58^ Congresso Nazionale
Società Italiana di Gerontologia e Geriatria

Torino, 27 novembre 2013

La regolazione del sistema nervoso simpatico dall'invecchiamento all'insufficienza cardiaca: *un approccio traslazionale*

Franco Rengo, MD

Direttore Istituto Scientifico di Telese Terme - IRCCS
Fondazione Salvatore Maugeri,

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

55 CONGRESSO NAZIONALE
Società Italiana di Gerontologia e Geriatria

Firenze, 30 novembre 2010

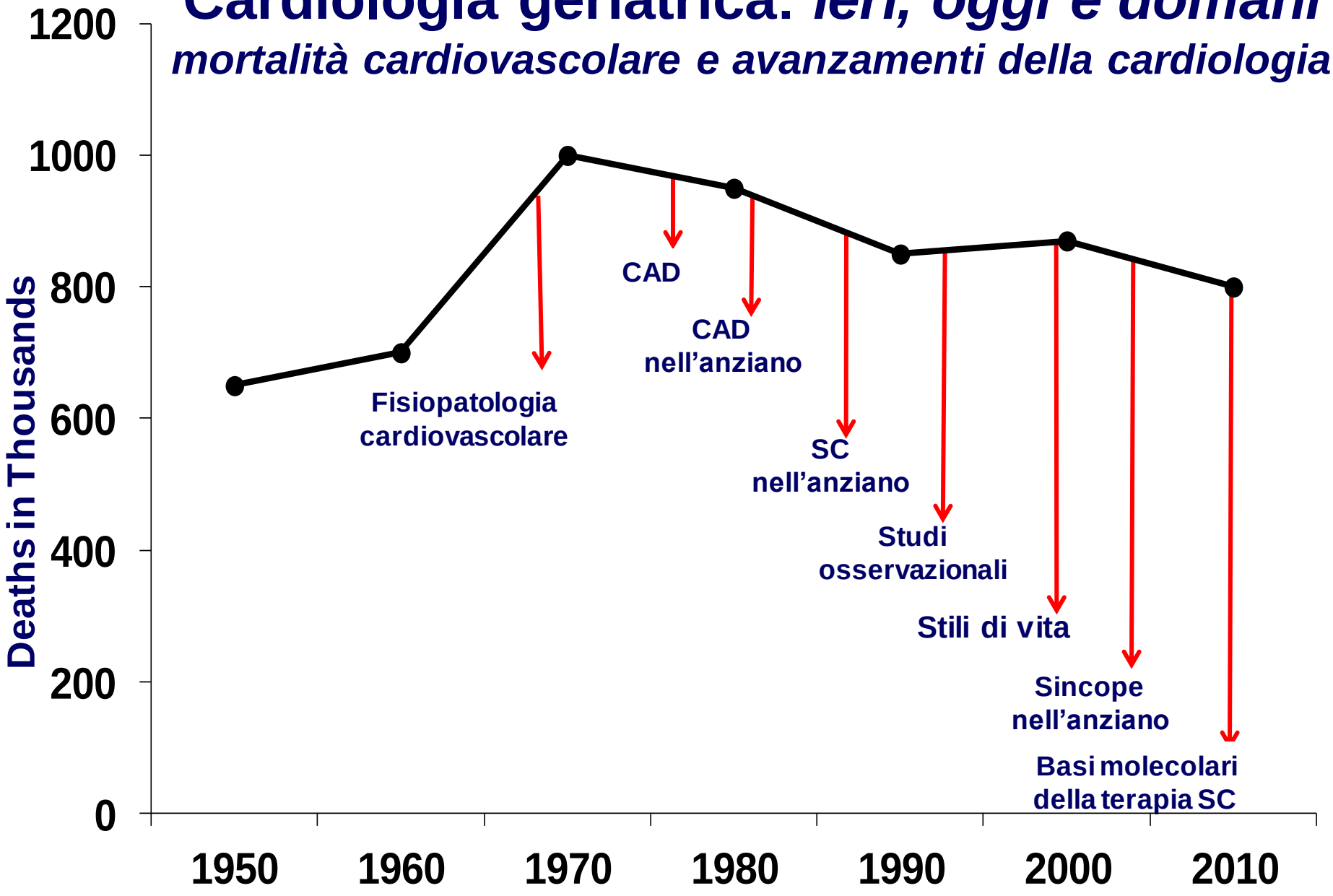
Cardiologia geriatrica:
ieri, oggi e domani

Franco Rengo
Direttore Dpt Medicina Interna, Geriatria, Patologia Cardiovascolare ed Immunitaria e Cardiochirurgia
Università degli Studi di Napoli "Federico II"

