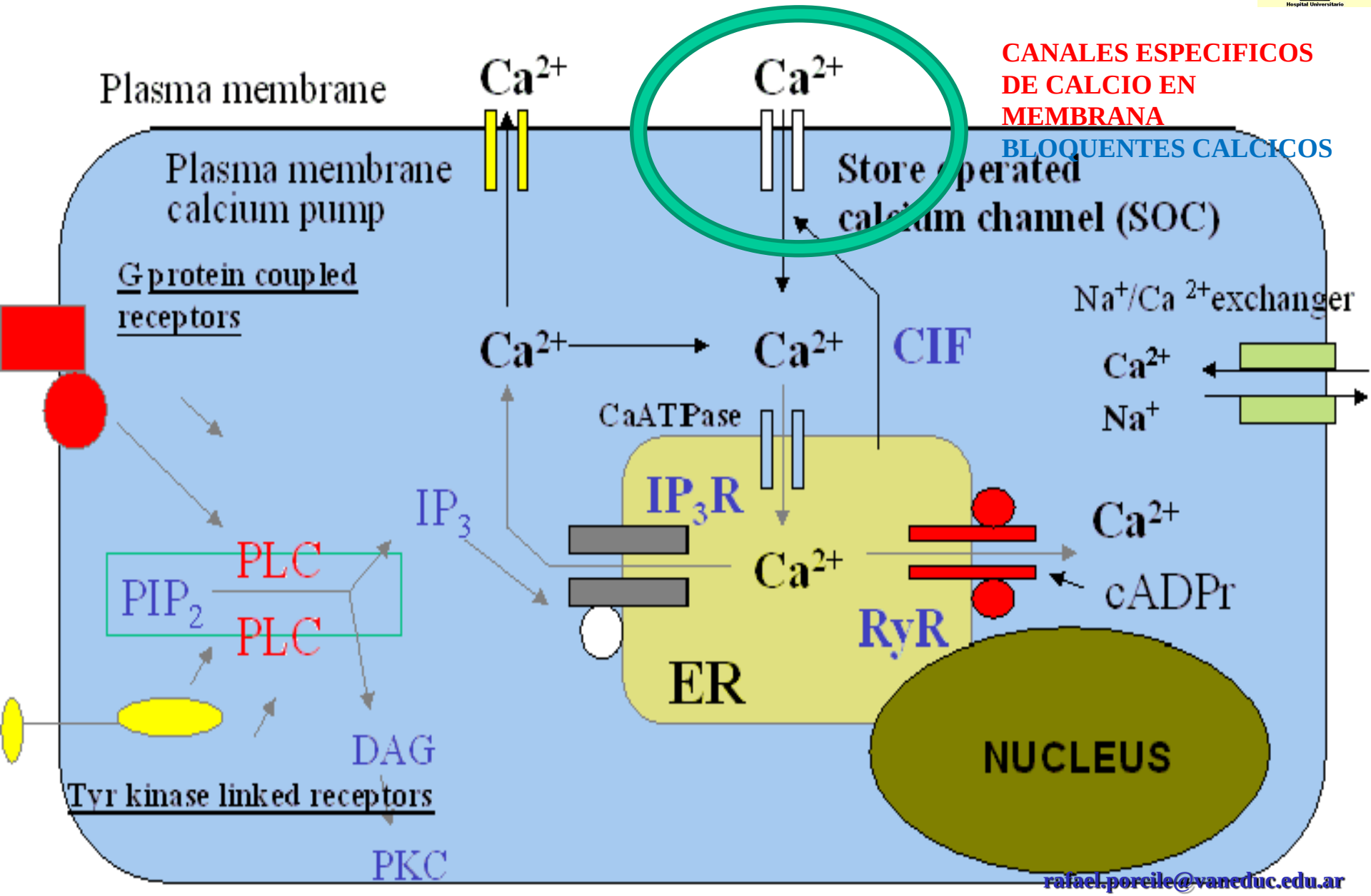
rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL
UNIVERSITARIO

BLOQUEANTES CALCICOS

rafael.porcile@vaneduc.edu.ar

Calcium homeostasis



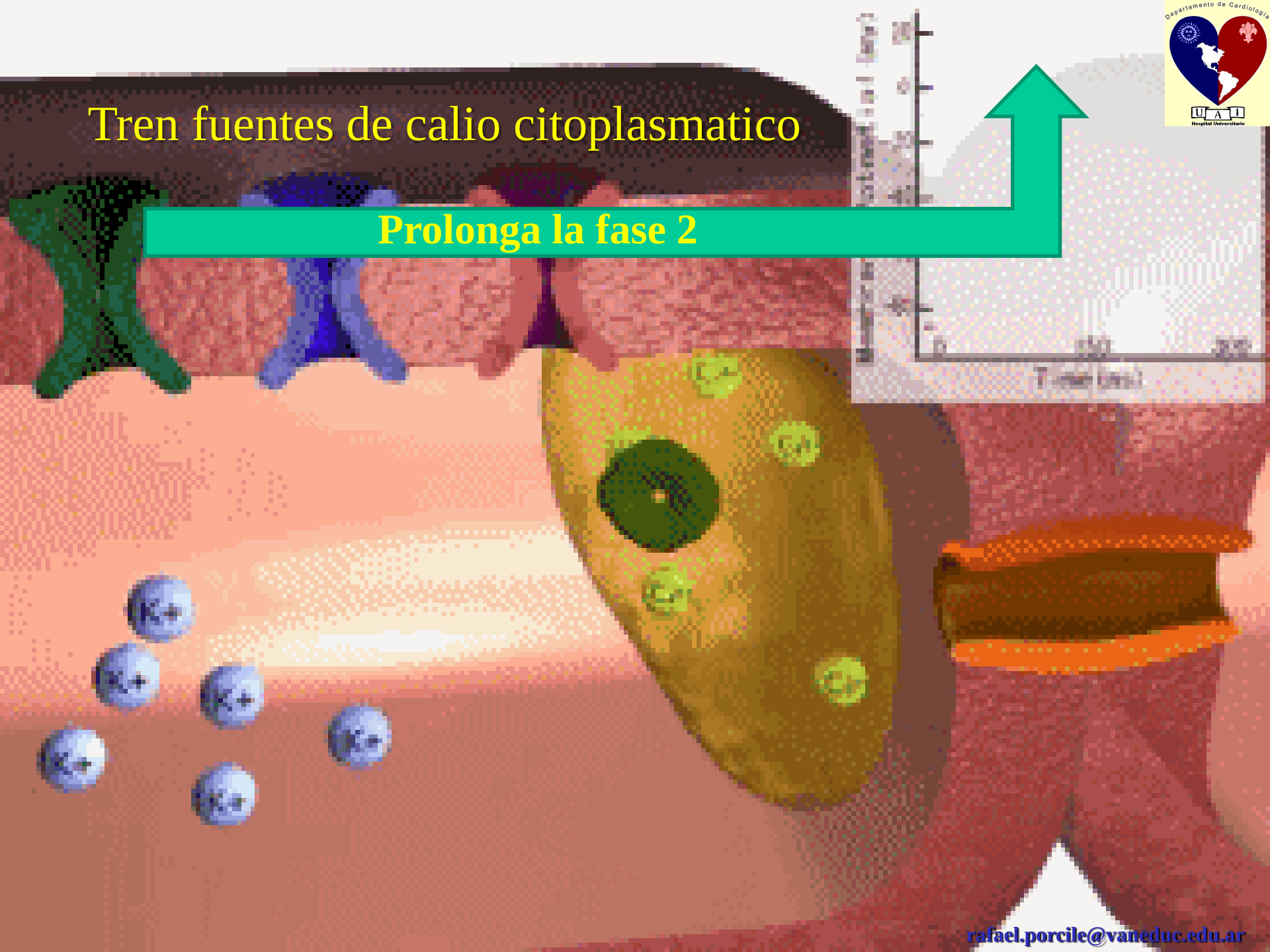
CANALES ESPECIFICOS DE CALCIO EN MEMBRANA

BLOQUENTES CALCICOS

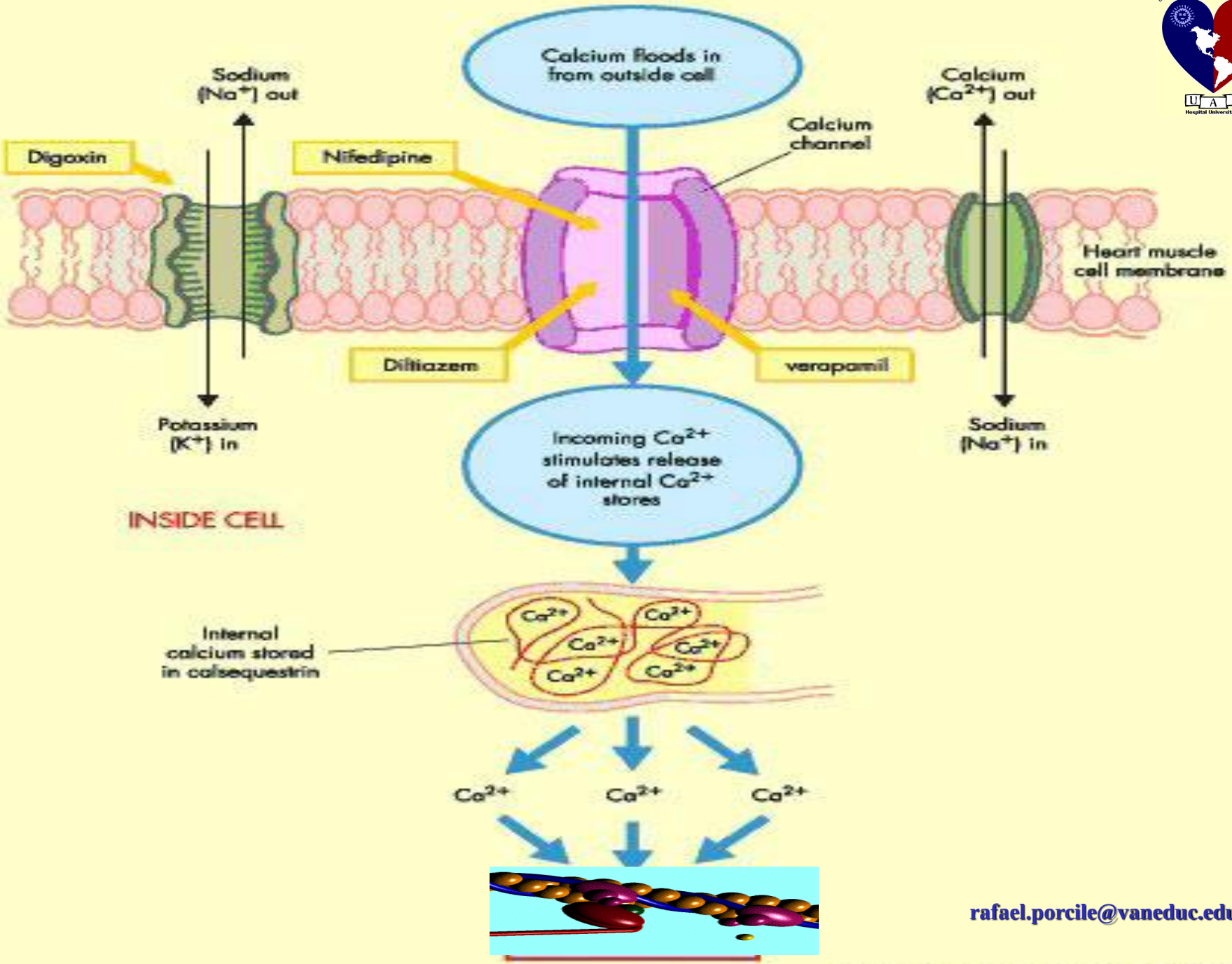
rafael.porcile@vaneduc.edu.ar

Tren fuentes de calio citoplasmatico

Prolonga la fase 2

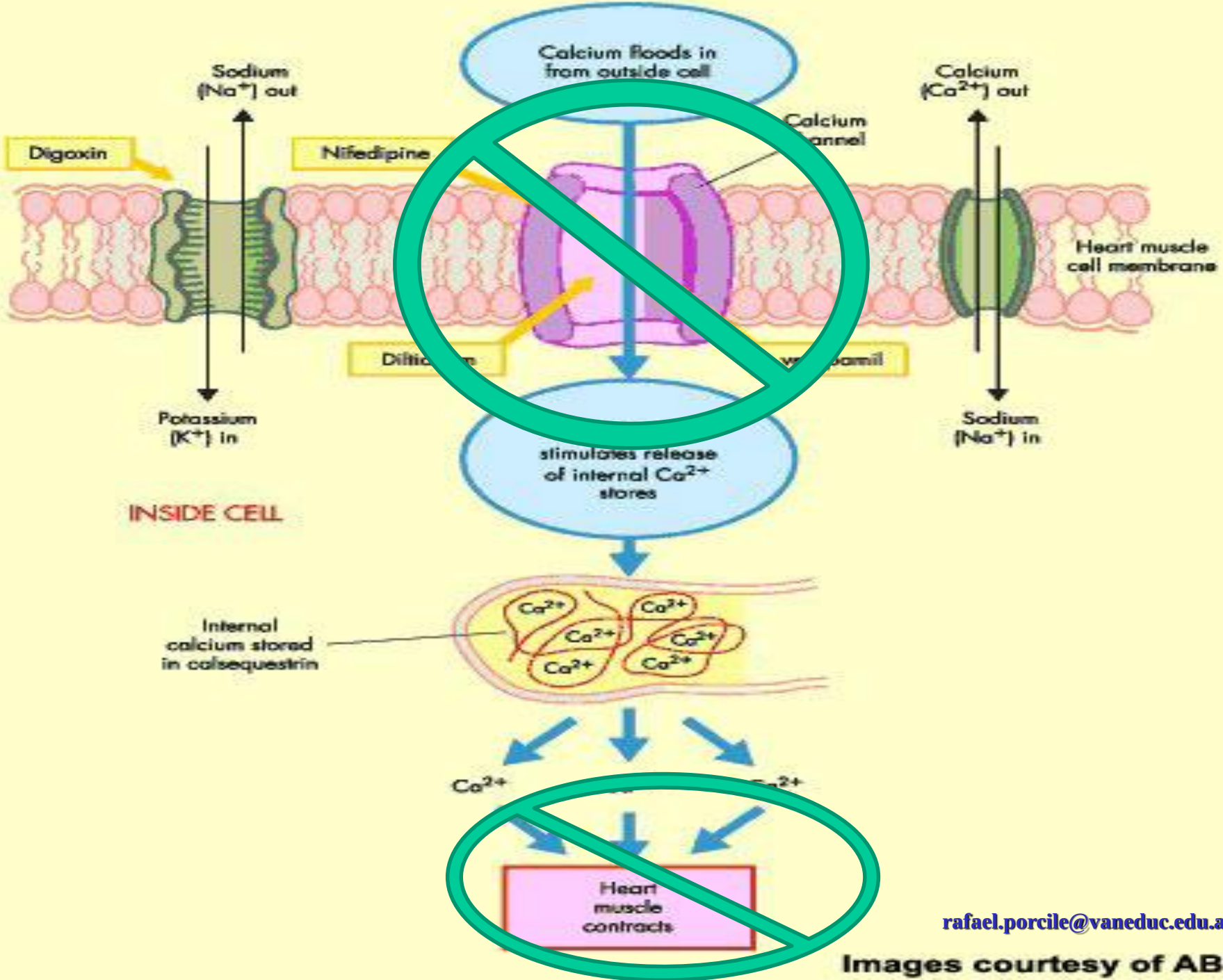


rafael.porcile@vaneduc.edu.ar



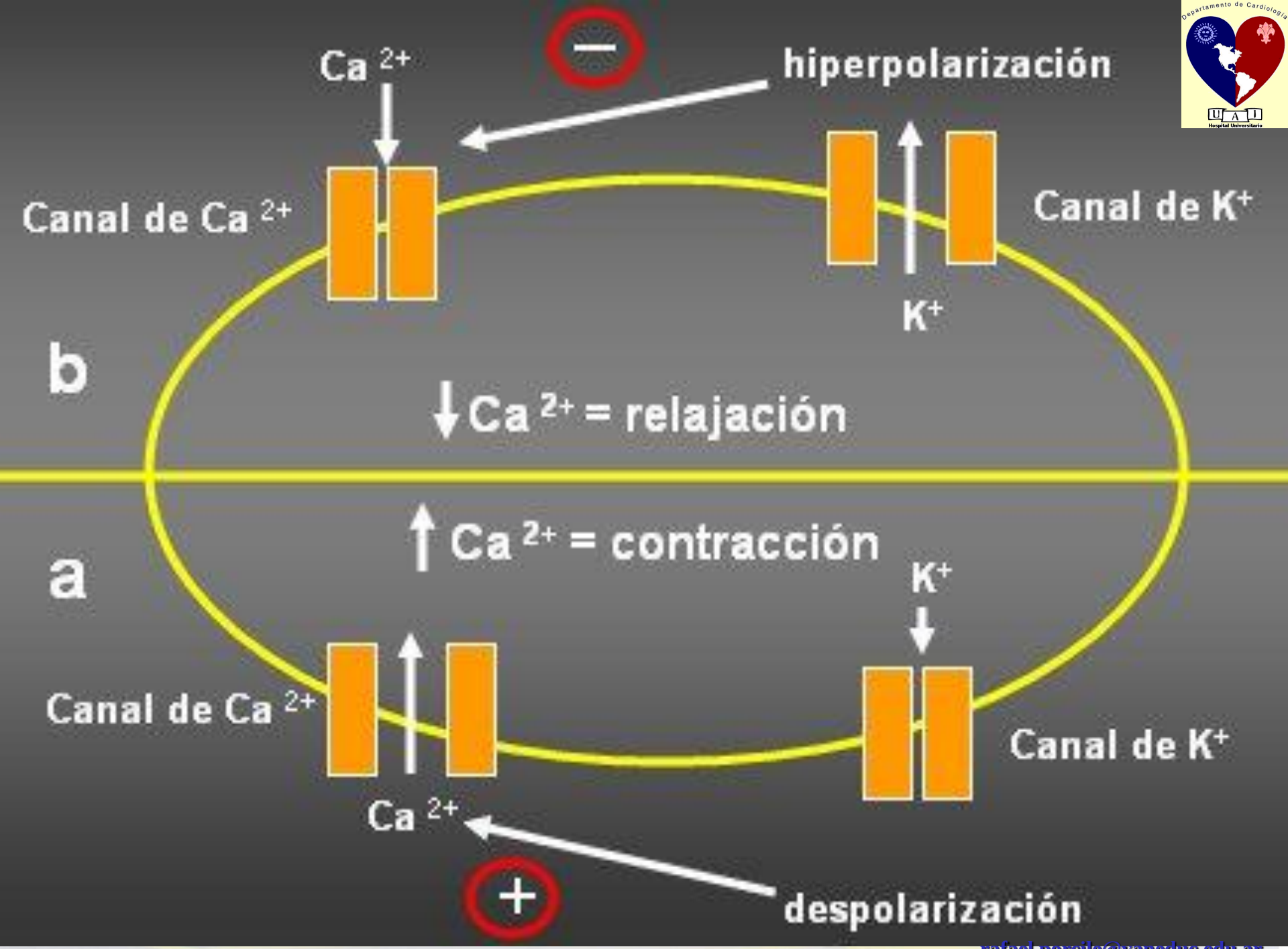
rafael.porcile@vaneduc.edu.ar

Images courtesy of ABPI



rafael.porcile@vaneduc.edu.ar

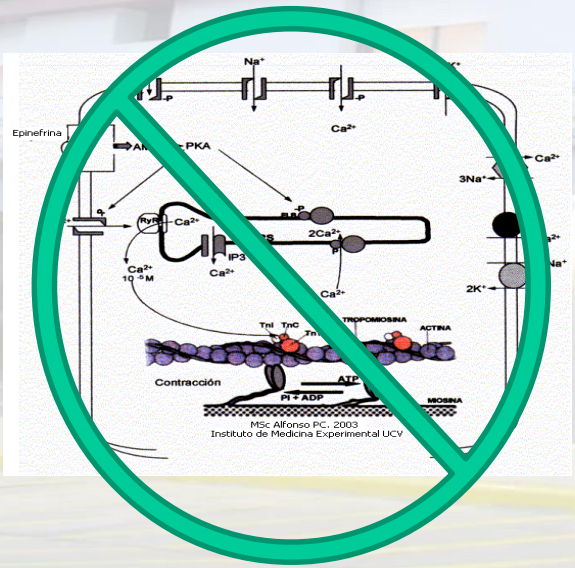
Images courtesy of ABPI

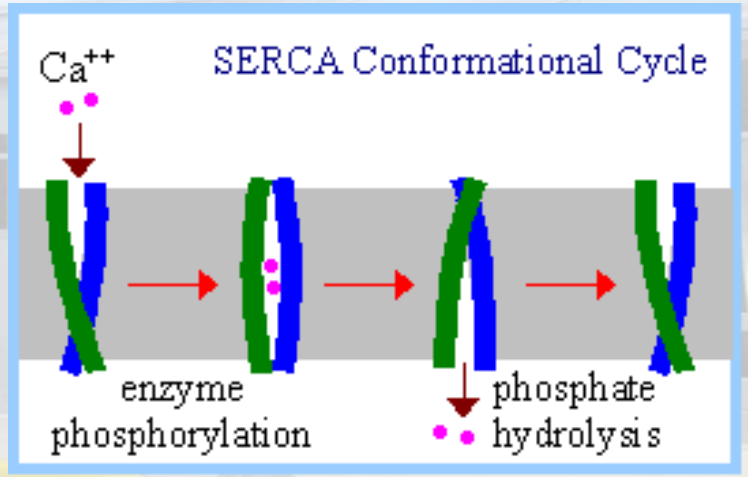


rafael.porcile@vaneduc.edu.ar

Bloqueantes Calcicos reducen el Calcio citoplasmatico

- Reducción de su ingreso extra celular
- Aumento de su bombeo al circuito sarcoplasmico





rafael.porcile@vaneduc.edu.ar

Abernethy DR, Schwartz JB (1999) Ca^{2+}-antagonist drugs. N Engl J Med 341: 1447-1457.