Presidente della Fondazione Italiana Ricerca Invecchiamento

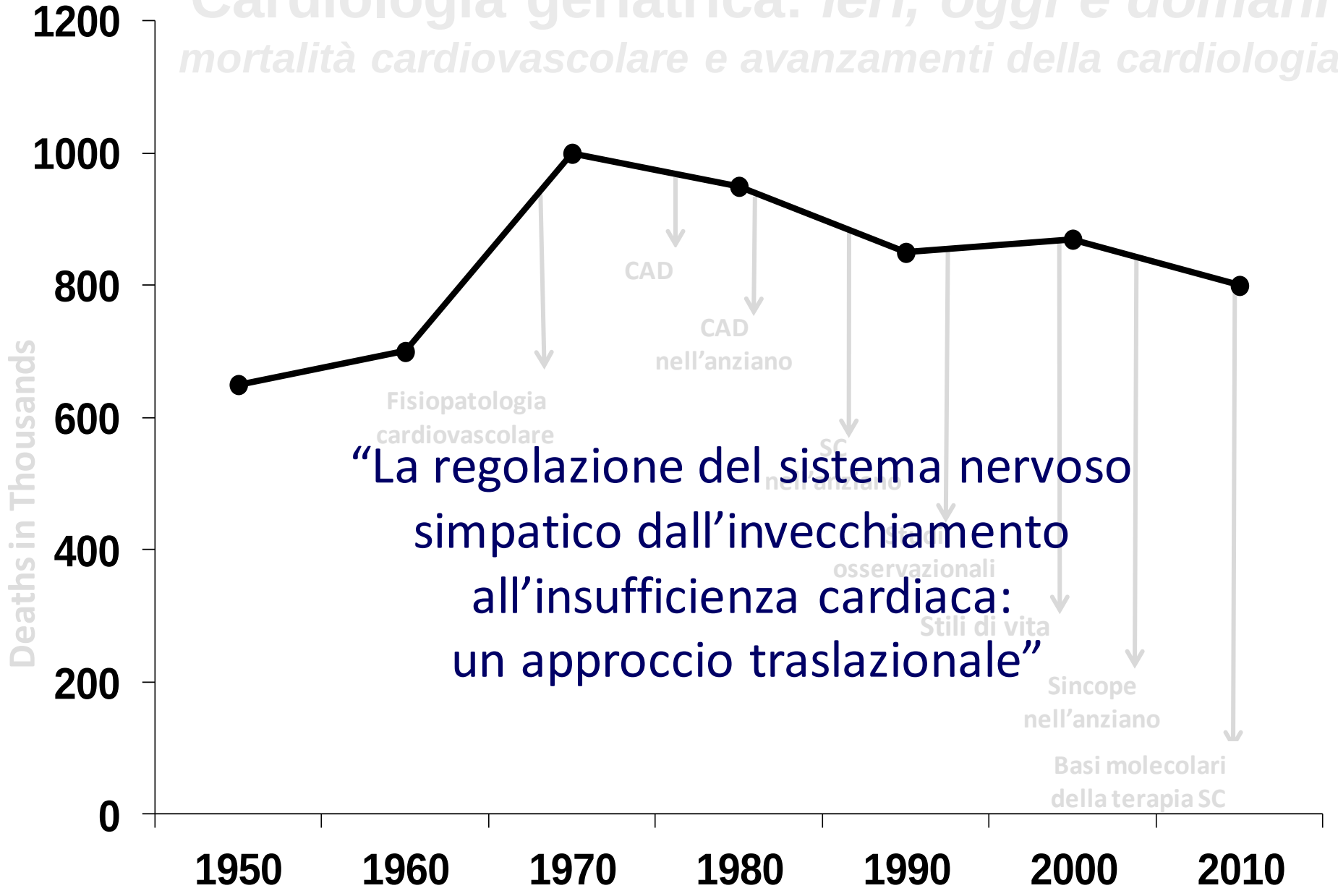
Cardiologia geriatrica: *ieri, oggi e domani*

mortalità cardiovascolare e avanzamenti della cardiologia



Cardiologia geriatrica: *ieri, oggi e domani*

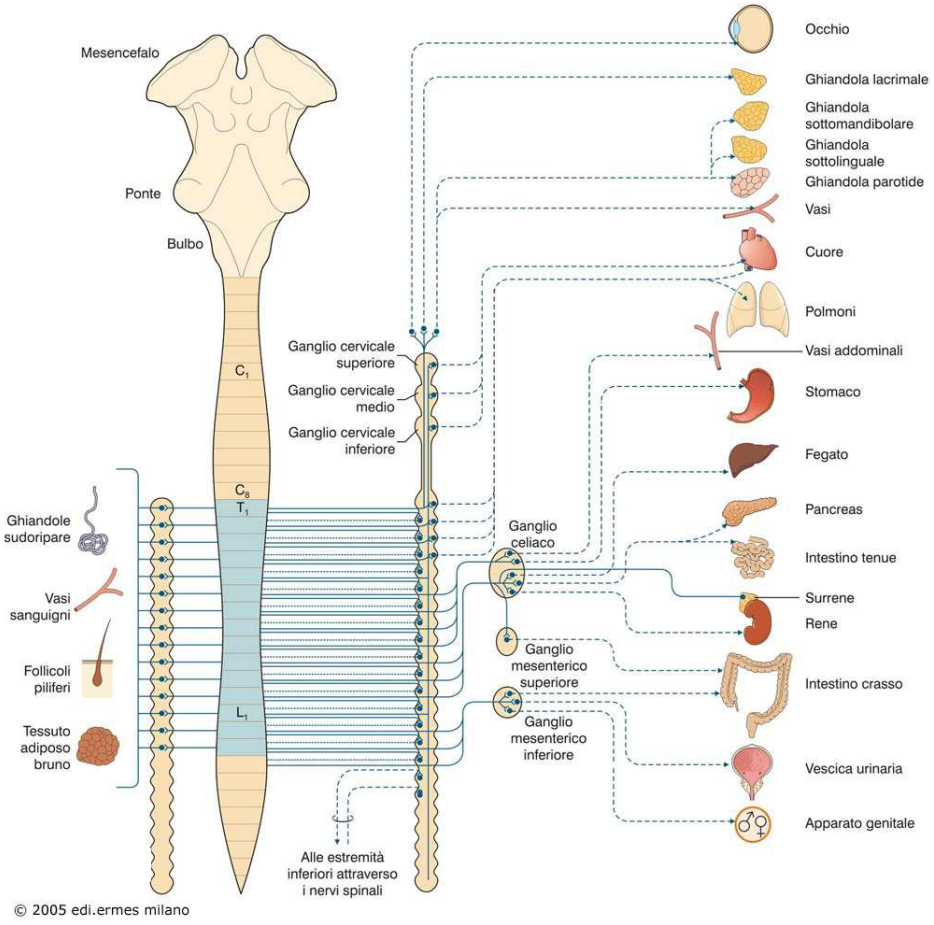
mortalità cardiovascolare e avanzamenti della cardiologia