However, verapamil may decrease left ventricular function in patients with congestive heart failure. Unlike b-adrenergic blockers, Ca^{2+}antagonists are not recommended for early treatment or secondary prevention of myocardial infarction.

rafael.porcile@vaneduc.edu.ar

Am Coll Cardiol. 1993 Oct;22(4 Suppl A):139A-144A.

Calcium channel blockers in heart failure.

Elkayam U, Shotan A, Mehra A, Ostrzega E.

- **long-term exposure to the drug in a large group of patients with chronic heart failure due to left ventricular systolic dysfunction after myocardial infarction resulted in an increased incidence of cardiac events, with worsening heart failure and death.**

rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

¿DE ACUERDO?

rafael.porcile@vaneduc.edu.ar

1 Medicamentos: Clasificación

Catecolaminas β Agonistas

Adrenalina	Dobutamina	Dopamina	Ibopamina

↓

Aumentan las concentraciones de AMPc

↓

Se bloquea la proteina inhibidora de la bomba de calcio del RS

Estimula a función de la bomba	Incrementa el Ca movilizado para la contracción

rafael.porcile@vaneduc.edu.ar

β-Blocker Therapy in Heart Failure
Scientific Review

JoAnne Micale Foody, MD
Michael H. Farrell, MD
Harlan M. Krumholz, MD

JAMA®
The Journal of the American Medical Association

CIBIS II,[5] 1999		US Carvedilol,[8] 1996		COPERNICUS,[95] 2001		BEST,[96] 2001	
Placebo (n = 1224)	Bisoprolol (n = 1222)	Placebo (n = 398)	Carvedilol (n = 696)	Placebo (n = 1133)	Carvedilol (n = 1156)	Placebo (n = 1354)	Bucindolol (n = 1354)
61	61	58	58	63	63	60	60
80	80	76	77	80	79	77	79
25	25	22	23	20	20	23	23
0	0	0	0	0	0	0	0
0	0	52	54	0	0	0	0
83	83	44	44	0	0	92	92
17	17	3	3	100	100	8	8
1.25		3.125 or 6.35		3.125		3	
10		50-100		50		100 (<75 kg), 200 (≥75 kg)	
None		2 weeks		None		None	
Mortality		Mortality, exercise tolerance, quality of life, progression of disease		Mortality, combined death and hospitalization		Mortality	
17	12	8	3	19	11	33	30
34		65		35		10 (NS)	
Significant reduction in primary end point of all-cause mortality with bisoprolol. Greatest reduction in sudden death. No benefit in death from pump failure.		Significant reduction in all-cause mortality with carvedilol. Stopped early because of mortality benefit. No effect on exercise tolerance or quality of life.		Significant reduction in primary and secondary end points in patients with severe heart failure with carvedilol		No significant mortality benefit with bucindolol	

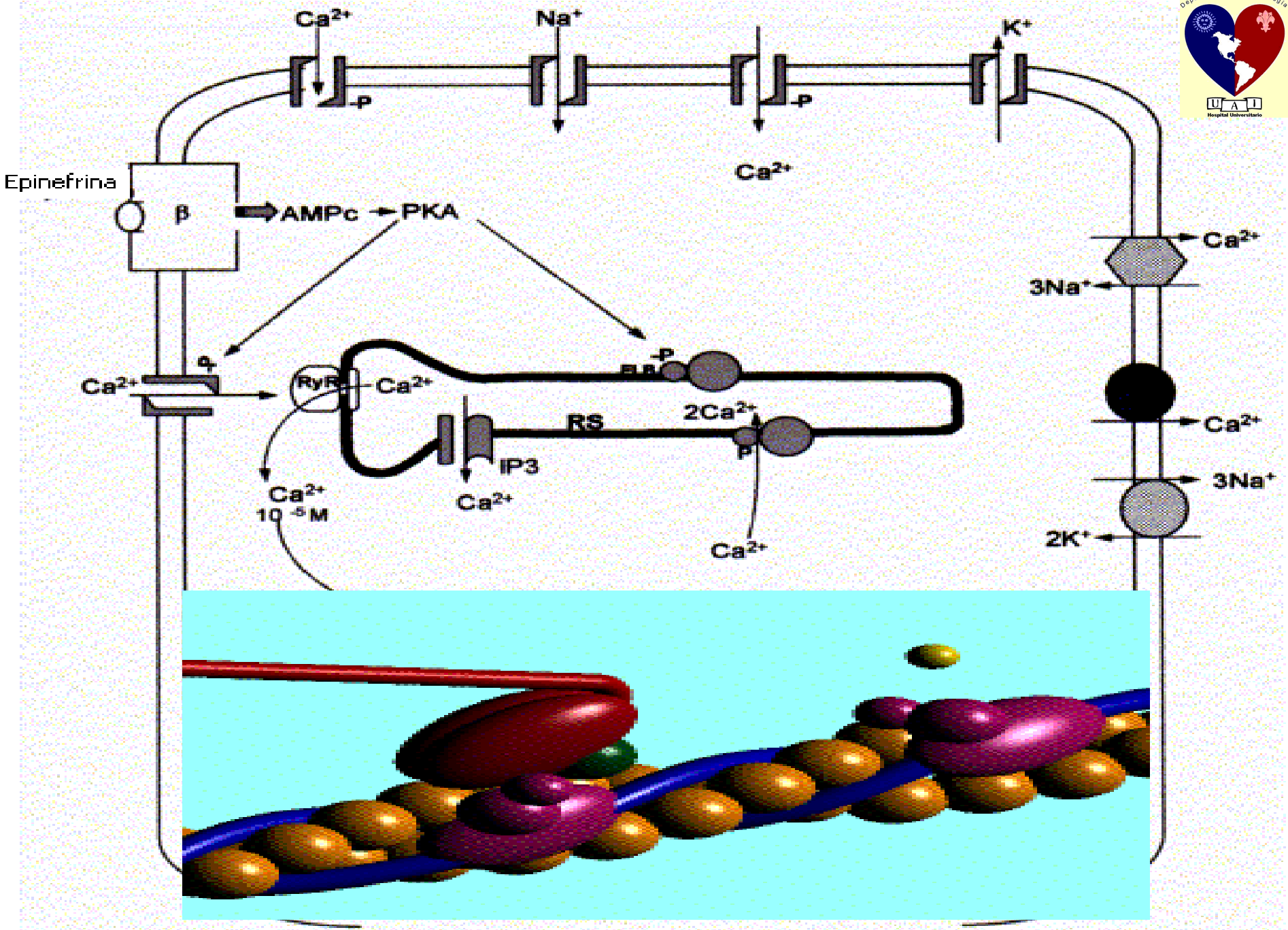
Foody JA JAMA 2002

rafael.porcile@vaneduc.edu.ar

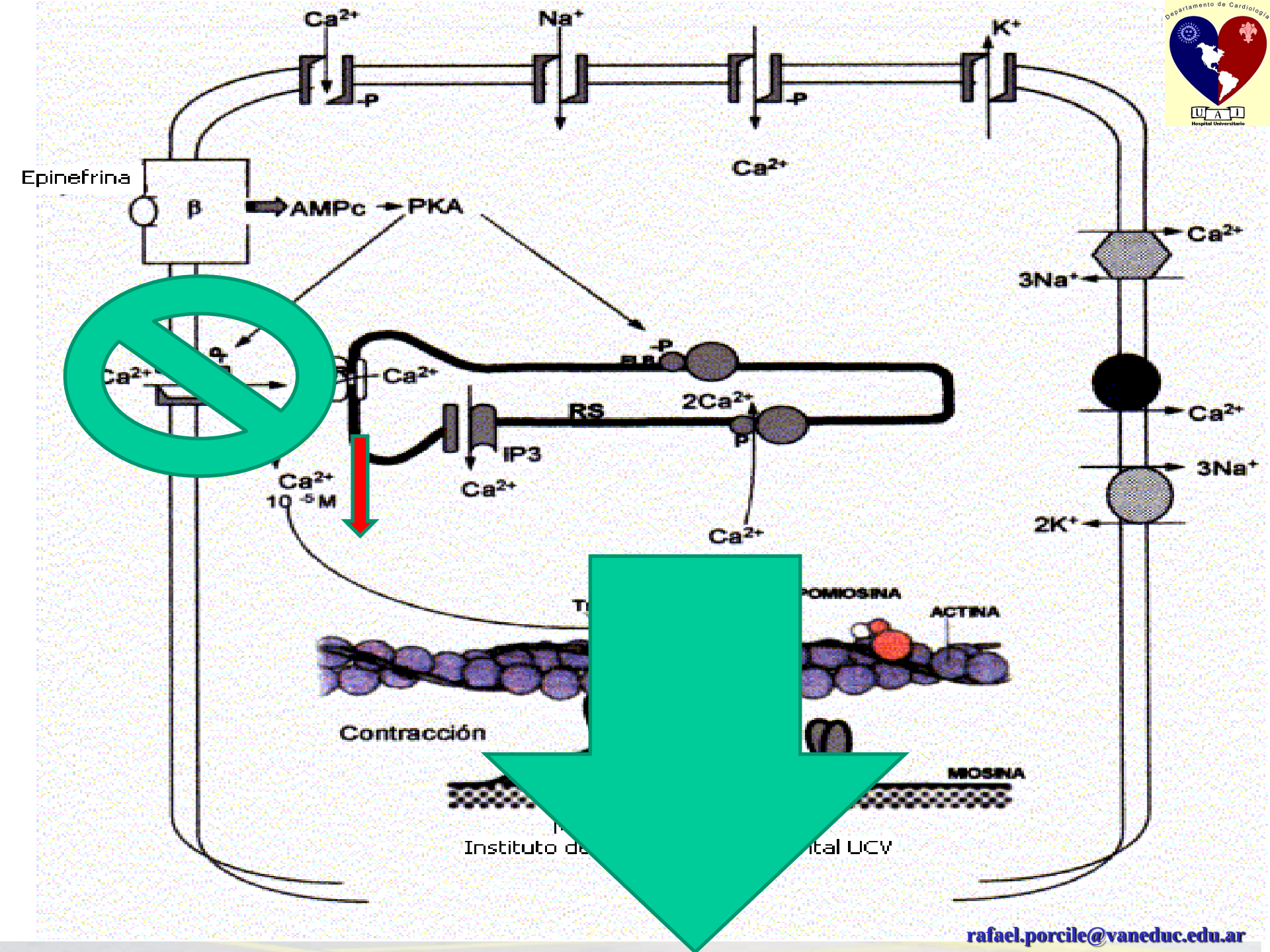
Beta Bloqueantes

- Mejora fraccion eyección
- Reduce tasa reinternación
- Reduccion Mortalidad b1 b2
  - Carbedilol MAYOR RED MORT ESPECIALMENTE ARRITMICA 17%
- Reduccion mortalidad en B 1 selectivos
  - Bisoprolol, Metoprolol

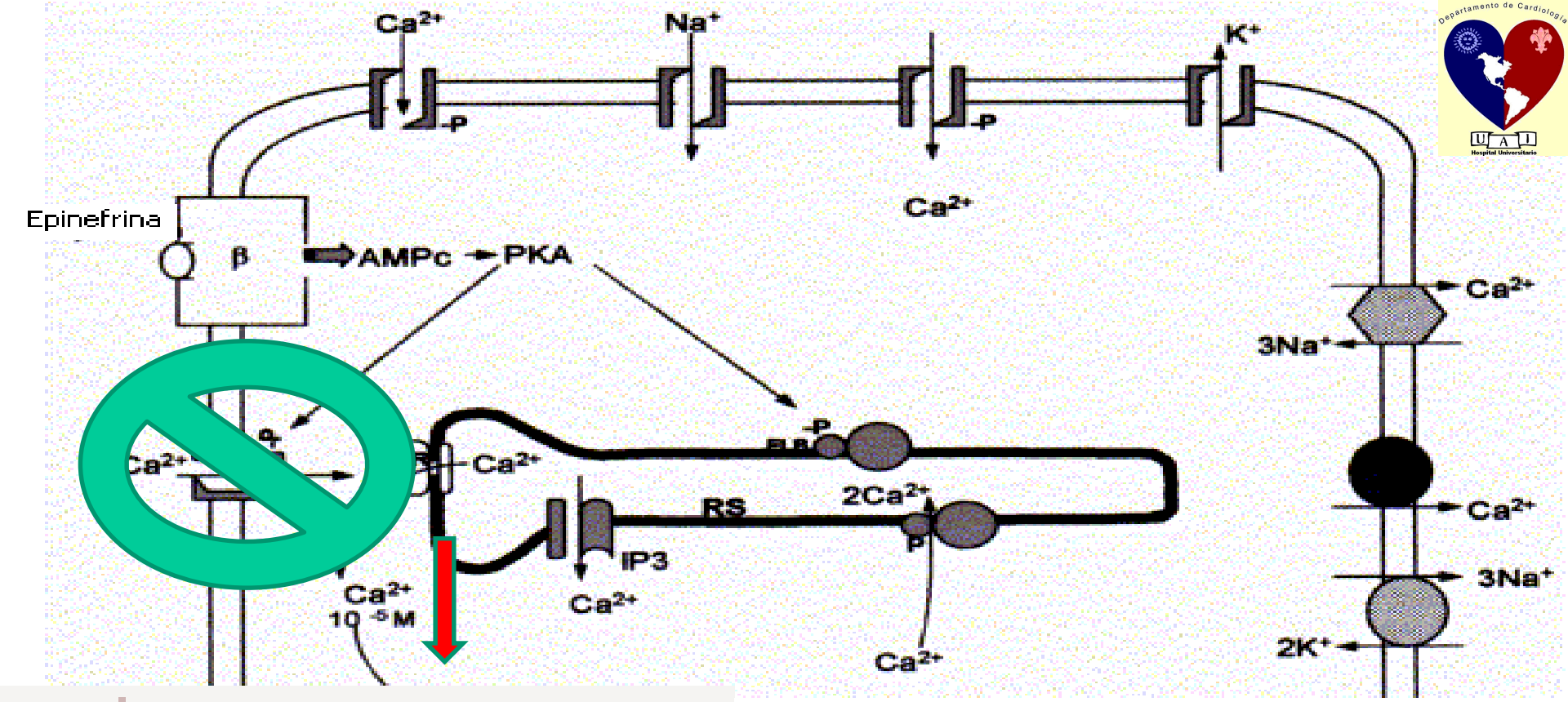
rafael.porcile@vaneduc.edu.ar

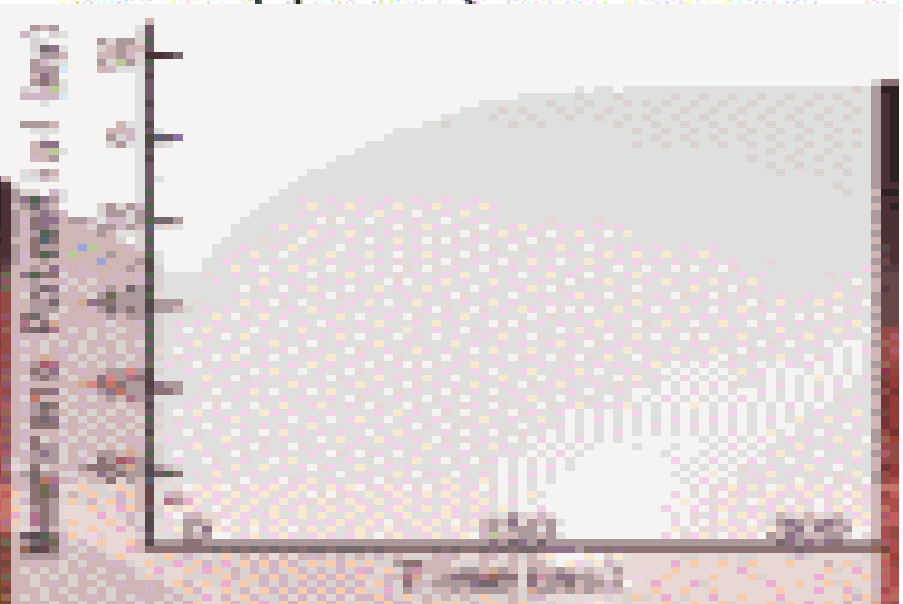


rafael.porcile@vaneduc.edu.ar



rafael.porcile@vaneduc.edu.ar

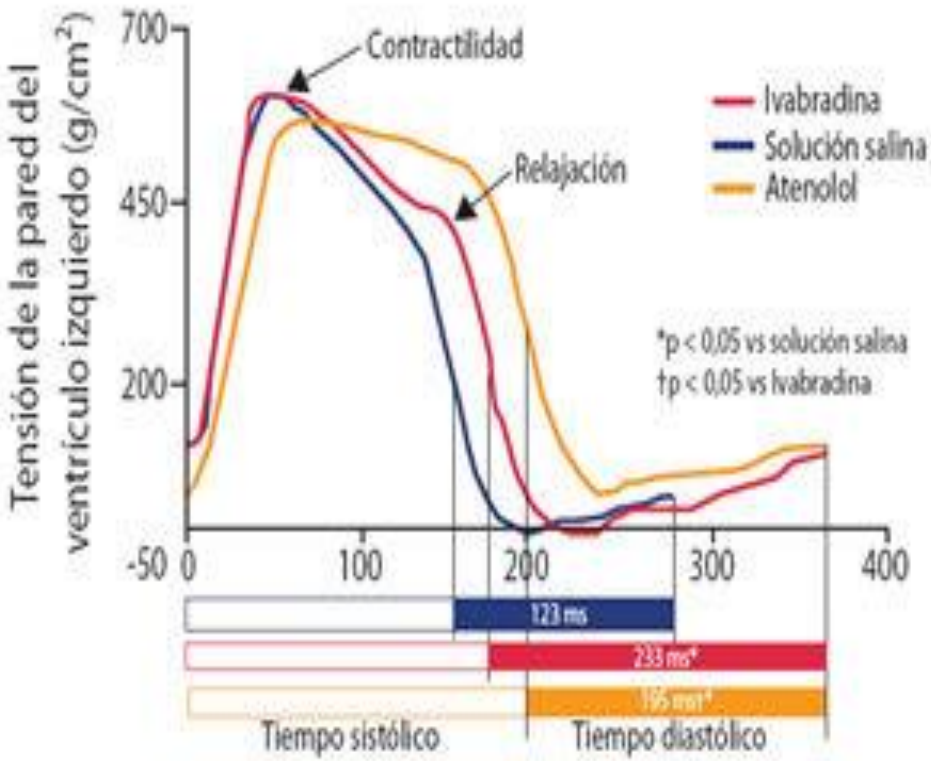


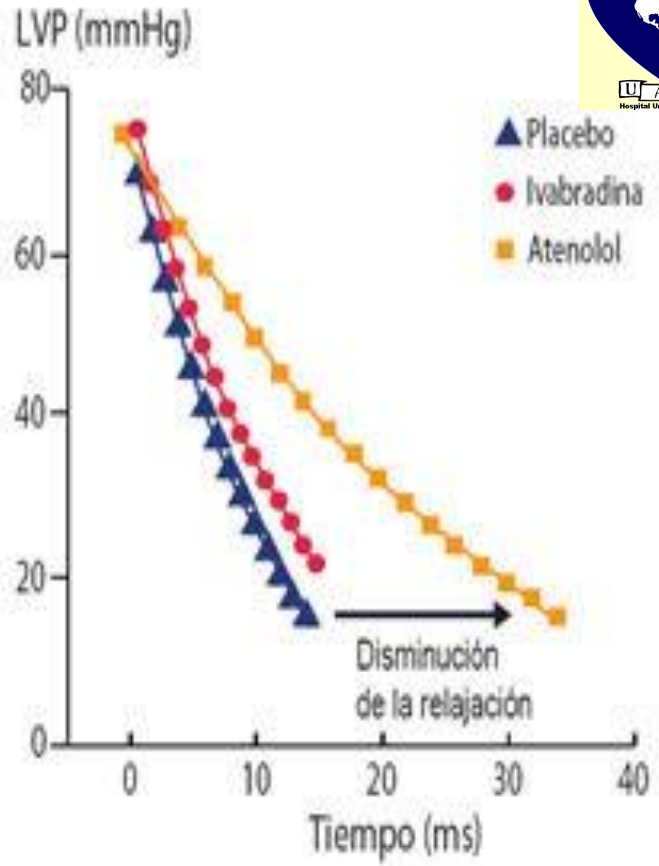


HIPERPOLARIZA LA CELULA MIOCARDICA REDUCIENDO LAS CARGAS POSITIVAS INTRA CELULRALES

rafael.porcile@vaneduc.edu.ar

MAS TIEMPO MENOS CALCIO ESTABILIDAD DE MEMBRABA





Mayor aumento del tiempo diastólico comparado con betabloqueantes debido a que:

– Se mantiene la fuerza contráctil (no se prolonga la duración de la sístole en contraste con betabloqueantes)

– Se preserva la relajación del VI (sin efecto lusitrópico negativo), permitiendo una relajación completa y rápida.

Colin P, et al. *Am J Physiol Heart Circ Physiol.* 2003;284:H676-H682.

Figura 1. Ivabradina aumenta en mayor medida la diástole para una misma reducción de la frecuencia cardiaca.

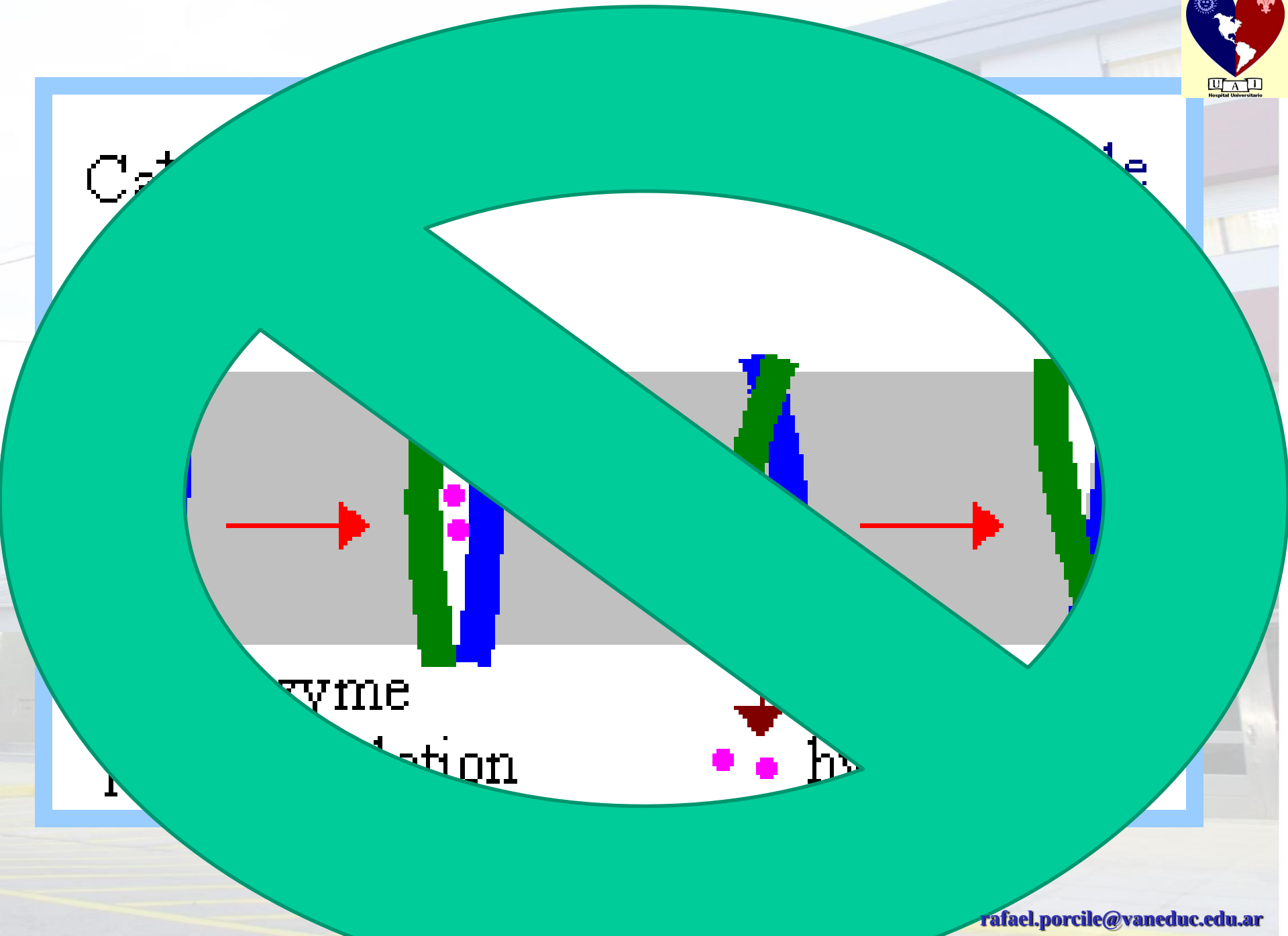
rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL UNIVERSITARIO

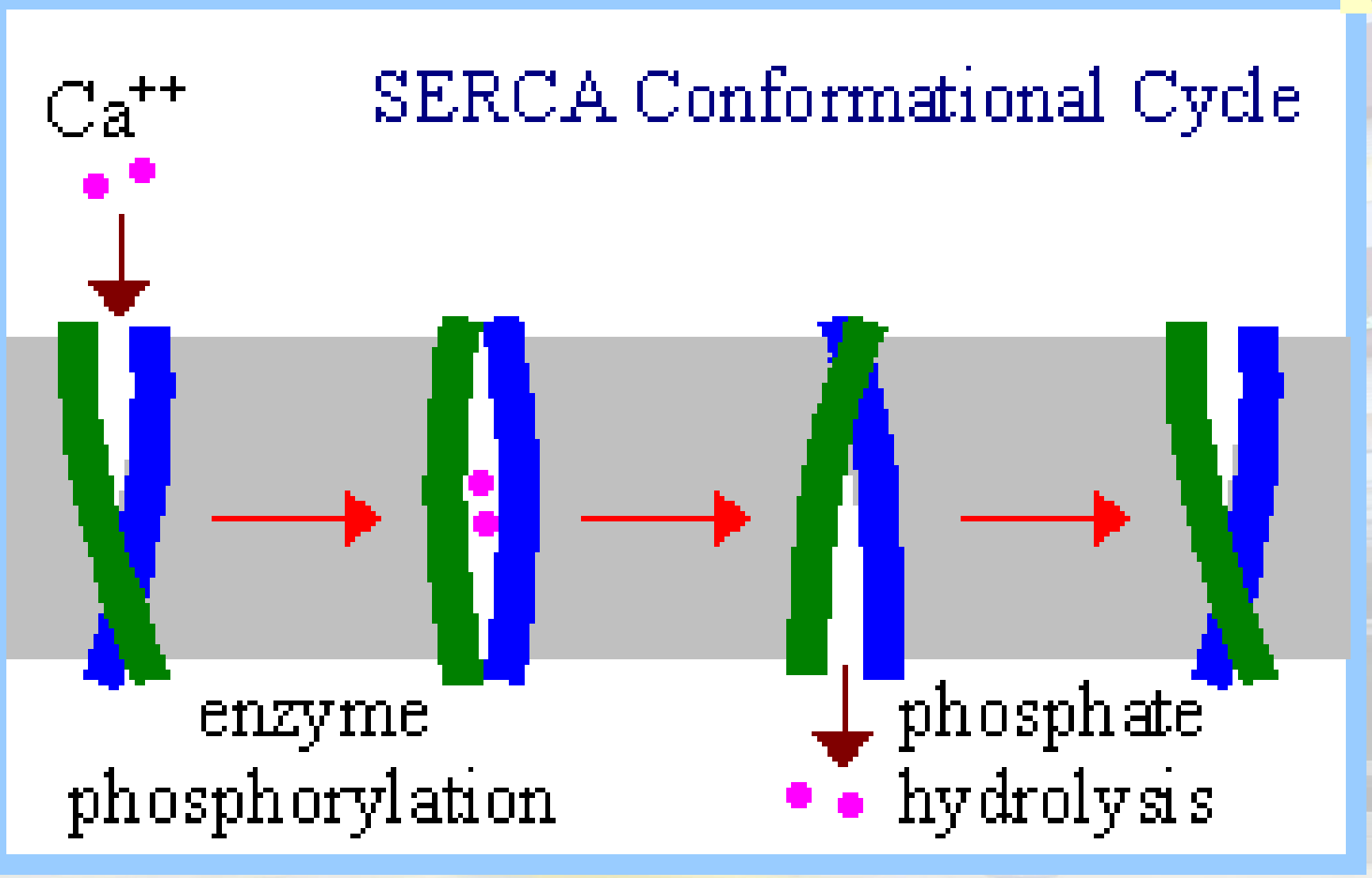
Departamento de Cardiología
UAI
Hospital Universitario

DEUDA DE OXIGENO

rafael.porcile@vaneduc.edu.ar



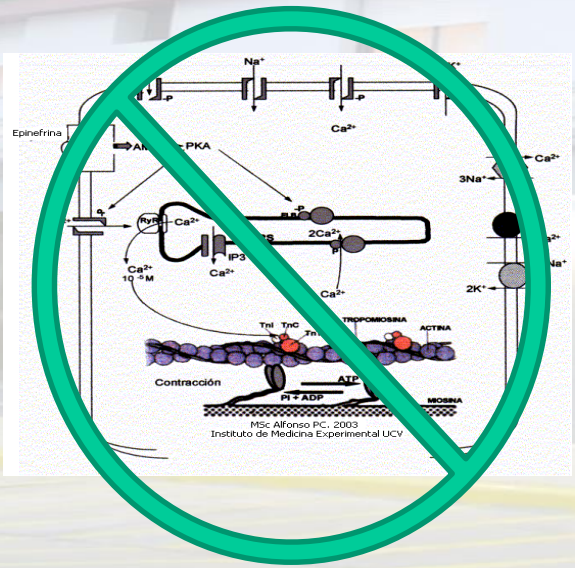
rafael.porcile@vaneduc.edu.ar

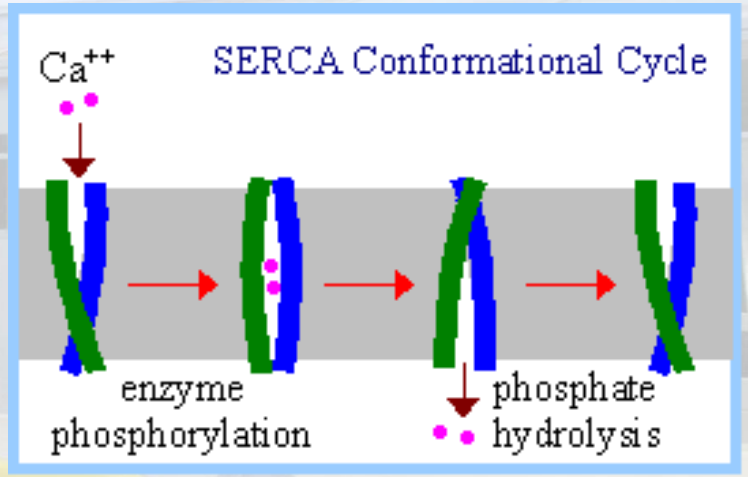


rafael.porcile@vaneduc.edu.ar

Betabloquentes reducen el Calcio citoplasmatico

- Reducción de su ingreso extra celular
- Aumento de su bombeo al circuito sarcoplasmico





rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

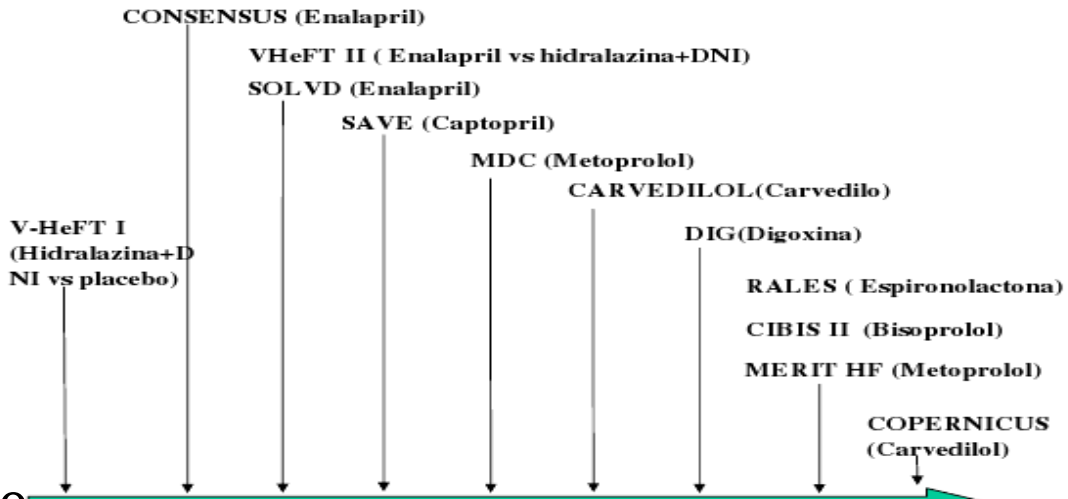
DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

¿DE ACUERDO?

rafael.porcile@vaneduc.edu.ar

Evolución de ensayos en insuficiencia cardíaca



	1970 / 1980								
Mortalidad/año en placebo		54	15,2 12	7,14		16	12	23 12 11	18,5
RAR		6,7	2,9 1,3	1,4		8,3		11 3,75 3,8	5,3

IVABRADINA

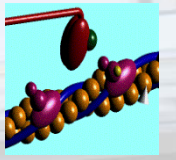
2010

rafael.porcile@vaneduc.edu.ar

IVABRADINA

✓ La ivabradina reduce la FC mediante una inhibición **específica** de la corriente If del nodo sinusal.

✓ A diferencia de los betabloqueantes (BB), **no Deprime la contractilidad miocárdica** ni la conducción intracardiaca, incluso en pacientes con disfunción sistólica.



✓No modifica el tenor adrenérgico

✓No modifica las resistencias vasculares sistémica

✓No es antialdosteronico ni interfiere en ciclo renina angiotensina aldosterona de manera directa

rafael.porcile@vaneduc.edu.ar

IVABRADINA

Cronotrópica negativa

Sin efecto dromotrópico

Sin efecto Vatmotrópico

rafael.porcile@vaneduc.edu.ar

Effect of metoprolol and ivabradine on left ventricular remodelling and Ca^{2+} handling in the post-infarction rat heart

Michał Mączewski*† and
Urszula Mackiewicz†

Cardiovascular Research (2008) 79, 42–51
doi:10.1093/cvr/cvn057

- Ivabradine, but not metoprolol, partially prevented the MI-induced depression of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) activity, while metoprolol, but not ivabradine, suppressed Na^{+}/Ca^{2+} exchanger (NCX) overactivity and normalized Ca^{2+} sensitivity of ryanodine receptors.

rafael.porcile@vaneduc.edu.ar

Heart rate in the sham-operated (A) and post-myocardial infarction (B) rats, immediately before the surgery (baseline), 1 and 8 weeks–2 days (week 8–2 days) after the surgery, 2 days after discontinuation of ivabradine or metoprolol (week 8), peak response to isoproterenol infusion (ISO) and in Langendorff perfused hearts (iHR).

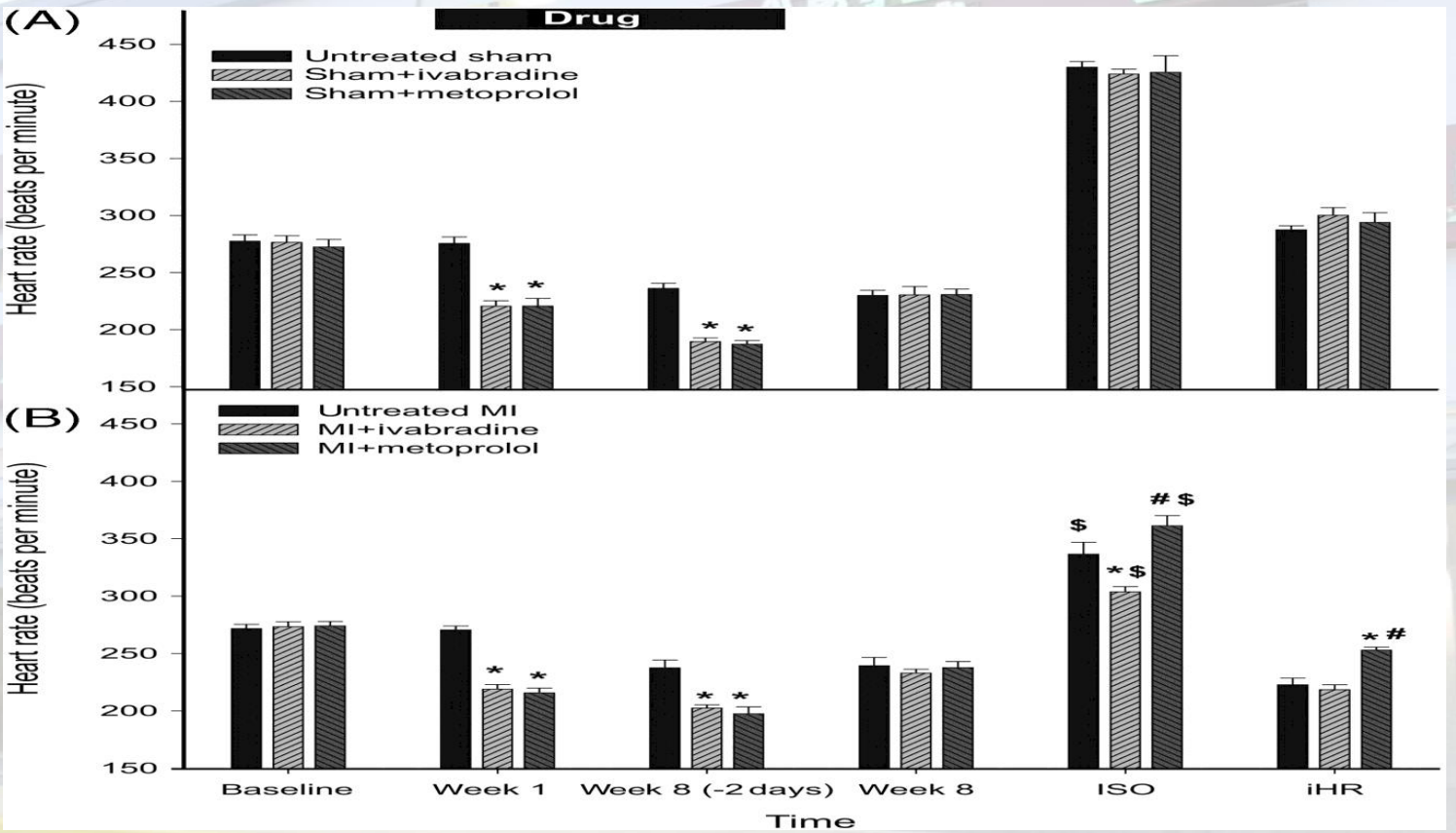
REDUCCION DE LA FRECUENCIA CARDÍACA COMPLETAMENTE COMPARABLE

Mączewski M , and Mackiewicz U Cardiovasc Res 2008;79:42-51

Cardiovascular Research

rafael.porcile@vaneduc.edu.ar

Heart rate in the sham-operated (A) and post-myocardial infarction (B) rats, immediately before the surgery (baseline), 1 and 8 weeks–2 days (week 8–2 days) after the surgery, 2 days after discontinuation of ivabradine or metoprolol (week 8), peak response to isoproterenol infusion (ISO) and in Langendorff perfused hearts (iHR).



Mączewski M , and Mackiewicz U Cardiovasc Res 2008;79:42-51

Cardiovascular Research

rafael.porcile@vaneduc.edu.ar

Effect of metoprolol and ivabradine on left ventricular remodelling and Ca^{2+} handling in the post-infarction rat heart

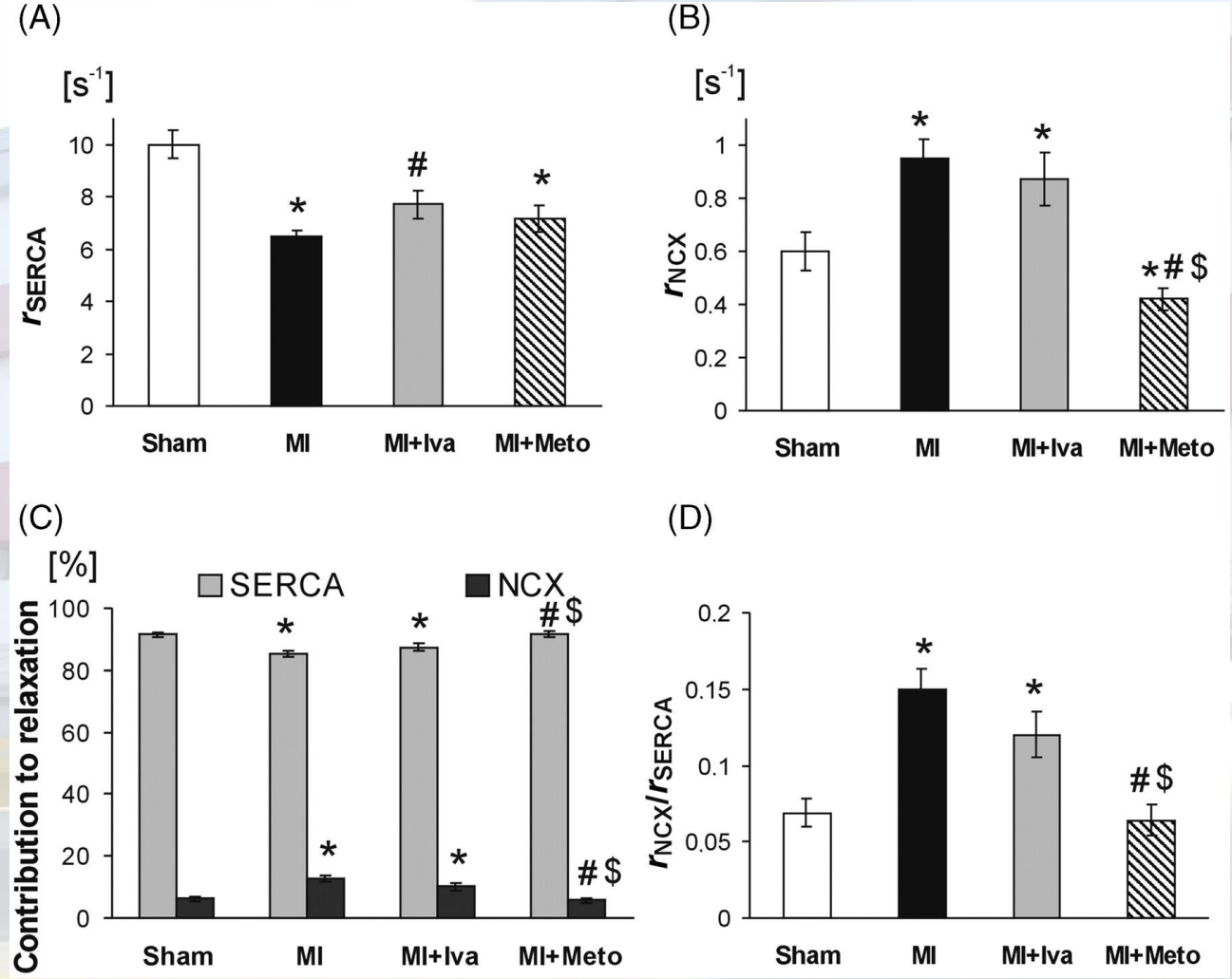
Michał Mączewski*† and
Urszula Mackiewicz†

Cardiovascular Research (2008) 79, 42–51
doi:10.1093/cvr/cvn057

Metoprolol, but not ivabradine, suppressed Na^{+}/Ca^{2+} exchanger (NCX) overactivity and normalized Ca^{2+} sensitivity of ryanodine receptors.

rafael.porcile@vaneduc.edu.ar

Ca2+ transport by sarcoplasmic reticulum Ca2+-ATP-ase and Na+/Ca2+ exchanger after myocardial infarction—the effect of ivabradine and metoprolol.