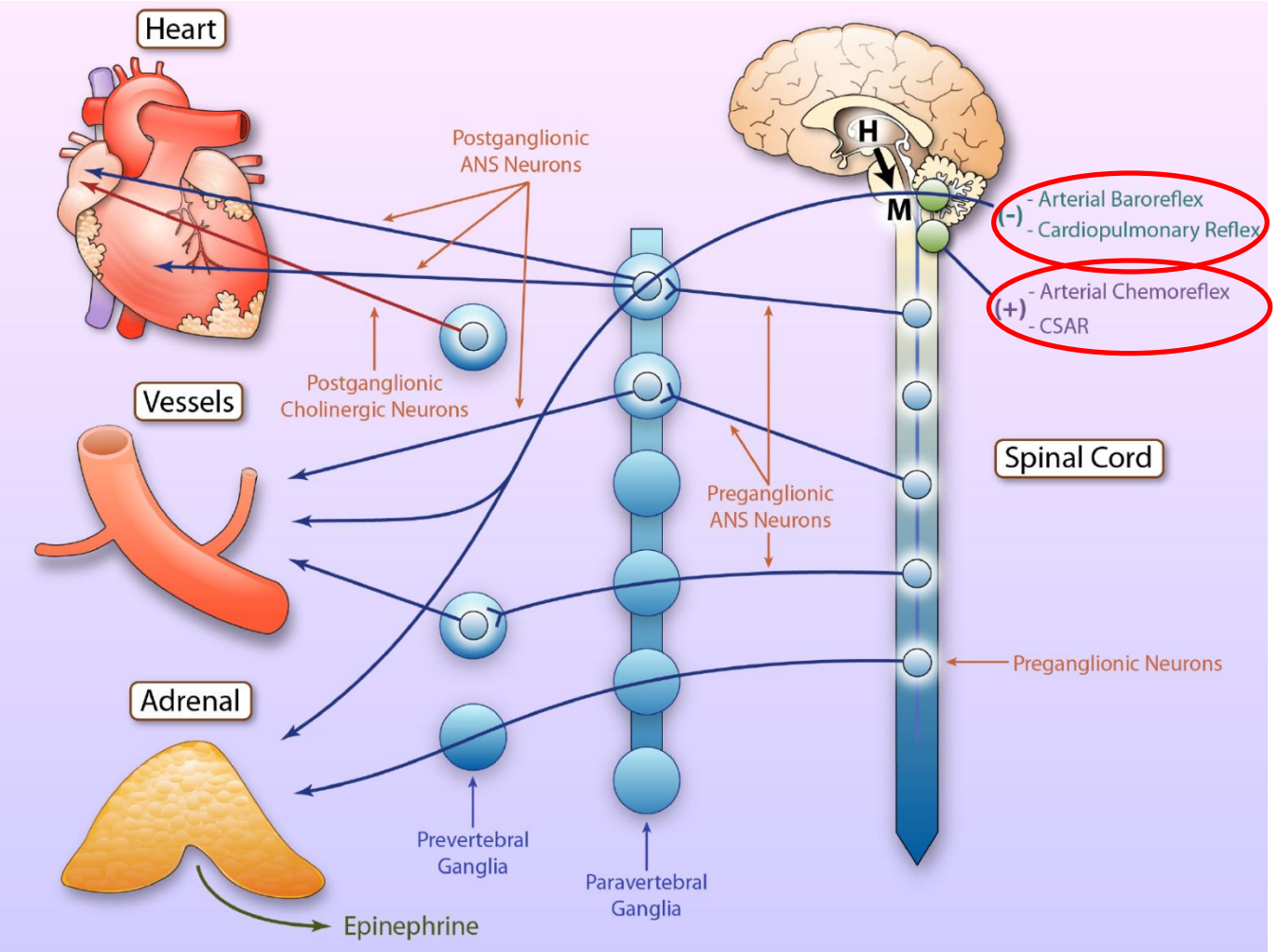
"La regolazione del sistema nervoso simpatico dall'invecchiamento all'insufficienza cardiaca: un approccio traslazionale"

Effetti fisiologici non cardiovascolari del SNS

Organo	Sistema nervoso simpatico
Pupilla	Dilatazione (αAR)
Ghiandole salivari	Secrezione muco ed enzimi (αAR e β2AR)
Polmoni	Broncodilatazione (β2AR)
Digerente	Diminuzione della motilità e secrezione (αAR e β2AR)
Pancreas endocrino	Inibizione della secrezione di insulina (α)
Pancreas esocrino	Diminuzione della secrezione enzimatica (α)
Vescica	Inibizione della minzione (αAR e β2AR)



Effetti fisiologici cardiovascolari del SNS



Lymperopoulos A, Rengo G, Koch WJ Circulation Research 2013

La regolazione del SNS

1. Meccanismi molecolari dell'iperattività simpatica nel surrene

2. Signaling β-adrenergico cardiaco e meccanismi molecolari della terapia con β-bloccanti e con l'inibizione di GRK2

3. GRK2 nuovo biomarker dell'iperattività simpatica

La regolazione del SNS

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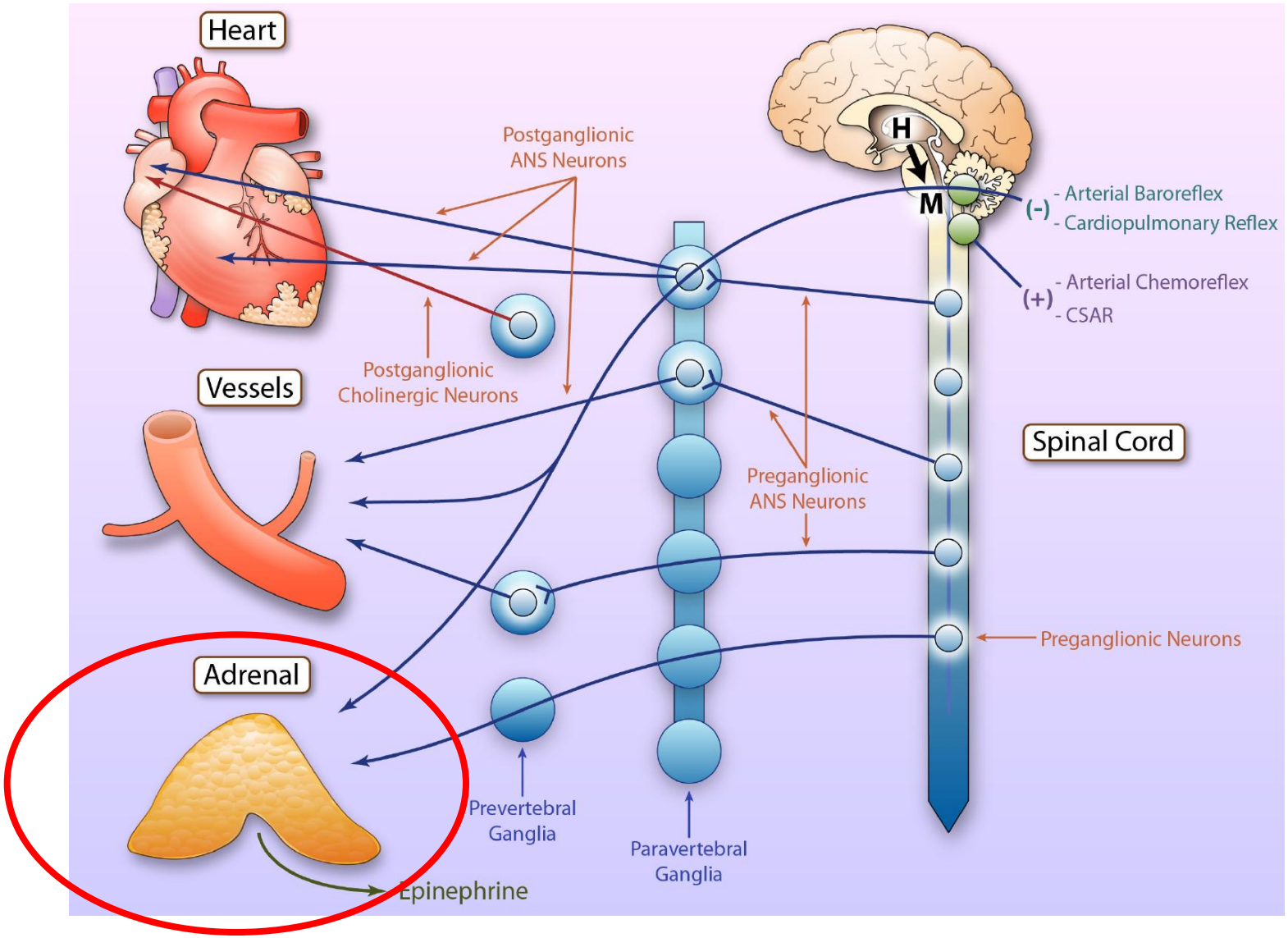
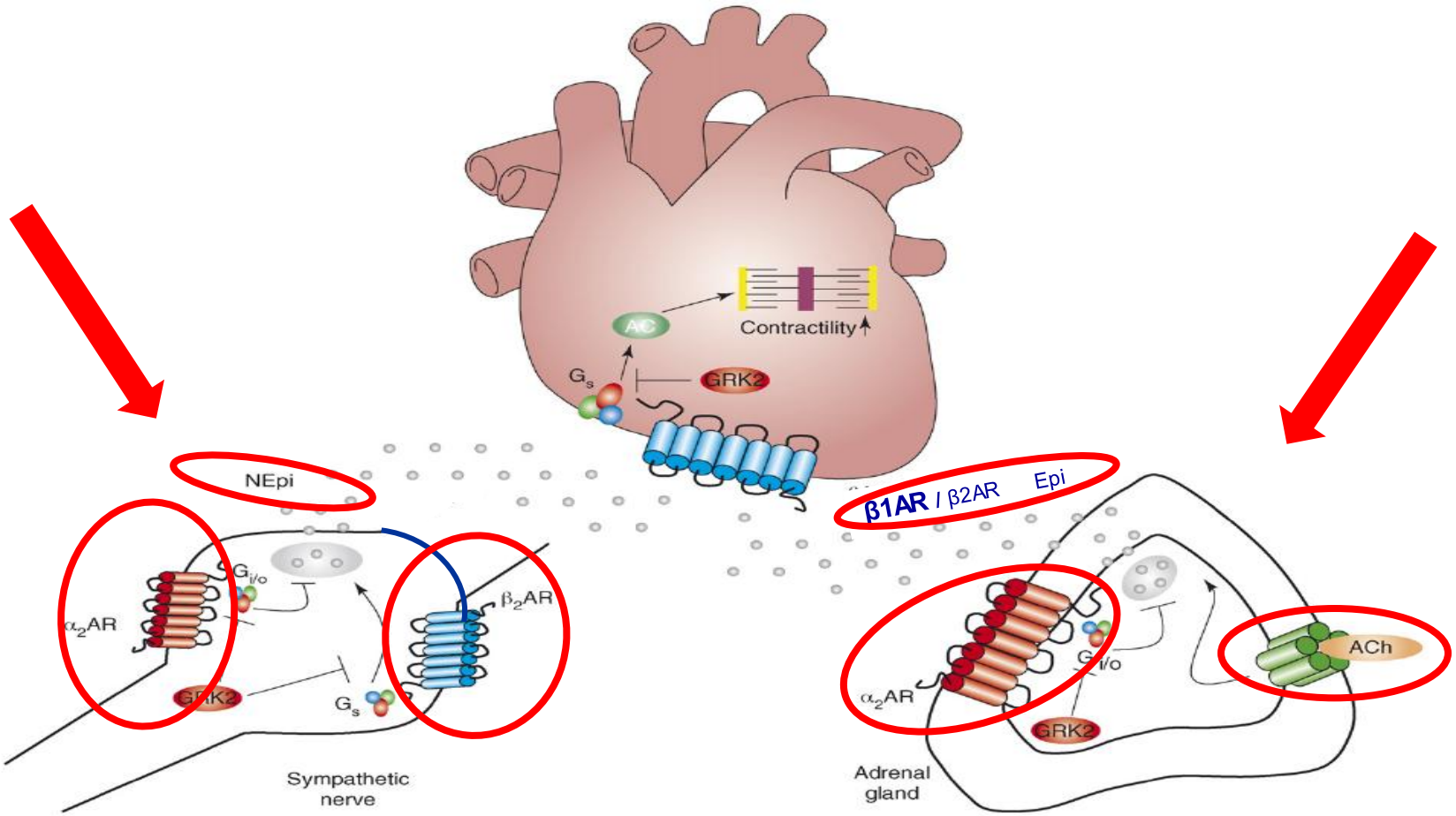
Il ruolo della midollare surrenalica nella regolazione del SNS