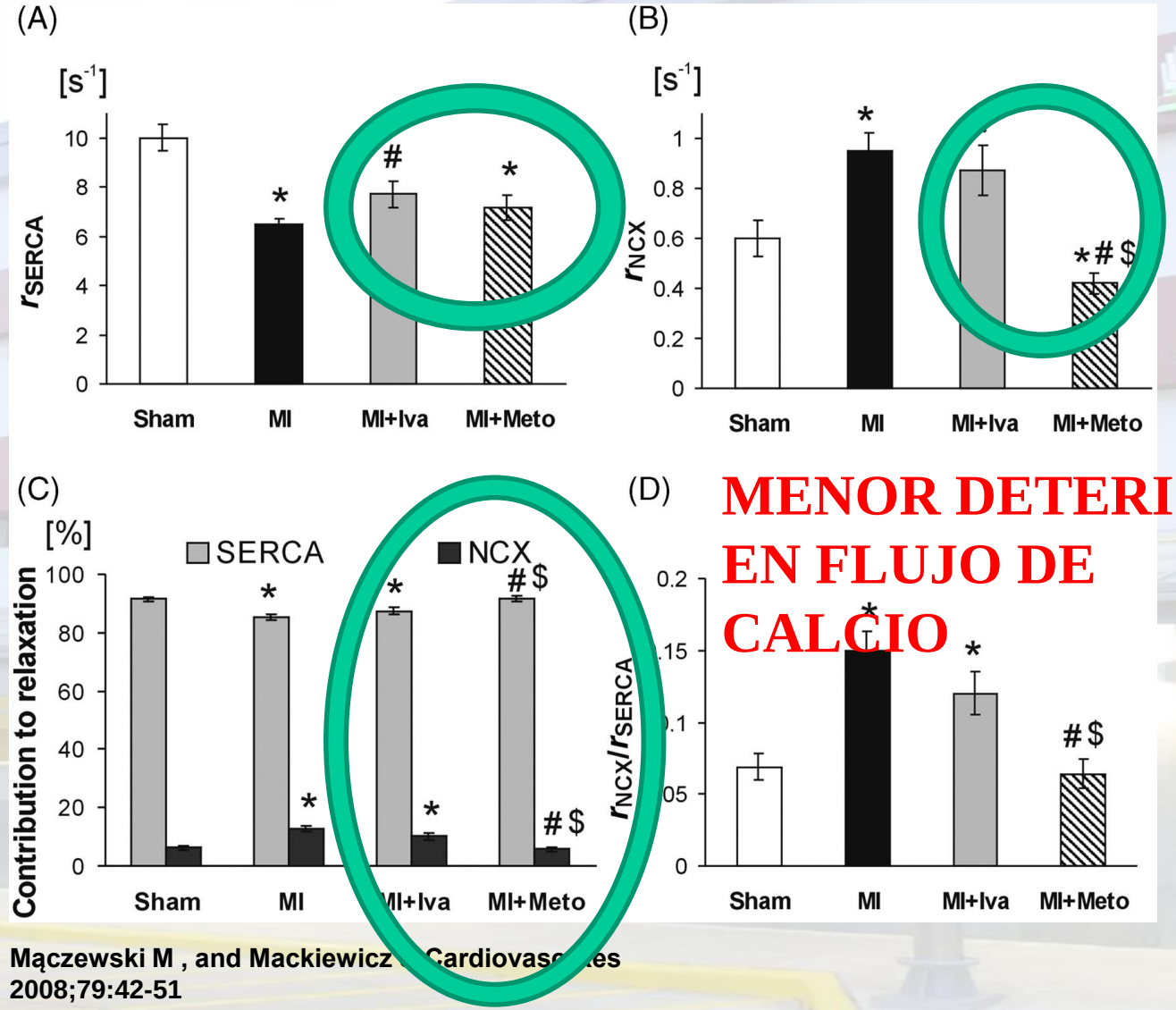


Mączewski M , and Mackiewicz U Cardiovasc Res 2008;79:42-51

Cardiovascular Research

rafael.porcile@vaneduc.edu.ar

Ca2+ transport by sarcoplasmic reticulum Ca2+-ATP-ase and Na+/Ca2+ exchanger after myocardial infarction—the effect of ivabradine and metoprolol.



MENOR DETERIORO EN FLUJO DE CALCIO

Mączewski M , and Mackiewicz Cardiovas es 2008;79:42-51

rafael.porcile@vaneduc.edu.ar

Effect of metoprolol and ivabradine on left ventricular remodelling and Ca^{2+} handling in the post-infarction rat heart

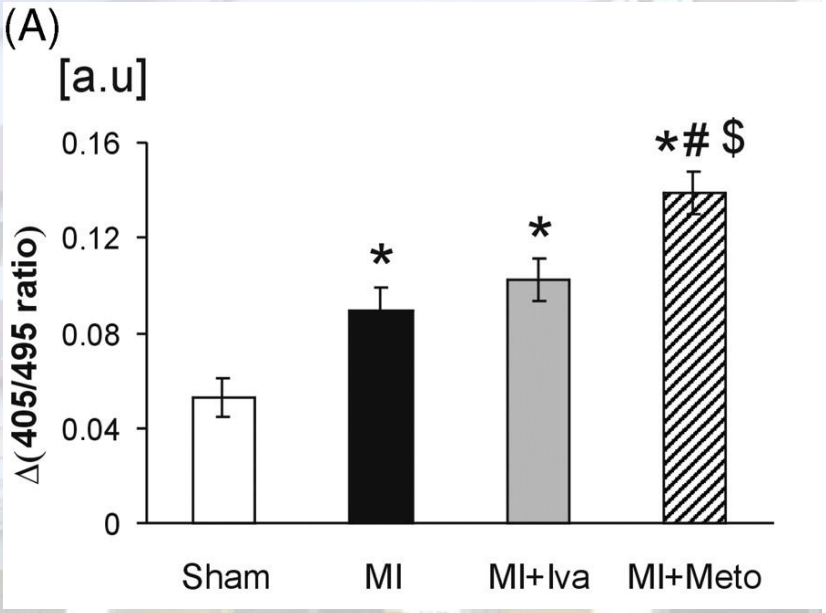
Michał Mączewski*† and
Urszula Mackiewicz†

Cardiovascular Research (2008) 79, 42–51
doi:10.1093/cvr/cvn057

Metoprolol, but not ivabradine, suppressed Na^{+}/Ca^{2+} exchanger (NCX) overactivity and normalized Ca^{2+} sensitivity of ryanodine receptors.

rafael.porcile@vaneduc.edu.ar

Diastolic sarcoplasmic reticulum Ca2+ leak after myocardial infarction—the effect of ivabradine and metoprolol.



The LV myocytes were incubated for 15 min with 10 μM Indo-1 acetoxymethyl ester as described by Spurgeon *et al.*[16] The ratio of 405–495 nm Indo-1 fluorescence for the diastolic and systolic Ca^{2+} concentration was obtained from the output of Dual Channel Ratio Fluorometer (Biomedical Instrumentation Group, University of Pennsylvania). The difference between the systolic and diastolic Indo-1 ratios was used as a measure of the amplitude of Ca^{2+} transients. Cell shortening was recorded with video edge detector (Cardiovascular Laboratories, School of Medicine, UCLA).

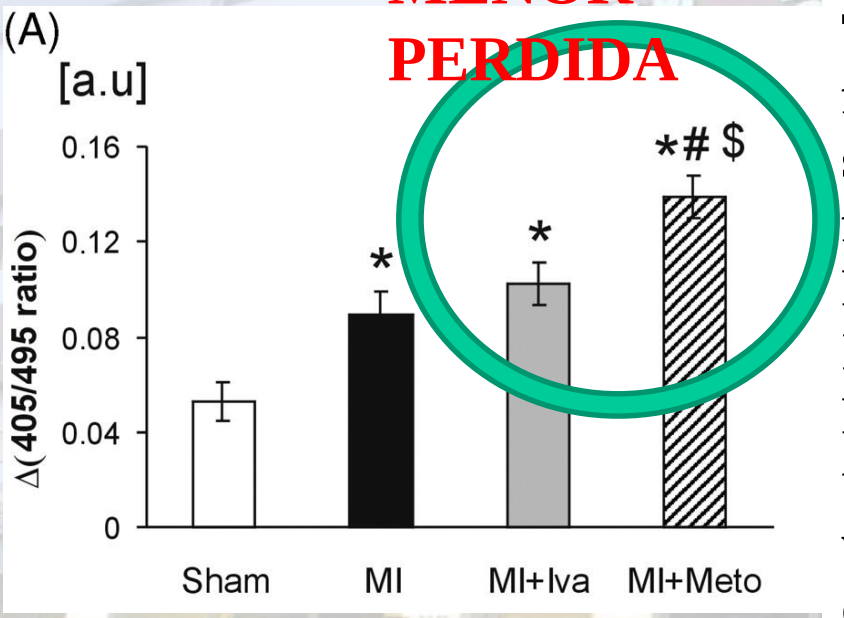
Mączewski M , and Mackiewicz U Cardiovasc Res 2008;79:42-51

Cardiovascular Research

rafael.porcile@vaneduc.edu.ar

Diastolic sarcoplasmic reticulum Ca2+ leak after myocardial infarction—the effect of ivabradine and metoprolol.

MENOR PERDIDA



The LV myocytes were incubated for 15 min with 10 μM Indo-1 acetoxymethyl ester as described by Spurgeon *et al.*[16] The ratio of 405–495 nm Indo-1 fluorescence for the diastolic and systolic Ca^{2+} concentration was obtained from the output of Dual Channel Ratio Fluorometer (Biomedical Instrumentation Group, University of Pennsylvania). The difference between the systolic and diastolic Indo-1 ratios was used as a measure of the amplitude of Ca^{2+} transients. Cell shortening was recorded with video edge detector (Cardiovascular Laboratories, School of Medicine, UCLA).

Mączewski M , and Mackiewicz U Cardiovasc Res 2008;79:42-51

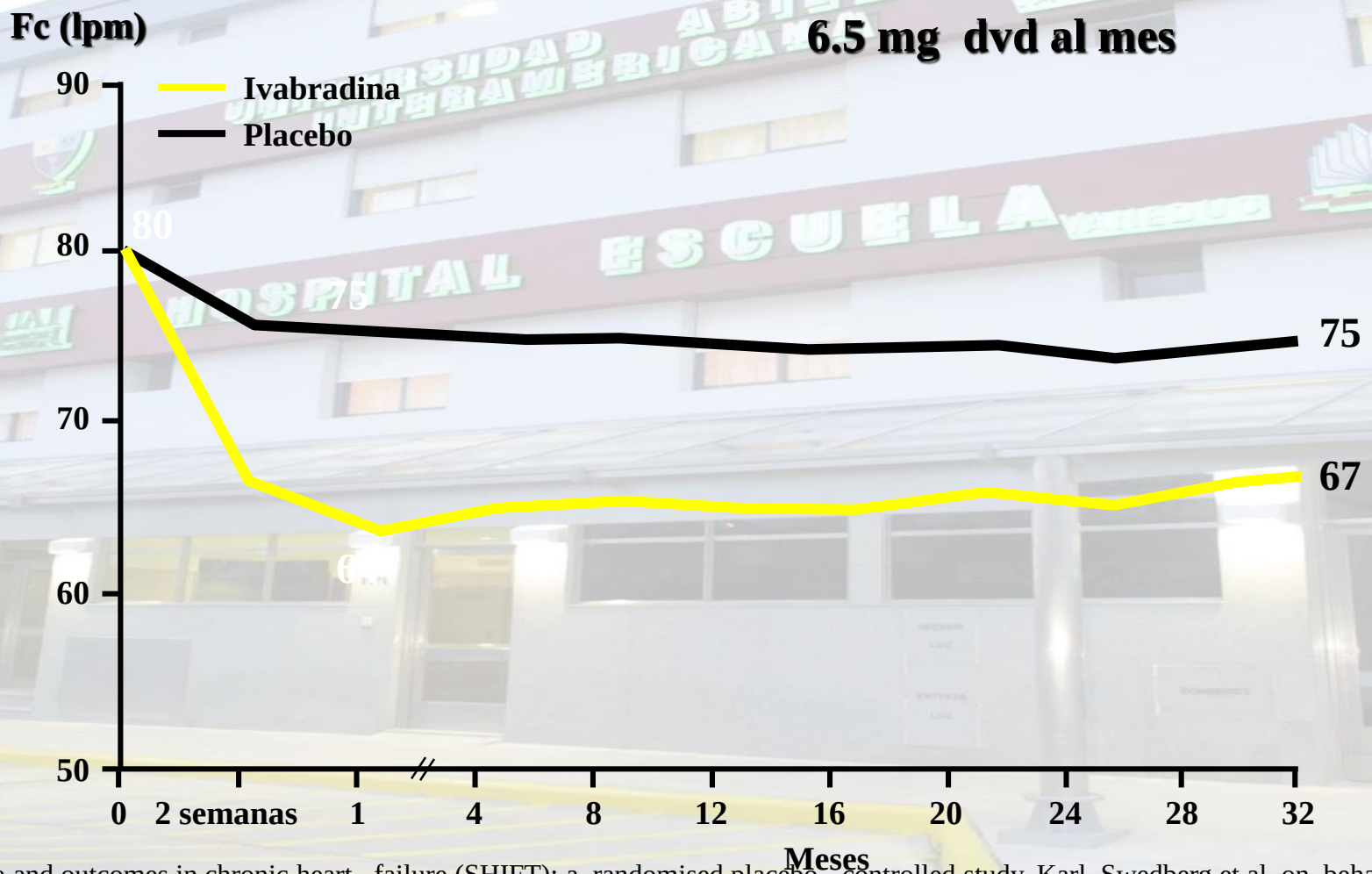
Cardiovascular Research

rafael.porcile@vaneduc.edu.ar

Reducción media de la Fc

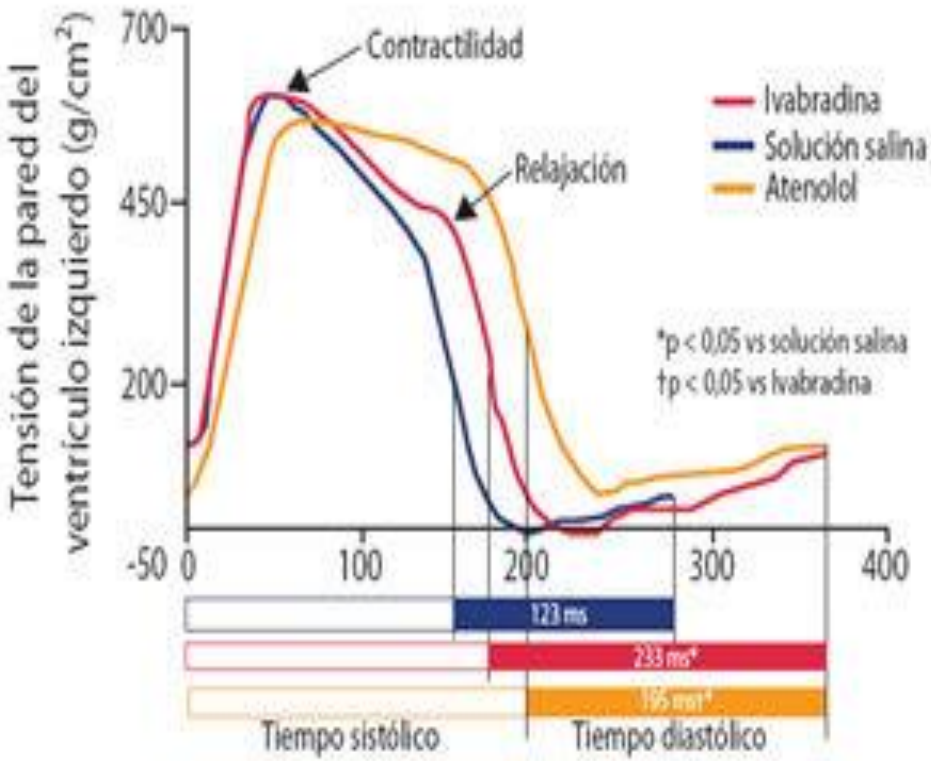
Dosis media de ivabradina: 6.4 mg dvd al mes

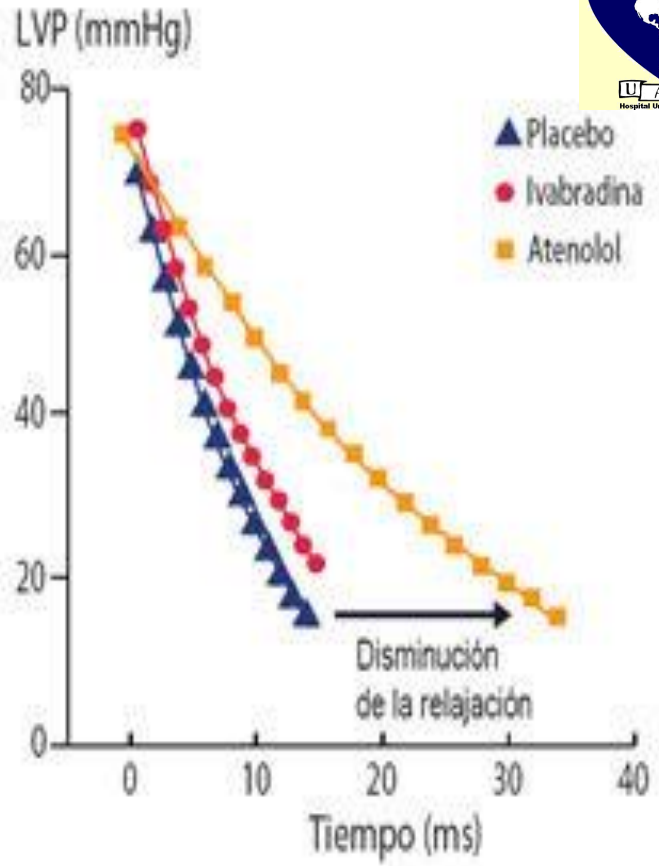
6.5 mg dvd al mes



Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo - controlled study. Karl Swedberg et al. on behalf of the SHIFT Investigators. Published on line August 29,2010. www.thelancet.com

rafael.porcile@vaneduc.edu.ar





Mayor aumento del tiempo diastólico comparado con betabloqueantes debido a que:

– Se mantiene la fuerza contráctil (no se prolonga la duración de la sístole en contraste con betabloqueantes)

– Se preserva la relajación del VI (sin efecto lusitrópico negativo), permitiendo una relajación completa y rápida.

Colin P, et al. *Am J Physiol Heart Circ Physiol.* 2003;284:H676-H682.

Figura 1. Ivabradina aumenta en mayor medida la diástole para una misma reducción de la frecuencia cardiaca.