Lymperopoulos A, Rengo G, Koch WJ Circulation Research 2013

Meccanismi fisiologici della regolazione del SNS



Lymperopoulos A & Rengo G Trends in Molecular Medicine 2007

Am J Physiol Heart Circ Physiol 283: H1838–H1845, 2002.
First published July 26, 2002; 10.1152/ajpheart.01063.2001.

Abnormal cardiac function associated with sympathetic nervous system hyperactivity in mice

PATRICIA C. BRUM,[2] JON KOSEK,[1] ANDREW PATTERSON,[3]
DANIEL BERNSTEIN,[4] AND BRIAN KOBILKA[2,5]
[1]*Department of Pathology, Veterans Administration Medical Center, Palo Alto 94305; and* [2]*Departments of Medicine and Molecular and Cellular Physiology,* [3]*Department of Anesthesia,* [4]*Division of Cardiology, Department of Pediatrics, and* [5]*Howard Hughes Medical Institute, Stanford University, Stanford, California 94305*

Received 4 December 2001; accepted in final form 12 July 2002

Brum, Patricia C., Jon Kosek, Andrew Patterson, Daniel Bernstein, and Brian Kobilka. Abnormal cardiac function associated with sympathetic nervous system hyperactivity in mice. *Am J Physiol Heart Circ Physiol* 283: H1838–H1845, 2002. First published July 26, 2002; 10.1152/ajpheart.01063.2001.—α_{2A}-Adrenergic receptors (ARs) in the midbrain regulate sympathetic nervous system activity, and both α_{2A}-ARs and α_{2C}-ARs regulate catecholamine release from sympathetic nerve terminals in cardiac tissue. Disruption of both α_{2A}- and α_{2C}-ARs in mice leads to chronically elevated sympathetic tone and decreased cardiac function by 4 mo of age. These knockout mice have increased mortality, reduced exercise capacity, decreased peak oxygen uptake, and decreased cardiac contractility relative to wild-type controls. Moreover, we observed significant abnormalities in the ultrastructure of cardiac myocytes from α_{2A}/α_{2C}-AR knockout mice by electron microscopy. Our results demonstrate that chronic elevation of sympathetic tone can lead to abnormal cardiac function in the absence of prior myocardial injury or genetically induced alterations in myocardial structural or functional proteins. These mice provide a physiologically relevant animal model for investigating the role of the sympathetic nervous system in the development and progression of heart failure.

α_2-adrenergic receptor; knockout mice; heart failure

and a progressive deterioration in cardiac function (4, 5, 9, 34). However, direct experimental evidence that the sympathetic nervous system plays a predominant role in the development of heart failure is lacking, and there are no suitable murine models of heart failure based on elevated sympathetic nervous system activity without concomitant alterations of myocardial structural or functional proteins. Most murine models of heart failure are based on the disruption of genes for cardiac specific proteins (2) or the use of cardiac-specific promoters to overexpress proteins that disrupt myocyte function (10, 12, 13, 15, 21, 33, 42). Whereas these models have been used to test novel approaches for the treatment of heart failure (17, 20, 25, 37, 38, 41, 43), they may not accurately reflect the pathogenesis of this disorder in humans. Here we report a model of heart failure based on the disruption of genes that regulate sympathetic nervous system activity.

There are three α_2-adrenergic receptor (α_2-AR) subtypes: α_{2A}, α_{2B}, and α_{2C}. α_2-ARs regulate the sympathetic nervous system in several ways. α_{2A}-ARs in the brain stem regulate sympathetic tone (1, 29), and both α_{2A}-AR and α_{2C}-AR act as presynaptic autoreceptors regulating catecholamine release in the murine atria (18).

nature medicine

ARTICLES

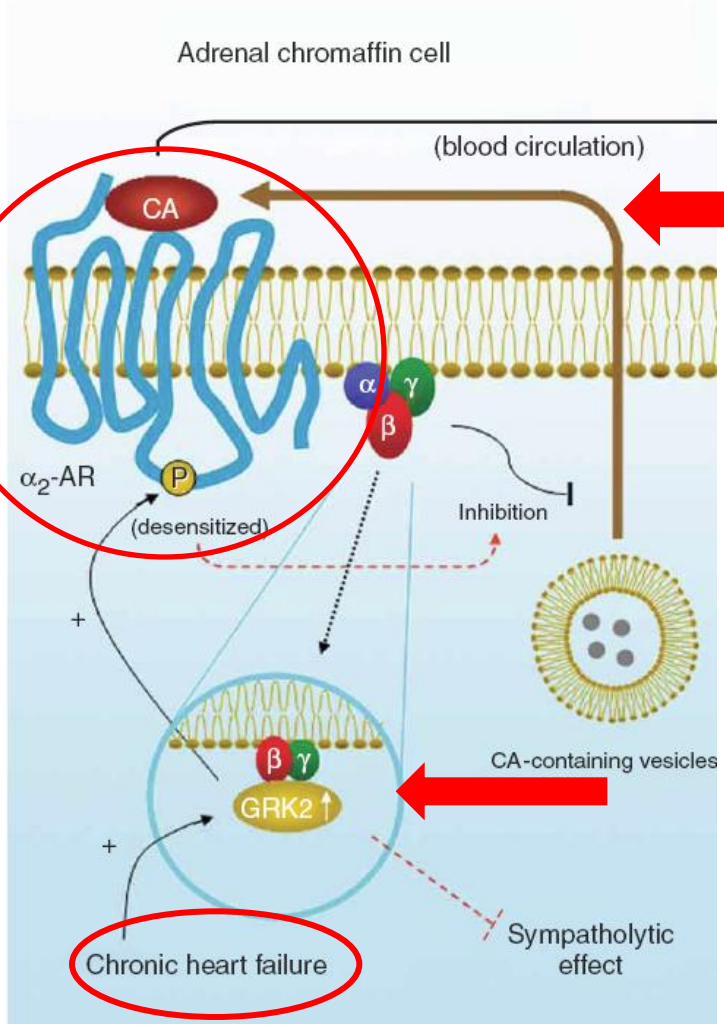
Adrenal GRK2 upregulation mediates sympathetic overdrive in heart failure

Anastasios Lymperopoulos[1,2], Giuseppe Rengo[1,2], Hajime Funakoshi[1], Andrea D Eckhart[1,3] & Walter J Koch[1,2]

Cardiac overstimulation by the sympathetic nervous system (SNS) is a salient characteristic of heart failure, reflected by elevated circulating levels of catecholamines. The success of β-adrenergic receptor (βAR) antagonists in heart failure argues for SNS hyperactivity being pathogenic; however, sympatholytic agents targeting α_2AR-mediated catecholamine inhibition have been unsuccessful. By investigating adrenal adrenergic receptor signaling in heart failure models, we found molecular mechanisms to explain the failure of sympatholytic agents and discovered a new strategy to lower SNS activity. During heart failure, there is substantial α_2AR dysregulation in the adrenal gland, triggered by increased expression and activity of G protein–coupled receptor kinase 2 (GRK2). Adrenal gland–specific GRK2 inhibition reversed α_2AR dysregulation in heart failure, resulting in lowered plasma catecholamine levels, improved cardiac βAR signaling and function, and increased sympatholytic efficacy of a α_2AR agonist. This is the first demonstration, to our knowledge, of a molecular mechanism for SNS hyperactivity in heart failure, and our study identifies adrenal GRK2 activity as a new sympatholytic target.