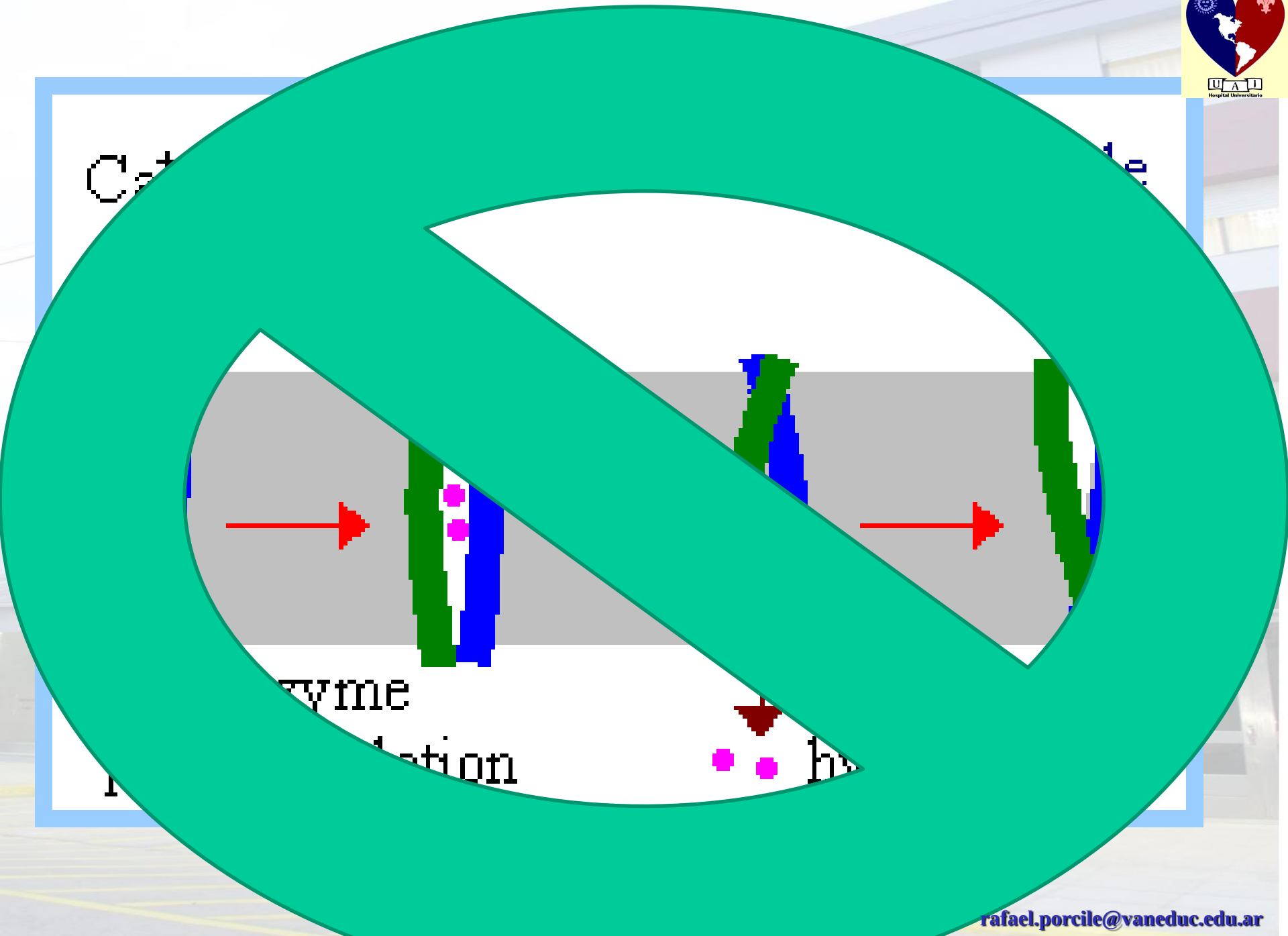
rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL UNIVERSITARIO

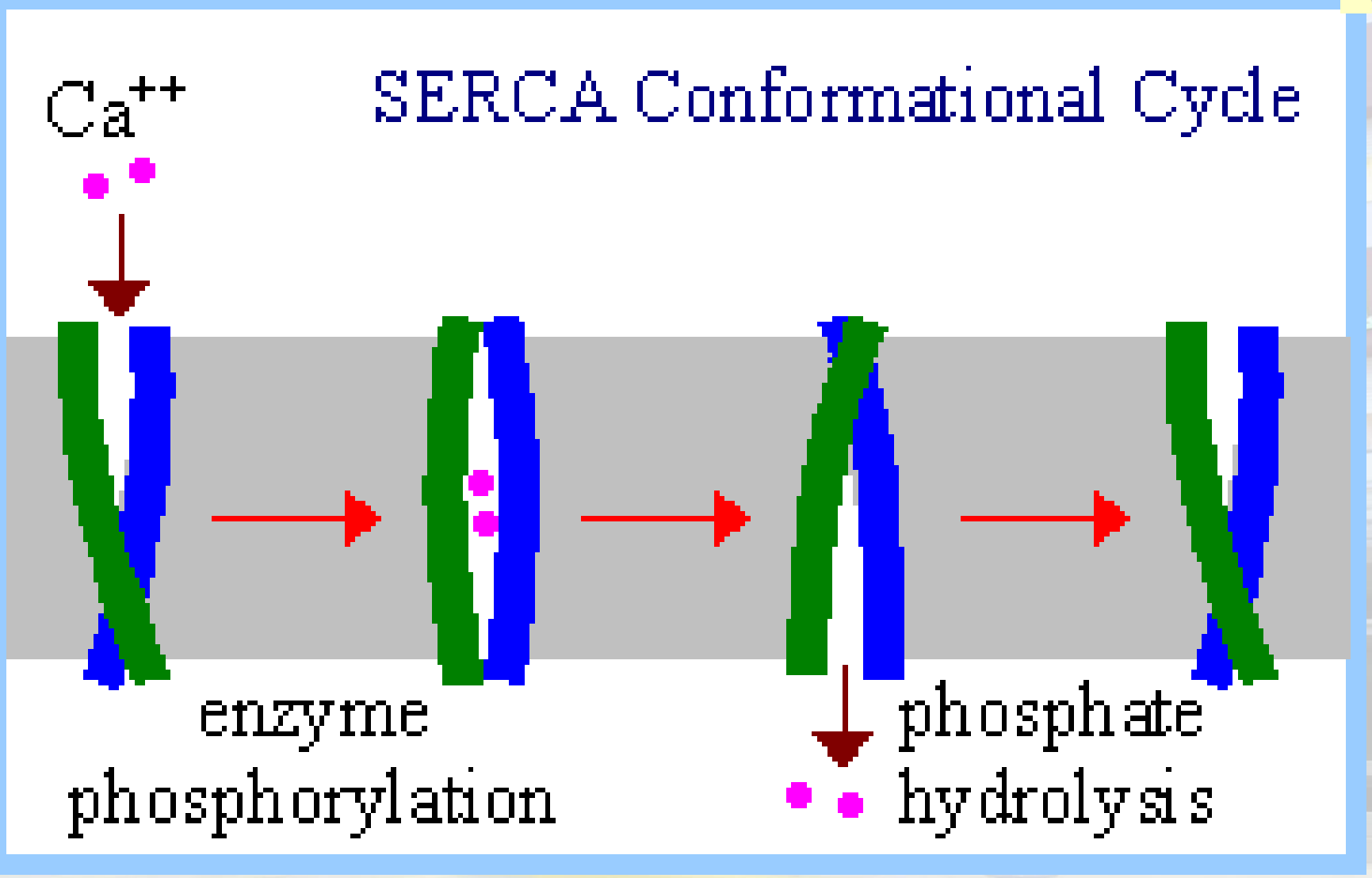
Departamento de Cardiología
UAI
Hospital Universitario

DEUDA DE OXIGENO

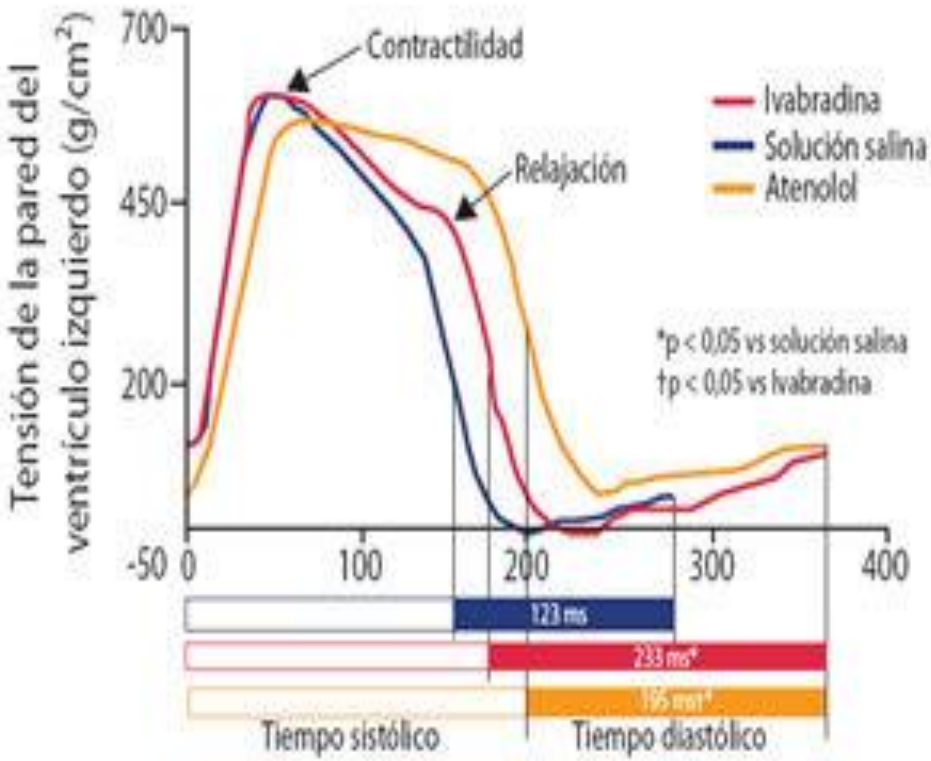
rafael.porcile@vaneduc.edu.ar

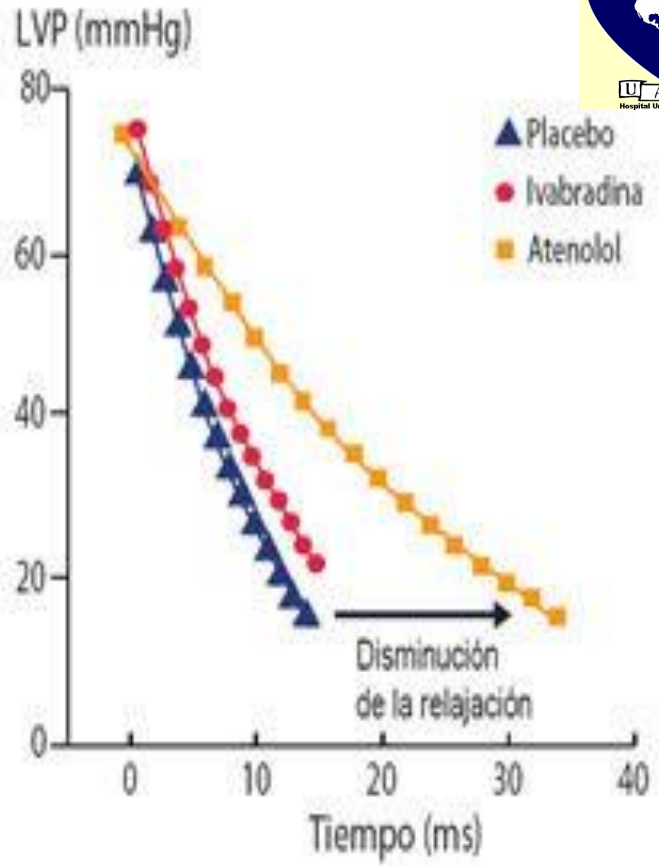


rafael.porcile@vaneduc.edu.ar



rafael.porcile@vaneduc.edu.ar





Mayor aumento del tiempo diastólico comparado con betabloqueantes debido a que:

– Se mantiene la fuerza contráctil (no se prolonga la duración de la sístole en contraste con betabloqueantes)

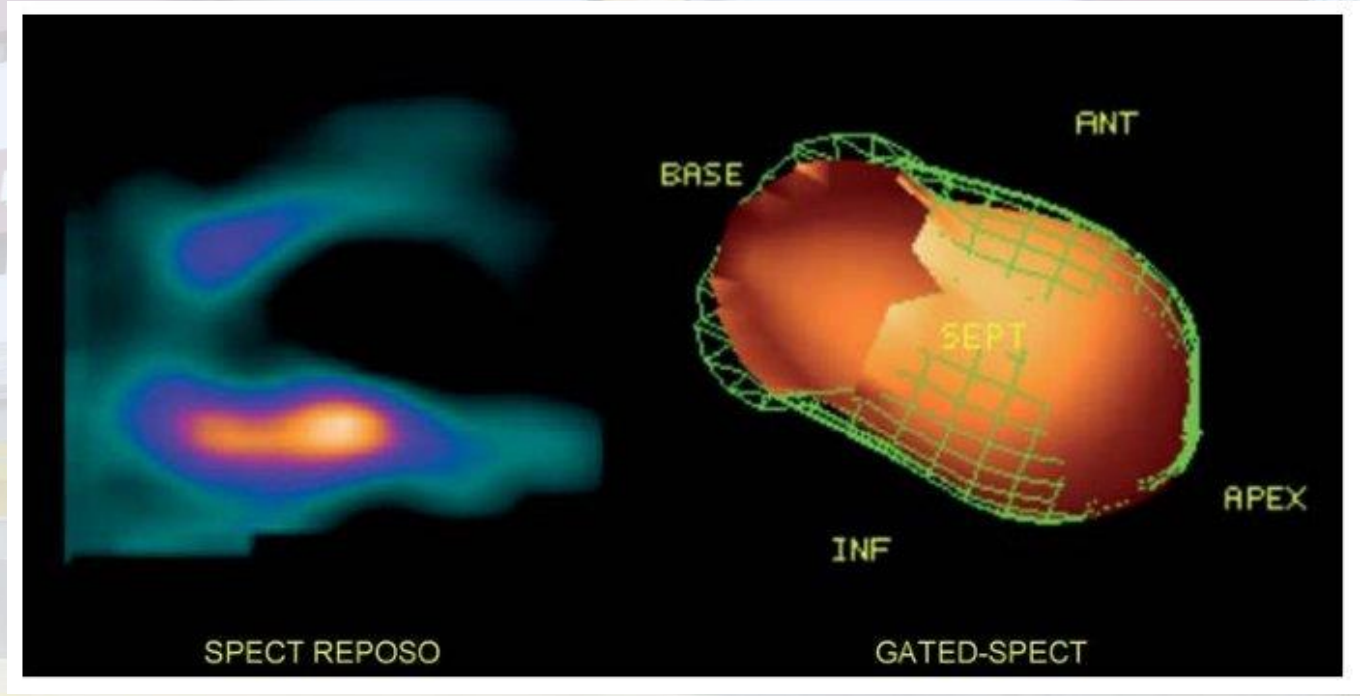
– Se preserva la relajación del VI (sin efecto lusitrópico negativo), permitiendo una relajación completa y rápida.

Colin P, et al. *Am J Physiol Heart Circ Physiol.* 2003;284:H676-H682.

Figura 1. Ivabradina aumenta en mayor medida la diástole para una misma reducción de la frecuencia cardiaca.

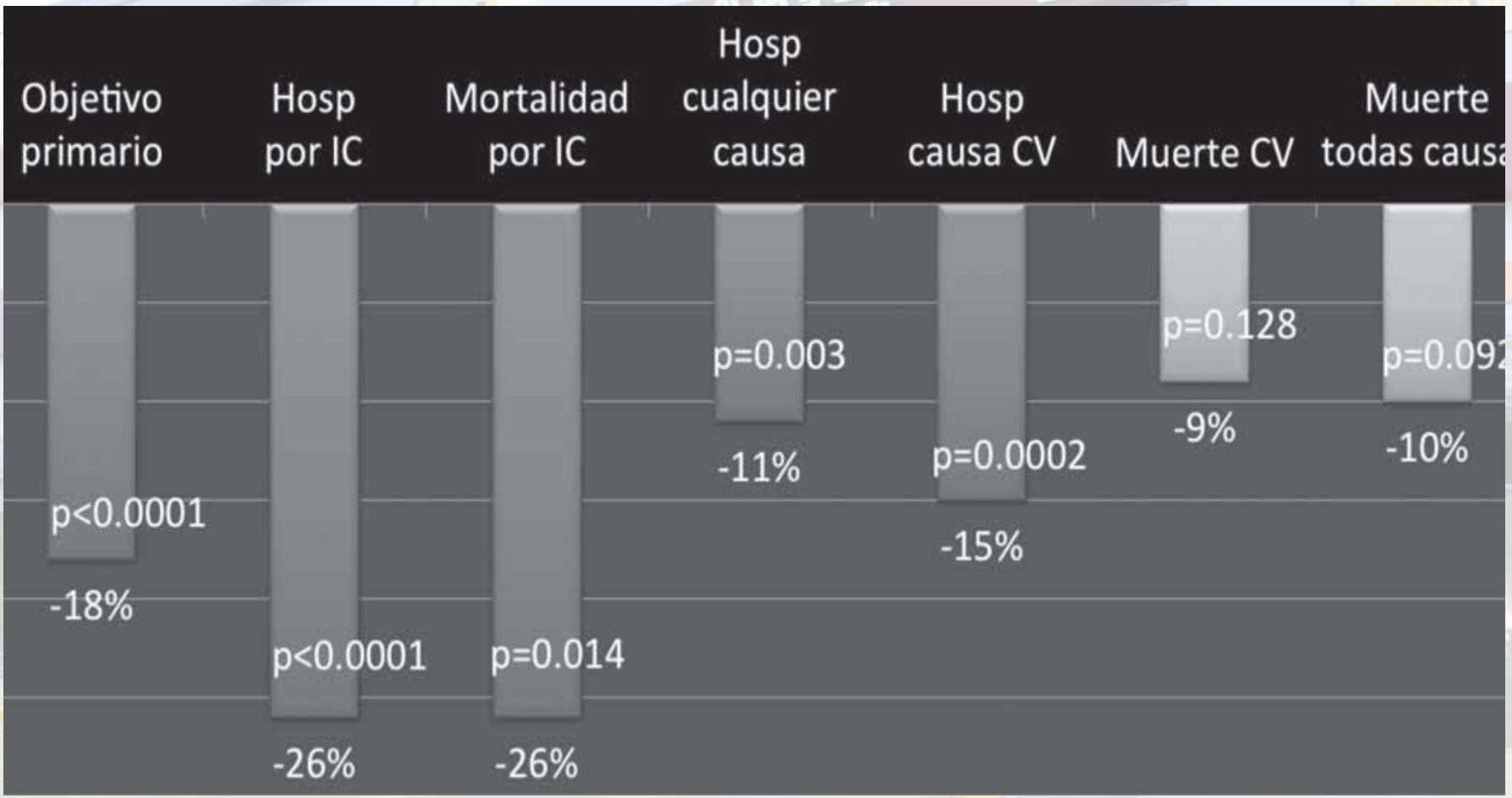
rafael.porcile@vaneduc.edu.ar

Aumenta el tiempo diastólico de perfusión



rafael.porcile@vaneduc.edu.ar

Efectos de la ivabradina



rafael.porcile@vaneduc.edu.ar

- Escaso calcio : Falla sistólica
- Calcio excesivo falla Diastólica
- Acortamiento critico del tiempo diastolico Falla sistodiastolica

rafael.porcile@vaneduc.edu.ar

- Calcio excesivo falla Diastólica
- Acortamiento critico del tiempo diastolico Falla sistodiastolica

rafael.porcile@vaneduc.edu.ar

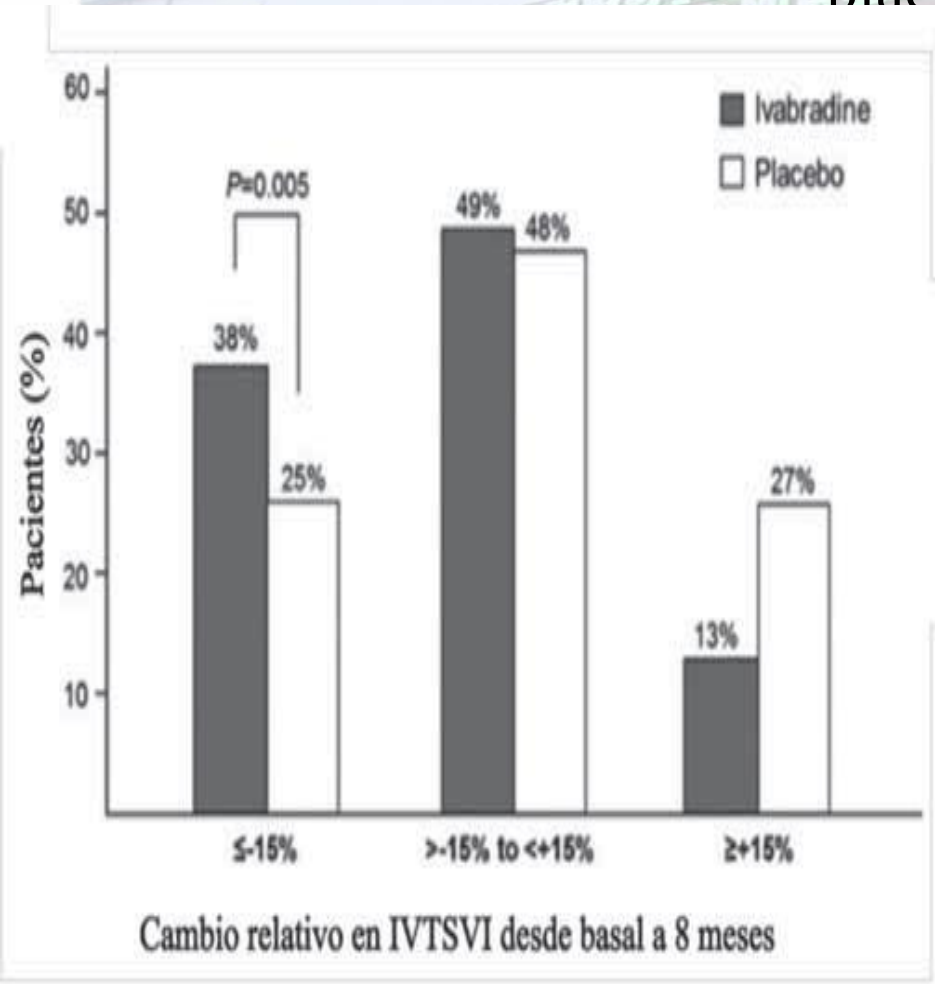
- Acortamiento critico del tiempo diastolico Falla sistodiastolica

rafael.porcile@vaneduc.edu.ar

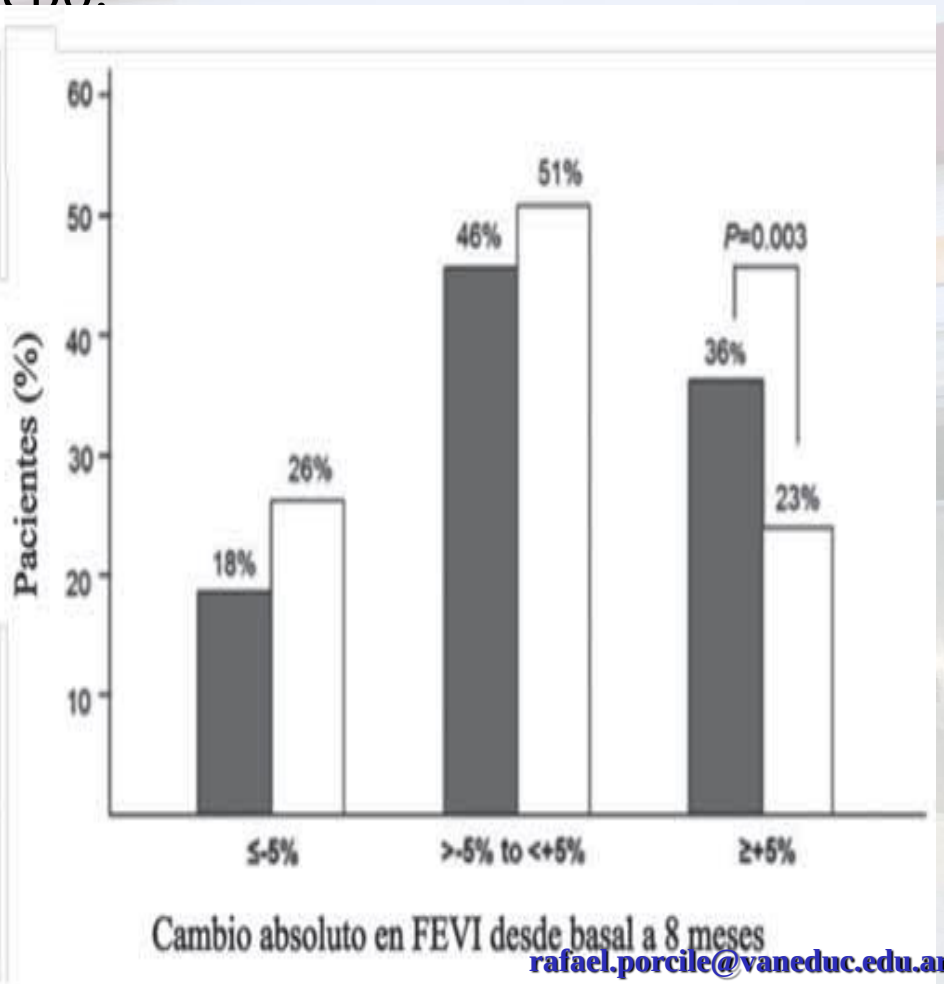
rafael.porcile@vaneduc.edu.ar

Remodelado ventricular, con cambio relativo en índice de volumen telesistólico ventricular izquierdo (IVTSVI)

y FEVI tras 8 meses de tratamiento, en grupo ivabradina y grupo placebo.



Cambio relativo en IVTSVI desde basal a 8 meses

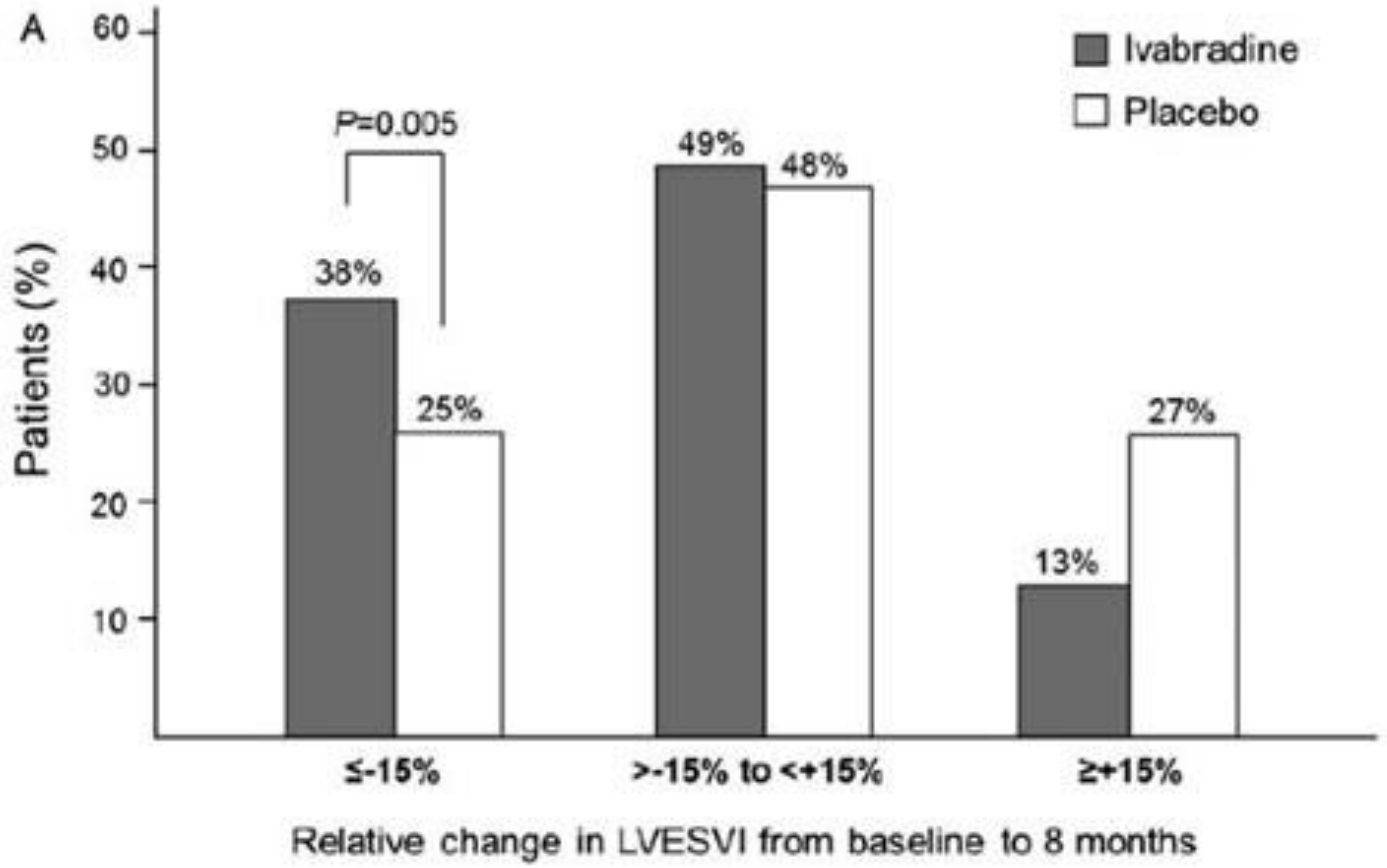


Cambio absoluto en FEVI desde basal a 8 meses

rafael.porcile@vaneduc.edu.ar

Studio SHIFT: sottostudio ECOcardiografico

Effetto di ivabradina sulla modificazione del volume ventricolare sinistro a 8 mesi di follow up.

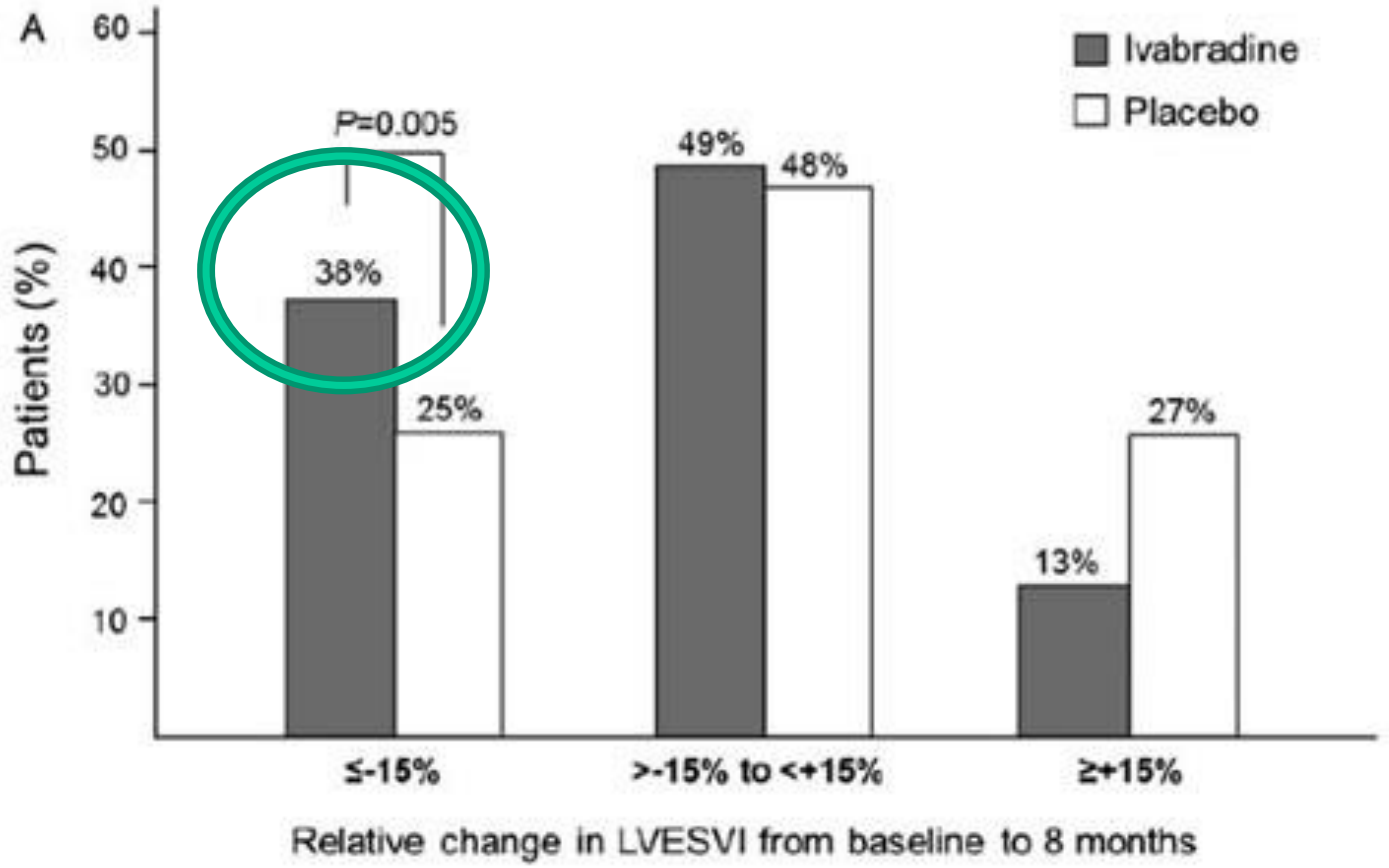


rafael.porcile@vaneduc.edu.ar

ESC Congress 2011, Parigi

Studio SHIFT: sottostudio ECOcardiografico

Effetto di ivabradina sulla modificazione del volume ventricolare sinistro a 8 mesi di follow up.

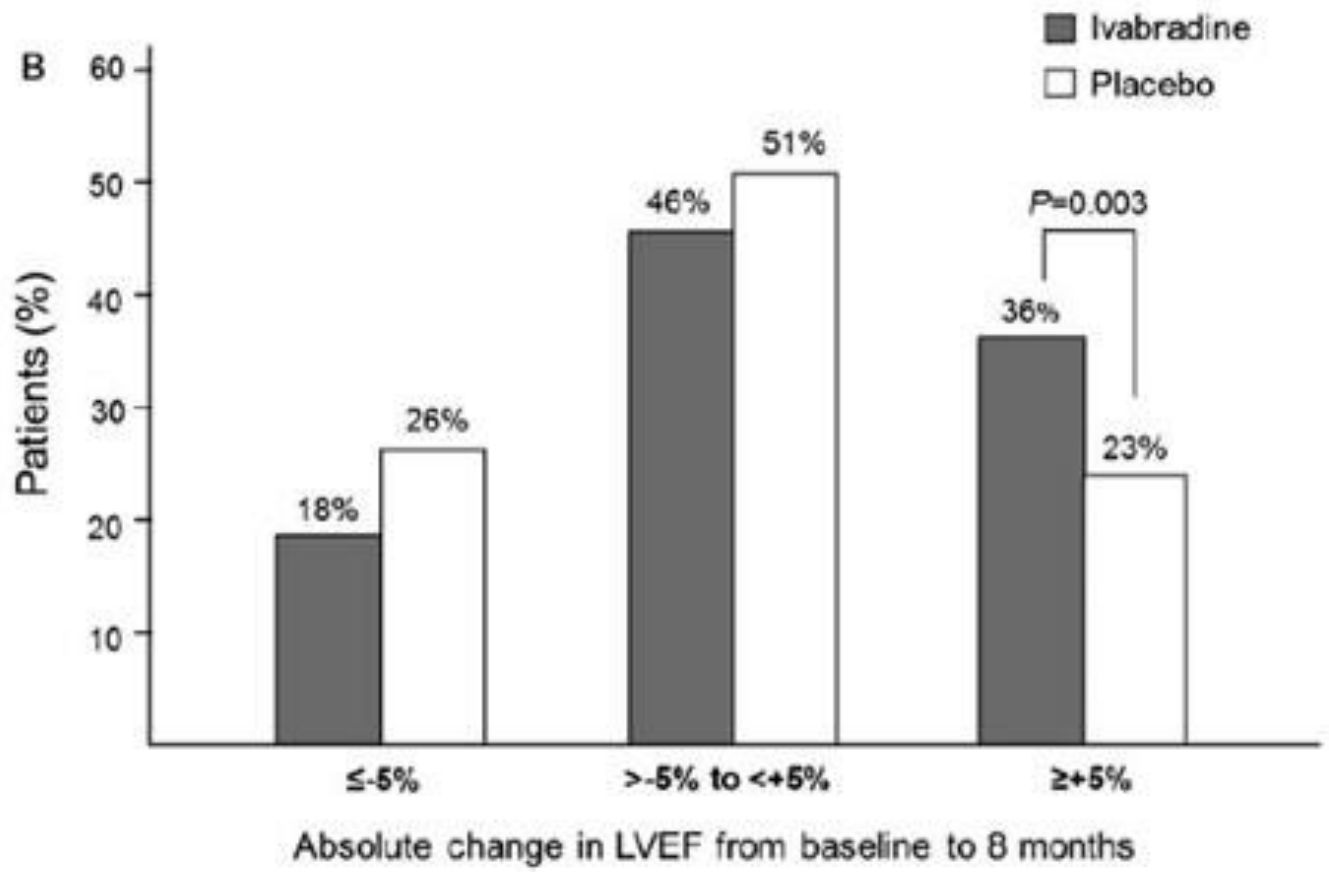


rafael.porcile@vaneduc.edu.ar

ESC Congress 2011, Parigi

Studio SHIFT: sottostudio ECOcardiografico

Effetto di ivabradina sulla modificazione della Frazione d
Eiezione a 8 mesi di follow up.

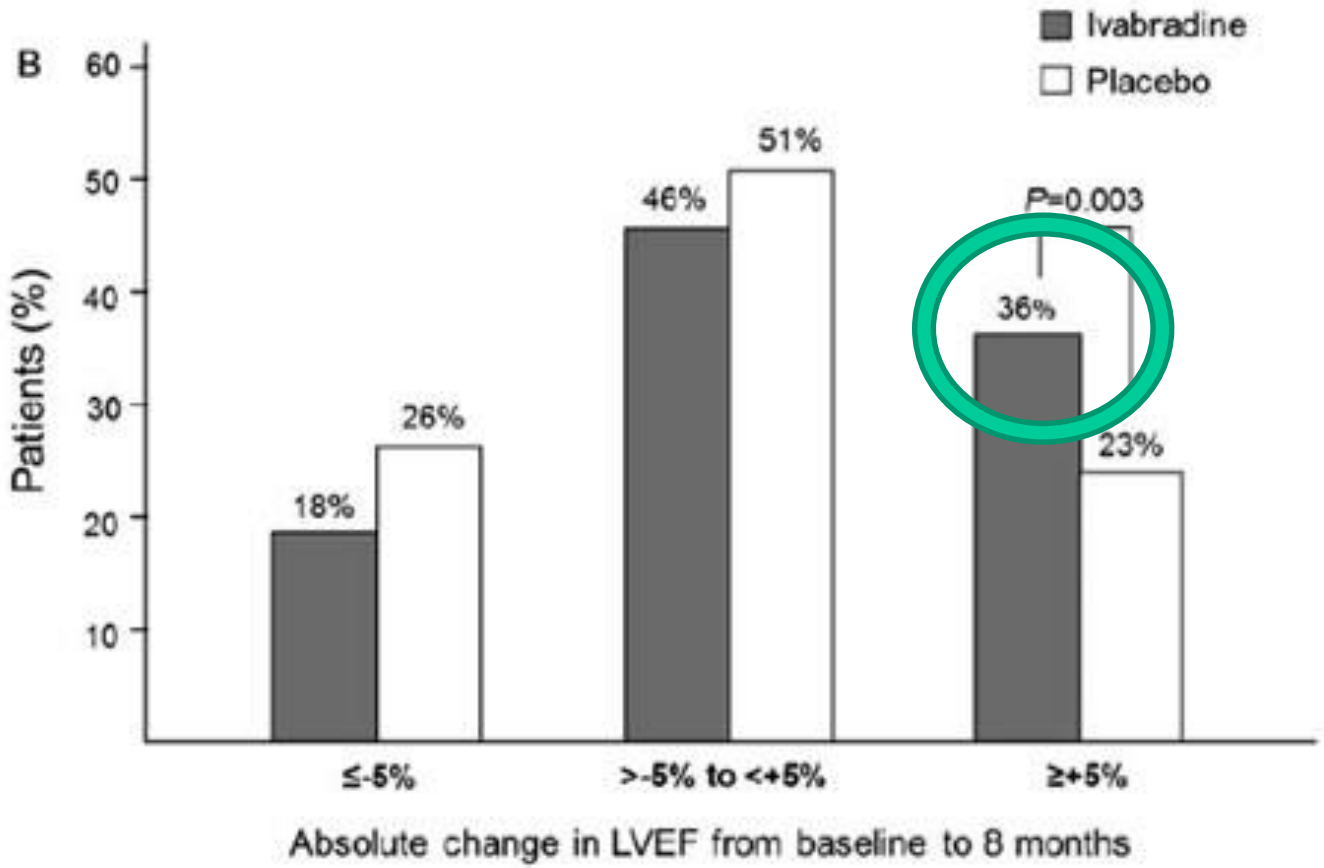


rafael.porcile@vaneduc.edu.ar

ESC Congress 2011, Parigi

Studio SHIFT: sottostudio ECOcardiografico

Effetto di ivabradina sulla modificazione della Frazione di Eiezione a 8 mesi di follow up.



rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

CRONOTROPICOS NEGATIVOS

DROGA	DIGITAL	Bloquentes Calcicos	BETA Bloquentes	IVABRADINA
FRECUENDIA CARDIACA	-	-	- -	- -
CALCIO CITOPLASMATICO	++	- - -	-	0
INOTROPISMO	+	-	-	+
DURACIÓN DIASTOLE	-	+	++	+++
EXITABILIDAD	++	0	--	0

rafael.porcile@vaneduc.edu.ar

8th International Conference on Acute Cardiac Care Jerusalem, Israel. June 1618, 2013

Hemodynamic Effects of Ivabradine in patients with acute circulatory decompensation and Tachycardia.