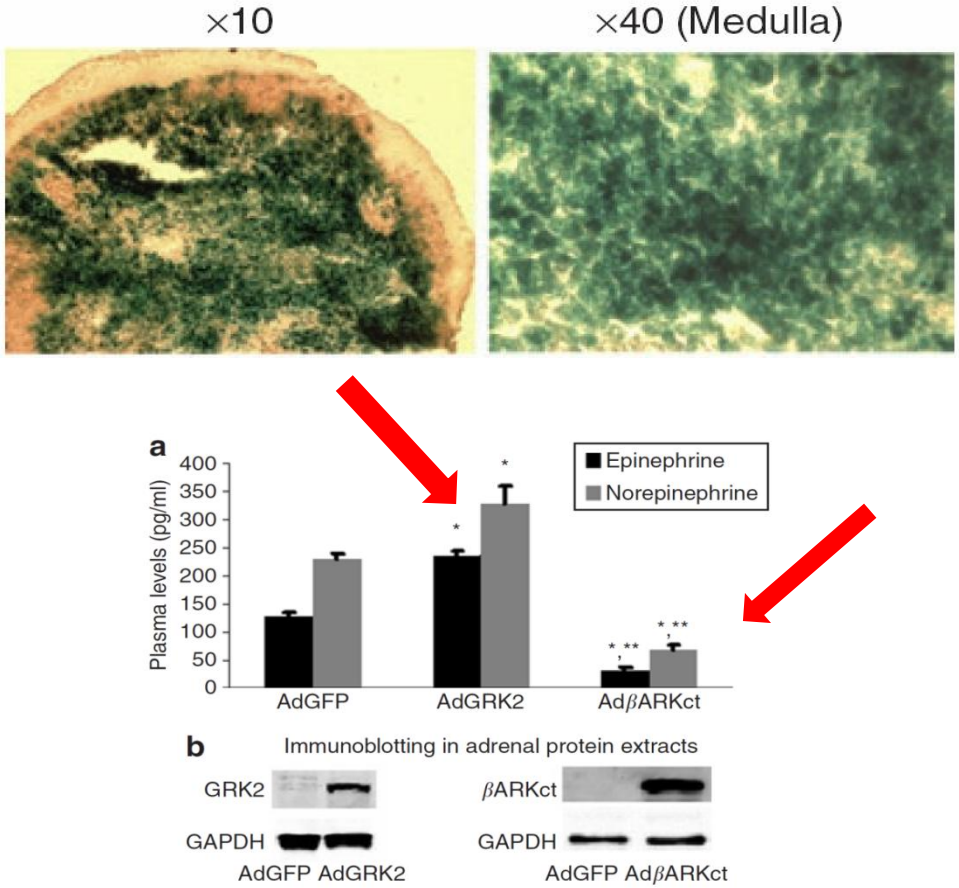
Lymperopoulos A, Rengo G et al Nature Medicine 2007

Upregulation GRK2 surrenalico secondario ad iperattività simpatica da IC



Lymperopoulos A , Rengo G et al Nature Medicine 2007

Modulazione della secrezione surrenalica di adrenalina mediante trasferimento genico e manipolazione di GRK2 in vivo



Lymperopoulos A , Rengo G et al Molecular Theraphy 2008

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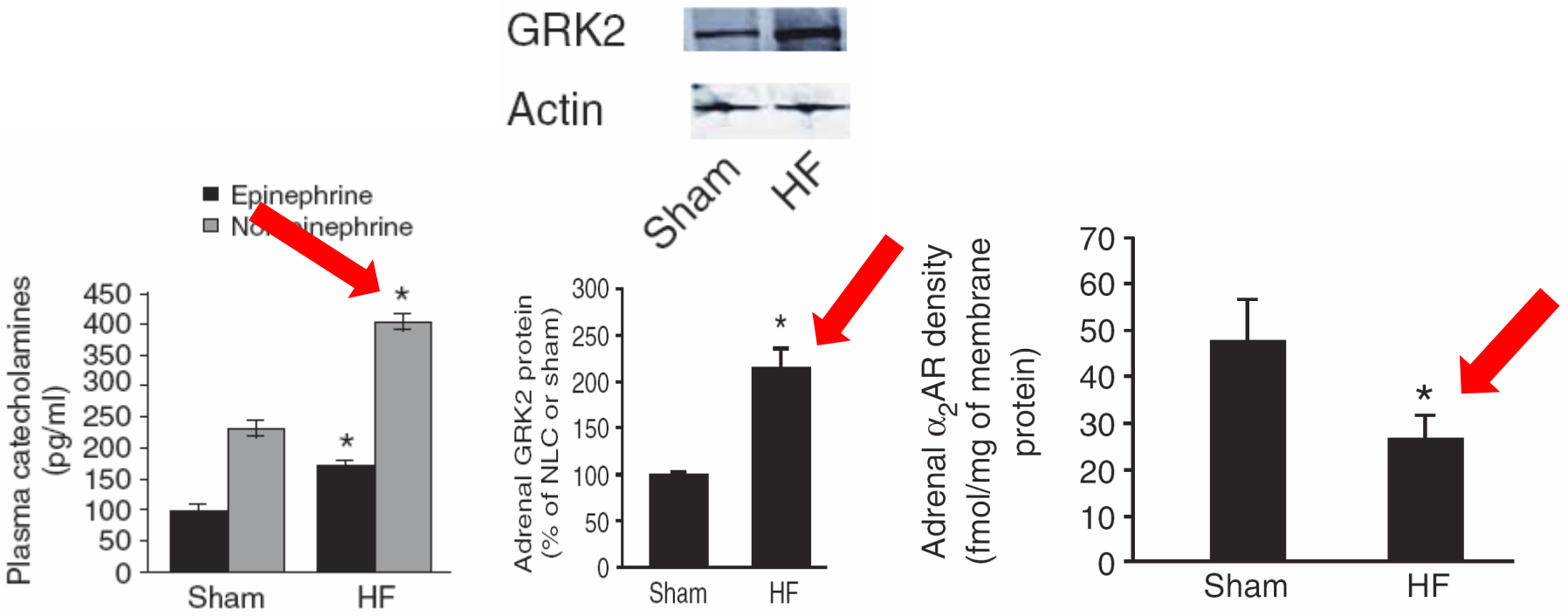