Porcile Rafael , Ricardo Levin, Gabriel Perez Baztarrica, Osvaldo Fridman, Flavio Salvaggio, Sebastian Villecco ,Norberto Blanco Alejandro Botbol

rafael.porcile@vaneduc.edu.ar

Objetivos: Evaluar el efecto hemodinámico de la ivabradina utilizada para reducir la taquicardia sinusal durante el tratamiento de la insuficiencia cardiaca avanzada bajo terapia inotrópica

rafael.porcile@vaneduc.edu.ar

- ENERO 2011 ENERO 2013
- Prospectiva consecutiva
- 39 PACIENTES
- Edad promedio 63+/-7
- 20 hombres 19 mujeres
- FEVI eco 28.5+/- 3

rafael.porcile@vaneduc.edu.ar

- Insuficiencia cardíaca avanzada
- Isquémico necrótica
- Al menos 10 gamas kg min de inotrópicos combinados
- Taquicardia sinusal

rafael.porcile@vaneduc.edu.ar

- Shock
- Fibrilación auricular
- Sepsis
- Asistencia circulatoria mecánica
- Asistencia respiratoria mecanica

rafael.porcile@vaneduc.edu.ar

Ivabradina vía ORAL

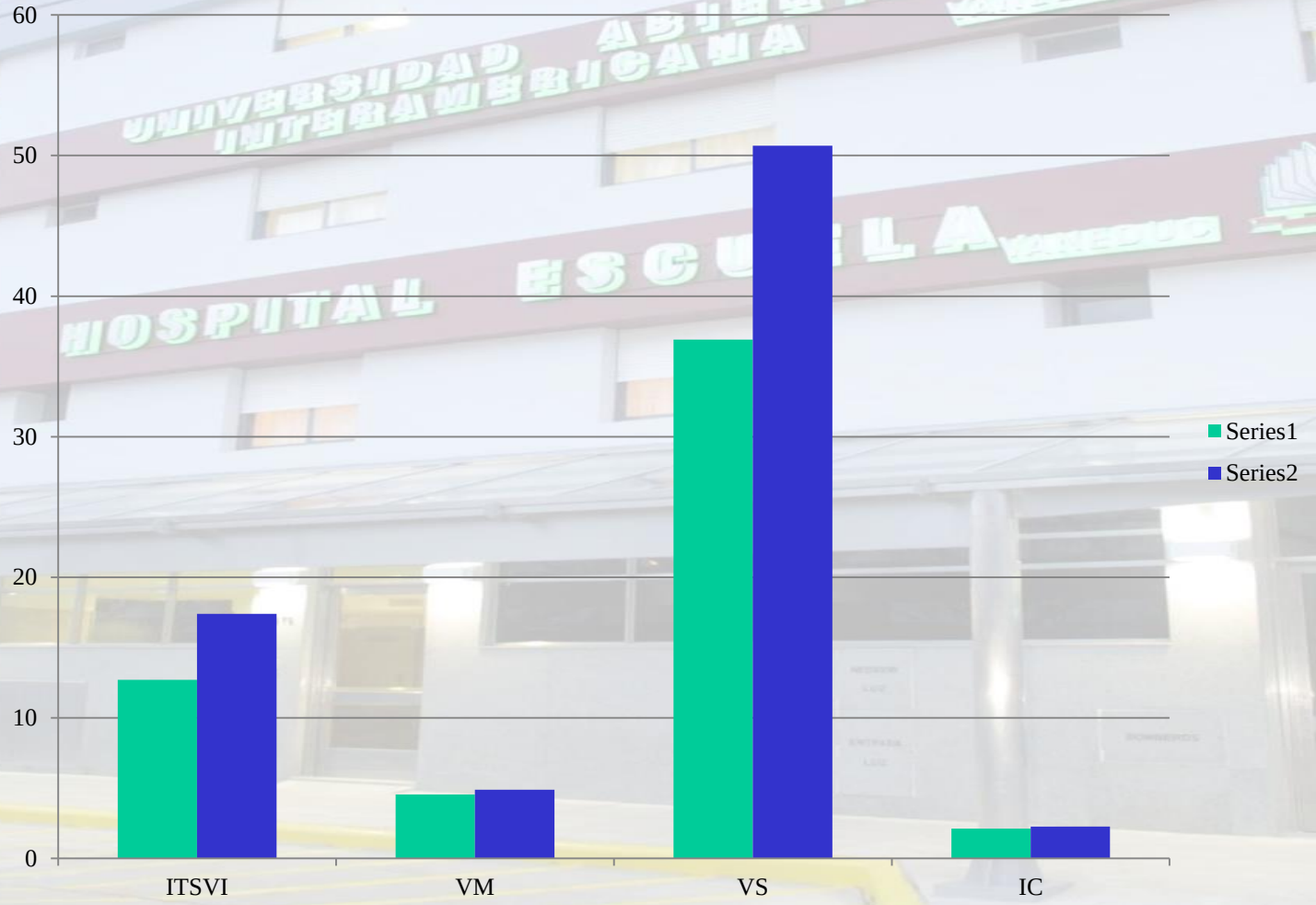
- 15 mg de como dosis inicial
- 7.5 mg vía oral cada 12 hs por 24 horas

rafael.porcile@vaneduc.edu.ar

Reducción de la frecuencia cardíaca 122 A 97 P0.0001

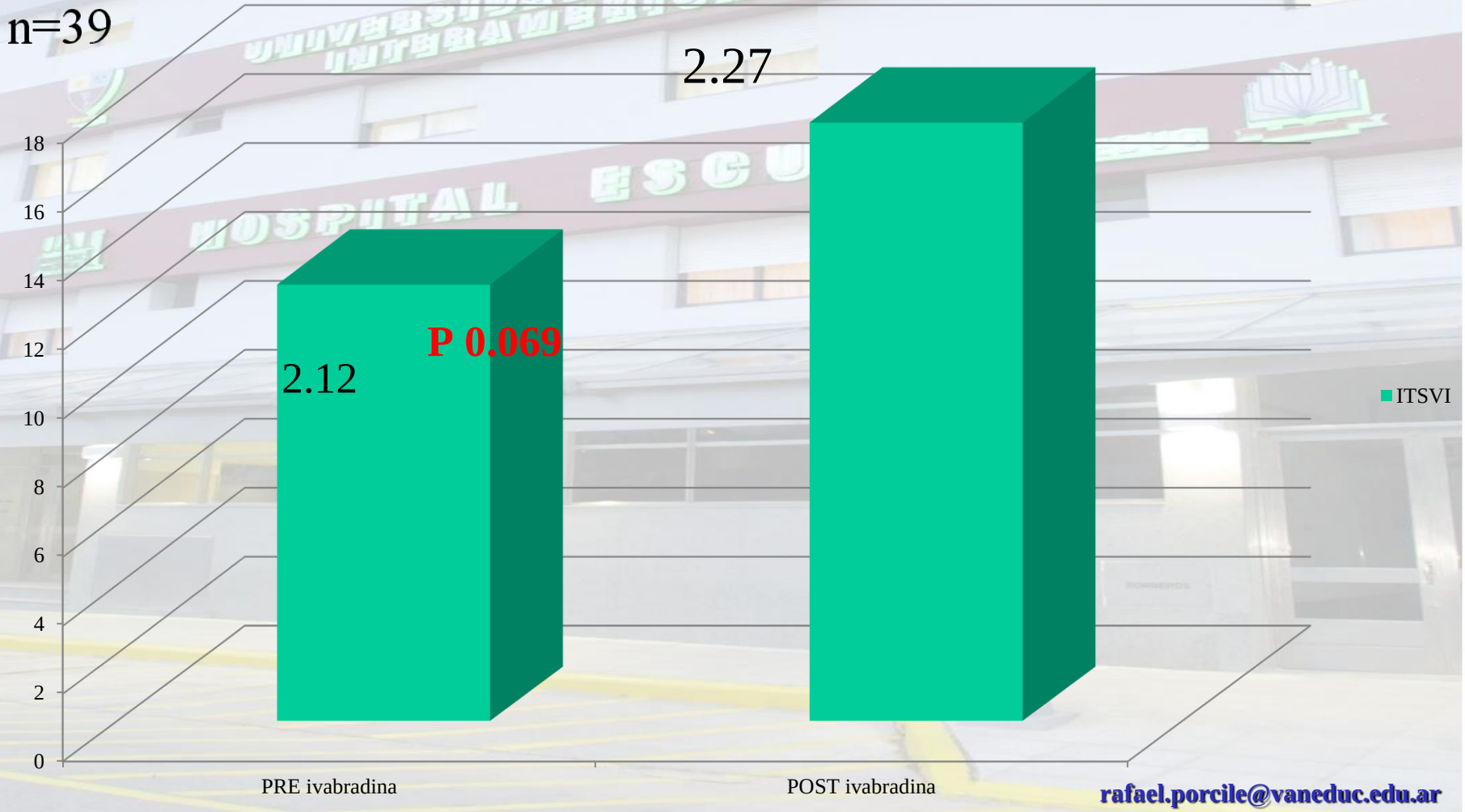
rafael.porcile@vaneduc.edu.ar

Parámetros de función sistólica



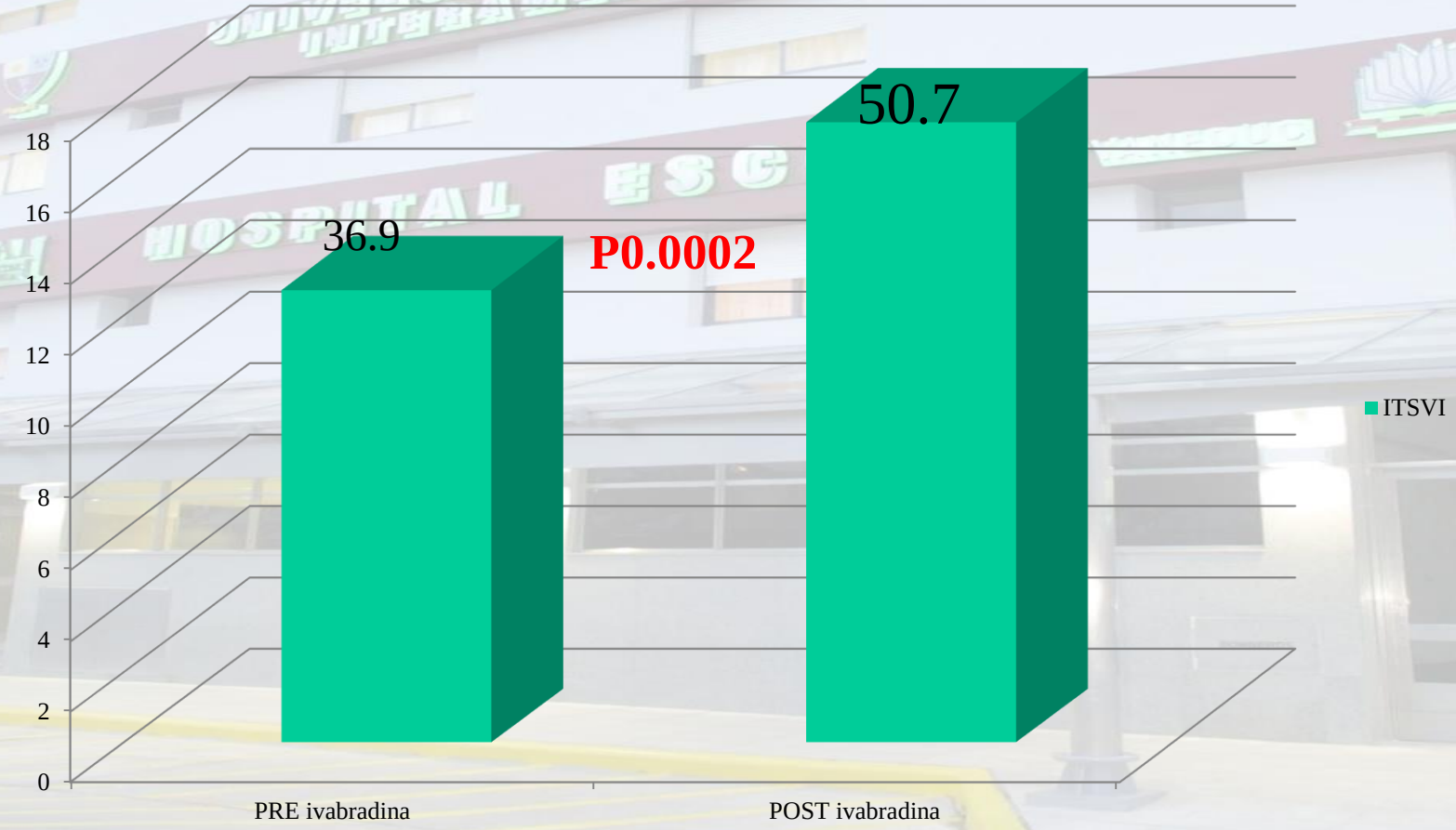
rafael.porcile@vaneduc.edu.ar

Diferencias en termino de índice cardíaco



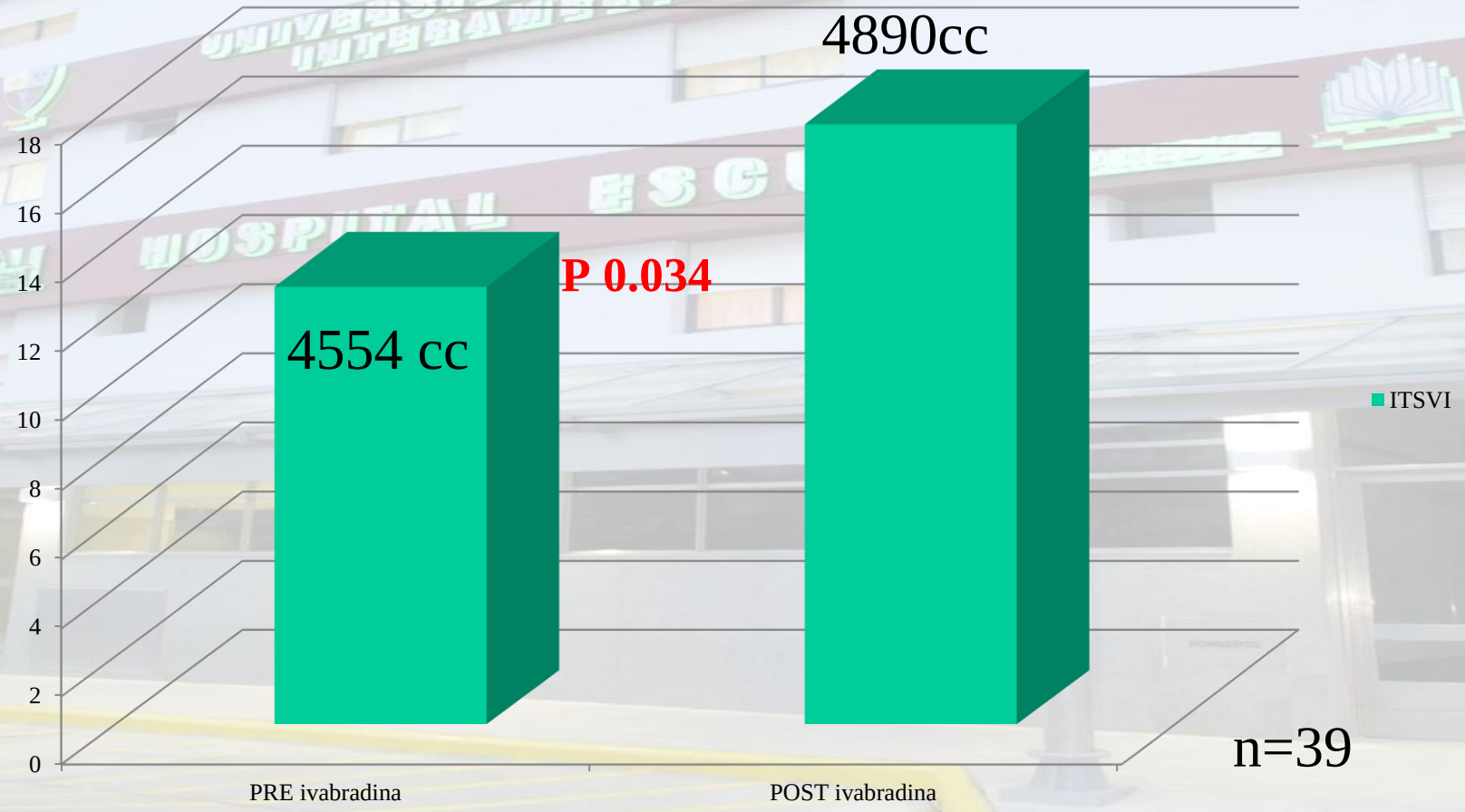
rafael.porcile@vaneduc.edu.ar

Diferencias en volumen sistólico



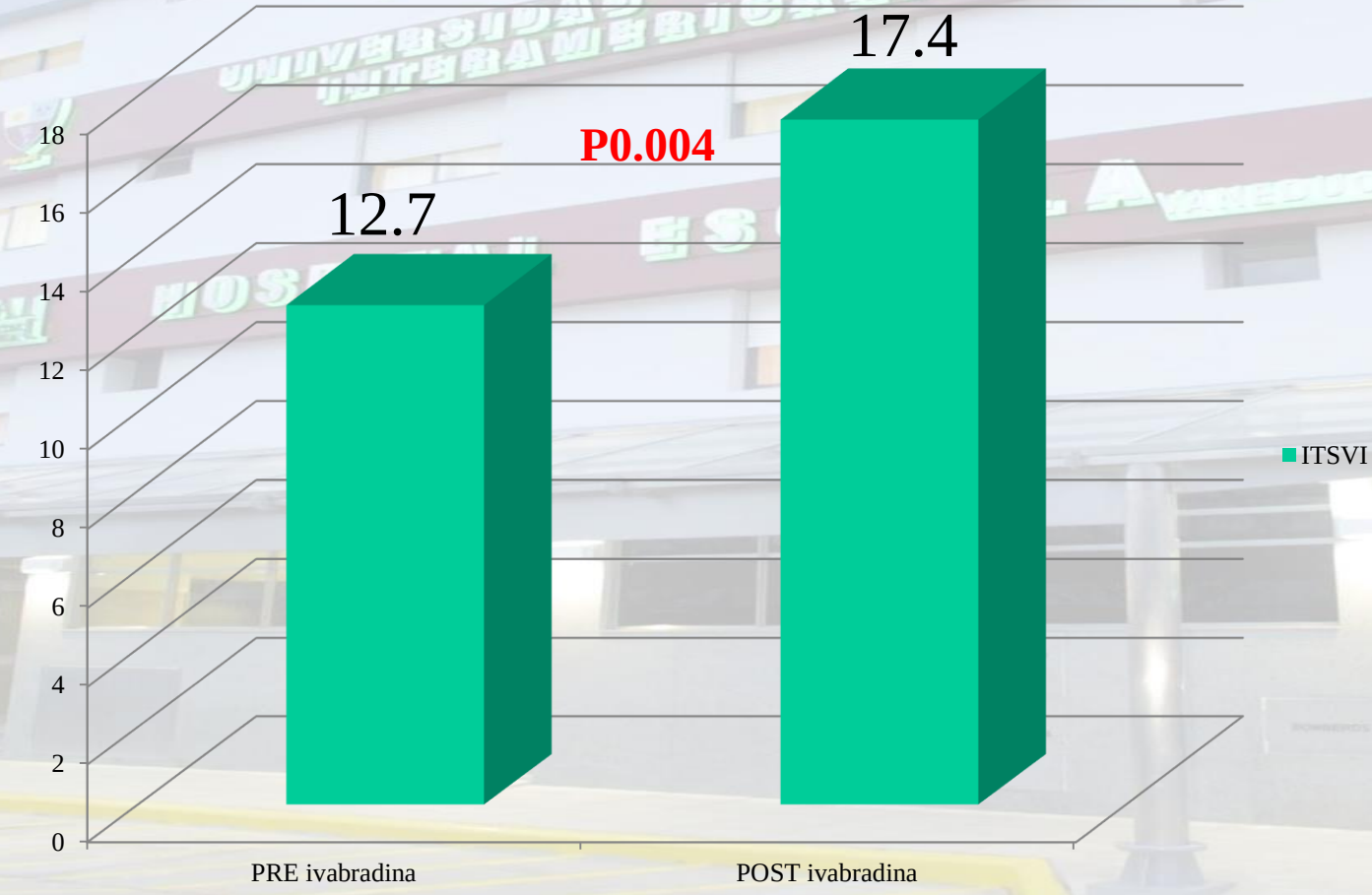
rafael.porcile@vaneduc.edu.ar

Cambios en el Volumen minuto cardiaco



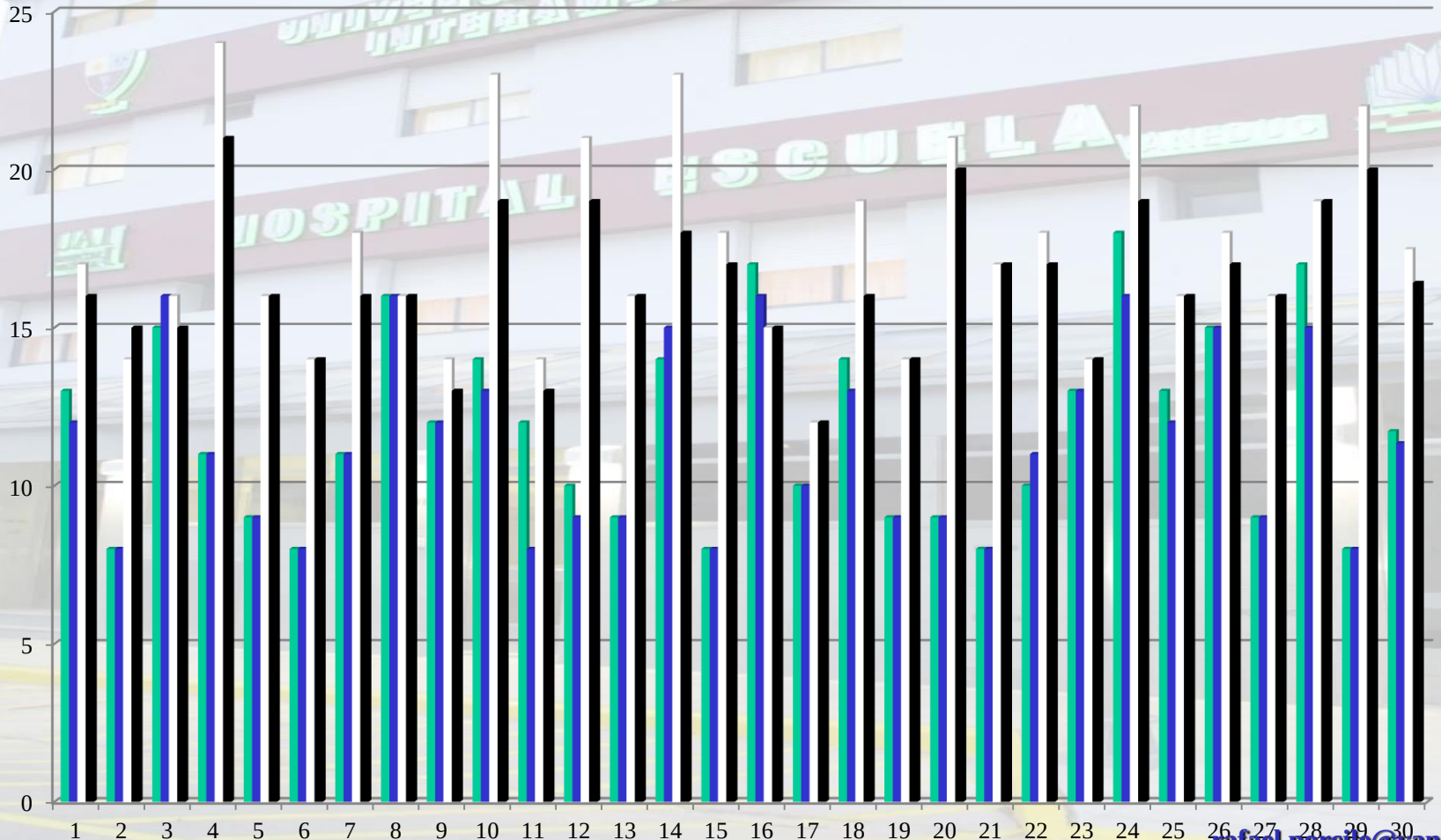
rafael.porcile@vaneduc.edu.ar

DIFERENCIAS EN INDICE DE TRABAJO SISTOLICO DEL VENTRICULO IZQUIERDO



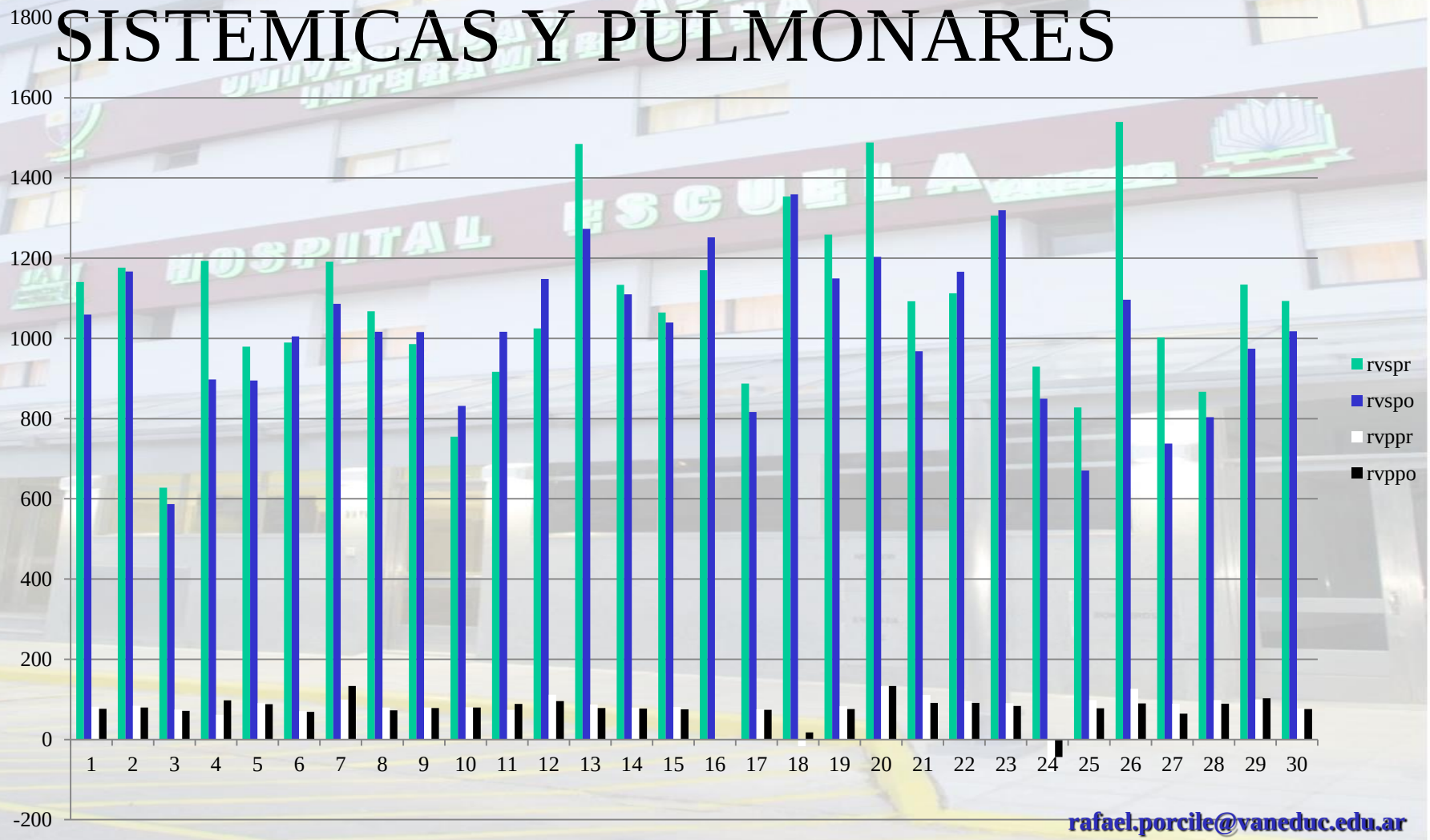
rafael.porcile@vaneduc.edu.ar

SIN DIFERENCIAS SIGNIFICATIVAS EN LA MEDICÍON DE PRESIONES IZQUIERDAS Y DERECHAS



rafael.porcile@vaneduc.edu.ar

SIN DIFERENCIAS SIGNIFICATIVAS EN LA MEDICÍON DE RESISTENCIAS VASCULARES SISTEMICAS Y PULMONARES



rafael.porcile@vaneduc.edu.ar

Efecros hemodinamicos de la ivabradina medidos con catetes de swan ganz en pacientes con descompensación circulatoria aguda, terapia inotropica y taquicardia sinusal

Dres : PORCILE Rafael ,FRIDMAN Osvaldo, PEREZ BAZTARRICA Gabriel, SALVAGGIO Flavio, VILLACCO Sebastian, BOTBOL L Alejandro

Departamento de Cardiología UAI Hospital Universitario; Cátedra de Fisiología y Biofísica, Universidad Abierta Interamericana (UAI)Consejo Nacional de Investigaciones Científicas y Técnica (CONICET) Buenos Aires

Objetivos: Evaluar el efecto hemodinámica de la ivabradina utilizada para reducir la taquicardia sinusal durante el tratamiento de la insuficiencia cardiaca avanzada bajo terapia inotrópica

Criterios de inclusión

insuficiencia cardíaca avanzada

Isquémico necrótica

Al menos 10 gamas kg min de inotrópicos combinados

Taquicardia sinusal

Crirerios de exclusión

Shock

Fibrilación auricular

Sepsis

Asistencia circulatoria mecánica

Asistencia respiratoria mecánica

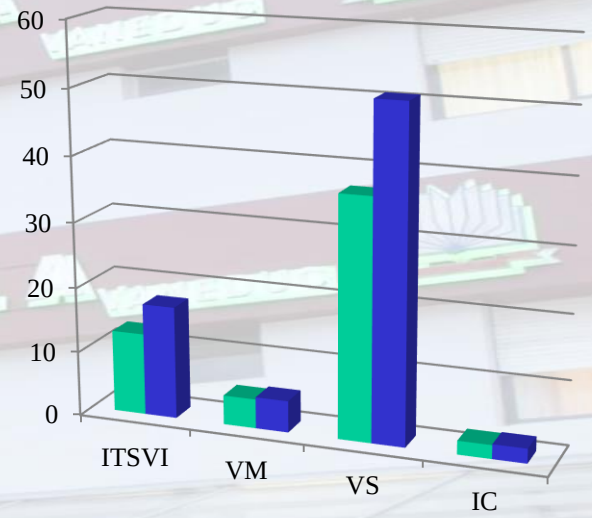
MATERIALES Y METODOS

-Ritmo sinusal con mas de 100 pm de frecuencia

-Insuficiencia cardíaca descompensada de etiología isquémico necrótica refractara al tratamiento oral y endovenoso convencional

-Terapia inotrópica endovenosa con , al menos, una sumatoria de 10gmas/Kgpeso/minuto y al menos 2.2 litros /m^2 superficie corporal de índice cardíaco.

-Se realizaron mediciones con catéter de Swan Ganz antes y tres horas después de la administración de 15 mg de ivabradina vía enteral.



Resultados: El estudio incluyó a 39 pacientes (20 hombres y 19 mujeres) con edad promedio de 63 +/-7 años, ingresados por insuficiencia cardíaca avanzada de etiología isquémico necrótica con indicación de terapia inotrópica . La fracción de eyección promedio del ventriculo izquierdo fue del 28,5%. La dosis de fármacos inotrópicos promedio fue de 13.5 gam/Kg/Min. Se observó una reducción de la frecuencia cardíaca promedio 3 horas después de la primera dosis de ivabradina de 122+/-7 lat/min a 97+/- 8 lat/min (p0.001). Leve pero significativo aumento del Volumen minuto cardíaco promedio de 4554cc+/-637 a 4890+/-516cc (p0, 034) El rendimiento cardíaco evaluado por el índice cardíaco promedio tambien aumento pero este incremento no resulto estadísticamente significativo subiendo de 2,12+/-0.3 l/m2 a 2.27+/--0.07 l/m2 (p0,069) . El volumen sistólico promedio se incrementó significativamente de 36.9 +/-6cc a 50.7 +/-7cc (p 0,0002). Aumento también significativamente el índice de trabajo sistólico del ventriculo izquierdo promedio de 12,7 +/-4 a 17,4+/5 (p 0,004). No se observaron cambios en la presión capilar pulmonar 17+/-3 mmHg vs 16+/- 4mmHg (p0.16), resistencias vasculares sistémicas 1.093 Dyn+/-211n vs 1.018+/-189Dyn (p 0.163)Tampoco se observaron cambios significativos en las presiones auriculares derechas 11.7+/-3 mmHg vs 11.3+/2mmhg(p0.063) ni en la tension artrerial media arterial sistemica promedio (73.1+/-10 vs 73.2+/-11) ni presión arterial pulmonar media promedio 21.7 mm Hg vs 21.1 mm Hg (p 0.18) . No observamos bradicardia o bloqueo auriculoventricular en ningún paciente . El tratamiento fue bien tolerado por todos los pacientes. No observaron óbitos relacionados a efectos esperados del fármaco dentro de las 5 vidas media luego de su discontinuación.

Conclusiones: En los pacientes con insuficiencia cardiaca bajo inotropicos y taquicardia sinusal la administración de ivabradina es útil y segura para reducir la frecuencia cardiaca sin reducir el gasto cardiaco, presiones ni resistencias Se ha observando un aumento del volumen minuto cardiaco estadisticamente significativo en centimetros cubicos asi como en todos los indices de funsión sistólica pero no se observó significación estadistica en terminos de indice cardiaco. Este es un efecto potencialmente útil en especial en paciente con falla cardiaca de etiología isquemico necrótica.

WCC 2014 Melbourne· Australia

Hemodynamic Effect Of Ivabradine Used To Reduce Sinus Tachycardia During Intra Aortic Conterpusation In Patiente Whit Advanced Cardiac Failure

Rafael Porcile 1,*, Osvaldo Fridman 2, Ricardo Levin 1, Gabriel Perez Baztarrica 1, Botbol Alejandro 1, Milanino Ana 3

1CARDIOLOGY and Physiology Dep, U.A.I Universitary Hospital , 2CARDIOLOGY, C.O.N.I.C.E.T., Buenos Aires , Argentina

rafael.porcile@vaneduc.edu.ar

Methods: Between January 2011 and August 2013 were prospectively included patients in sinus rhythm with more than 100 heart beat pm admitted in to the U.A.I. critical cardiology unite with decompensated dilated ischemic cardiomyopathy .
All patients treated with at least 10gmas/Kg/min of one or more IT (unchanged during measurement period).
No less than 2,2 liters/m2 SG measered cardiac index.
Optimized IABP setting remain unchanged durin measurement period.
Were excluded patients in schock of others causes, infections, renal failure, anemia, requiring or mechanical ventilation support or whith acute digestive desease.
SG measurements were performed one hour before and three hours after a single oral dosis of 15mg ivabradine.

rafael.porcile@vaneduc.edu.ar

Results:

The study included 22patients (12men).
All whith miocardial infarction history.
Age average of 65.5 years.
Left ejection fraction average was 27.3%.
Dose of intravenous inotropic drug average was **17.2Kg/w/min.**
Three hours after ivabradine **heart rate decreased from 123+/-5 to 97+-5 (P0.0003)**
Increase cardiac output of 4452+-550 ml minute at 4925+-535 ml/min(p0.031).
Increase in cardiac index without statistical significance of 2.21+/-0.3 to 2.37+/-0.3 liters/m (p0.08).
The average stroke volume increased significantly from 33.9 +-5 to 52.3 +-8 ml(p0.0007).
The left ventricule work index increased from 12.9 +-3 to 17.3 +-4 (p0.00003).
No differences were observed in the records of right atrial pressure ,wedge ,systemic vascular and pulmonary resistance.
After five ivabradine half-lives suspension no ecg or clinical adverse effects were observed

rafael.porcile@vaneduc.edu.ar

Conclusion: Ivabradine is useful to moderate sinus tachycardia an and improve efficiency of IABP in advanced heart failure.
Ivabradine use did not interfere with IT showing an improvement in some cardiac output parameters.
No changes were observed in preload and afterload parameters in this set of patients.
No electrocardiographic or clinical adverse effects were observed.

rafael.porcile@vaneduc.edu.ar

If Channels blocker Ivabradine Counteracts Undesirable Tachycardia in Patients Supported With Inotropic Agents

(*Safety, tolerability and efficacy of Ivabradine for control of sinus tachycardia in patients undergoing inotropic therapy*)

Ricardo Levin MD, Marcela Degrange MD, Flavio Salvaggio MD, Gabriel Perez Baztarrica MD, Norberto Blanco MD, Alejandro Botbol MD, Rafael Porcile MD

Department of Cardiology, University Hospital, Universidad Abierta Interamericana University. Buenos Aires. Republica Argentina

Authors have no disclosure to declare

INTRODUCTION

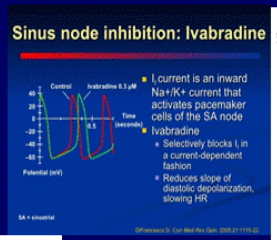
Use of intravenous inotropic therapy in decompensated patients is associated with several adverse consequences such as increased myocardial oxygen consumption, pro-arrhythmic effects and myocardial ischemia, and unavoidably produces undesirable sinus tachycardia.

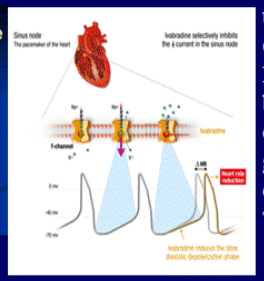
Therapeutic options for patients presenting with undesirable sinus tachycardia are extremely limited. Beta-blockers cannot be considered due to their negative inotropic effects and use of calcium channel blockers has proved to be deleterious. Furthermore, digitalis increases myocardial oxygen consumption.

Published results support the utility of the If channel inhibitor Ivabradine in patients with low ejection fraction, heart failure and sinus rhythm, as well as in individuals developing undesirable sinus tachycardia induced by exogenous catecholamines after major surgery.

Accordingly, the current study aimed to analyze the safety, tolerability and efficacy of Ivabradine in patients with ischemic cardiomyopathy admitted for decompensated heart failure who developed undesirable sinus tachycardia while undergoing treatment with intravenous inotropic agents.

OBJECTIVES: To assess the safety, tolerability and efficacy of Ivabradine administered to patients with decompensated heart failure who were undergoing inotropic therapy and developed undesirable sinus tachycardia.





METHODS

Population : patients with ischemic cardiomyopathy and low ejection fraction (<35%) admitted for decompensated heart failure who experienced sinus tachycardia (heart rate >100) while undergoing inotropic therapy (≥10 mcg/kg dopamine or dobutamine separately or in combination) were included Patients were treated with oral Ivabradine in an attempt to counteract sinus tachycardia.

Inclusion criteria
- Ischemic cardiomyopathy
- age >18 years
- systolic blood pressure >90 mmHg without vasopressors
- ''stabilized CI''>2.2 L/min/m2 (6 h before administration of Ivabradine)
- absence of hypovolemia (CVP >10, PCOP >15 mmHg)

Exclusion criteria
- nonischemic etiology
- shock (of any cause)
- respiratory mechanical support
- need for circulatory mechanical support
- inability to take oral medications
- concomitant active infections
- oncological or acute digestive pathologies
- hemodynamic instability (6 h)
- hypersensitivity to Ivabradine
- inability to place a PAC
- a heart rhythm other than sinus.

Treatment : Ivabradine was administrated as a single oral dose of 15 mg. Hemodynamic monitoring was performed using PAC. Complete hemodynamic measurements were collected 1 h before and 3 h after the administration of Ivabradine. Safety and tolerance: The development of sinus bradycardia, new atrioventricular disturbances, requirement of temporary pacemakers, symptomatic hypotension, and general intolerance presenting as nausea, vomiting, diarrhea or visual side effects was evaluated.

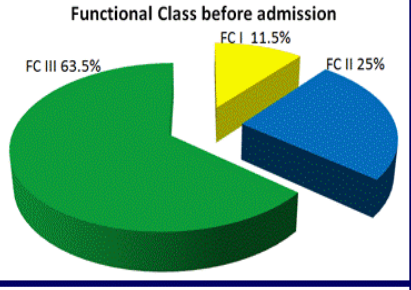
The institutional research ethics committee approved the present study. Informed consent was obtained from all patients or their guardians. Statistical analysis : P<0.05 was considered to be

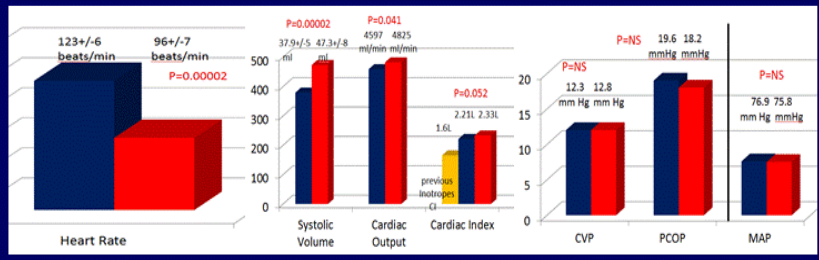
RESULTS: 52 patients were admitted between 1/1/2011 and 6/1/2013. Table 1 summarizes patient's general characteristics. Average Left Ventricle EF was 31.5%

Immediately before Ivabradine the mean dose of inotropes was 11.2 mcg/kg

Table I

Characteristic	Number (n=52)	Percentage
Males (p)	32	(61.5%)
Females (p)	20	(38.5%)
Average age (years)	65.6	
Age range (years)	42-76	
Diabetes (p)	10	(19.2%)
Smoking (p)	18	(34.6%)
Hypertension (p)	28	(53.8%)
Dyslipidemia (p)	37	(71.15 %)
Previous myocardial infarction (p)	33	(63.5%)
Previous surgery (p)	4	(7.7%)
Previous angioplasty (p)	41	(78.8%)

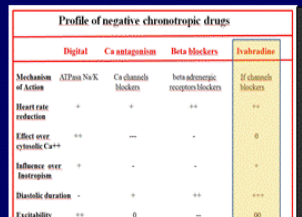


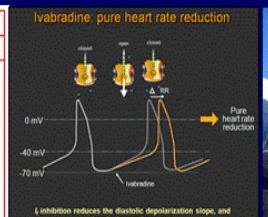


Side effects : None of the patients experienced bradycardia, new AV conduction disturbances, or required transitory pacemaker.

Intolerance to Ivabradine was not observed in any patients during a length of time equal to 5 half lives of the drug (60 hs of observation)

Conclusion: Ivabradine was useful and safe for achieving selective negative chronotropic effects , counteracting undesirable sinus tachycardia which developed in patients with decompensated HF treated with inotropic agents, who could not receive beta blockers. Randomized studies with an appropriate number of patients are needed to collect more information regarding this suggested benefit





rafael.porcile@vaneduc.edu.ar

UAI
HOSPITAL UNIVERSITARIO

MUCHAS GRACIAS POR SU ATENCIÓN

Departamento de Cardiología
U A I
Hospital Universitario