Lymperopoulos A, Rengo G et al Nature Medicine 2007

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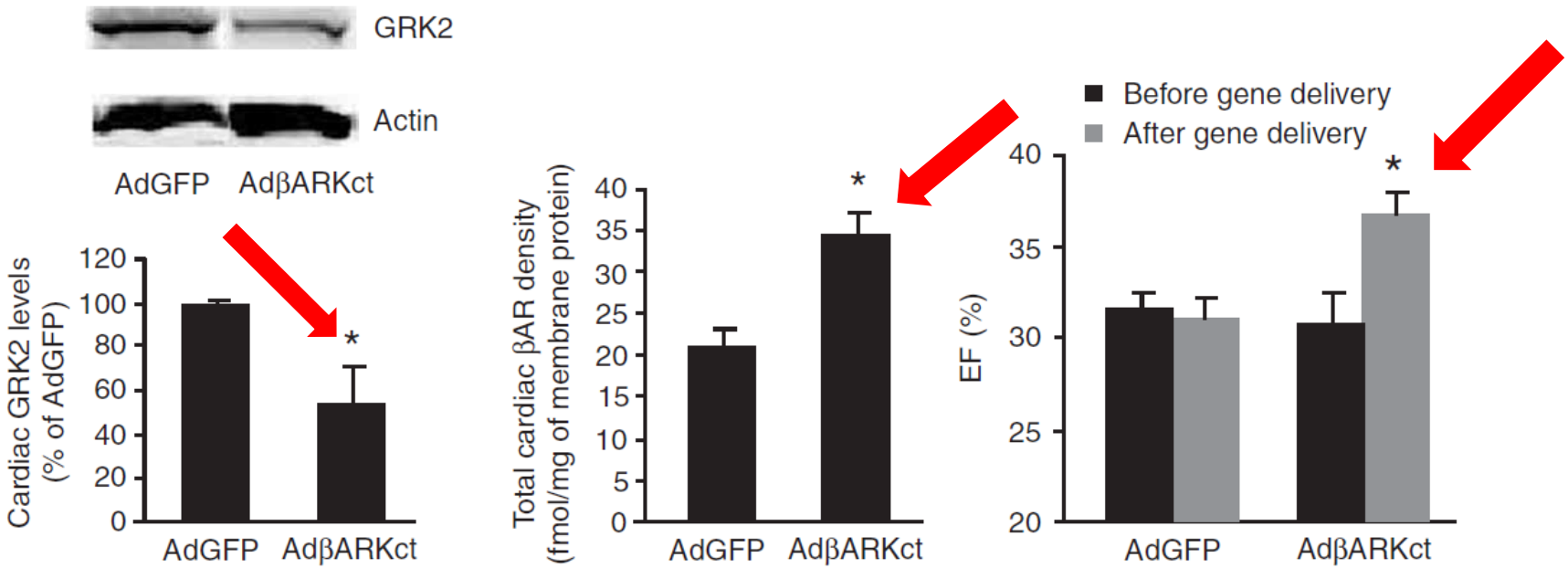
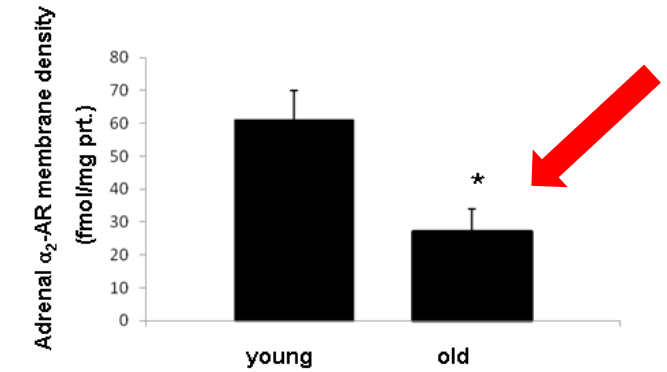
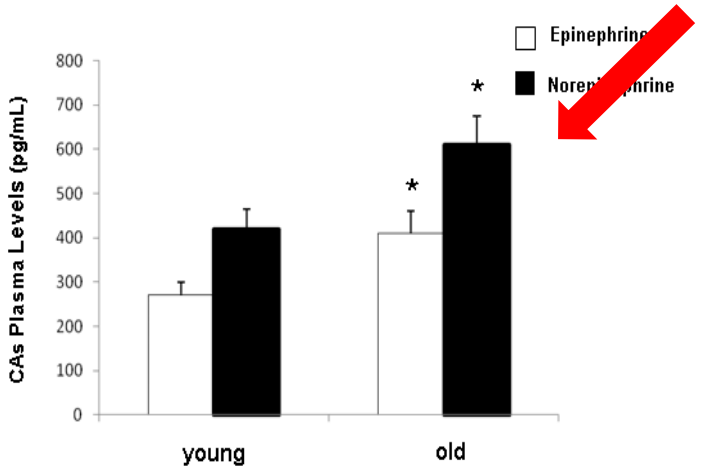


Lymperopoulos A, Rengo G et al Nature Medicine 2007

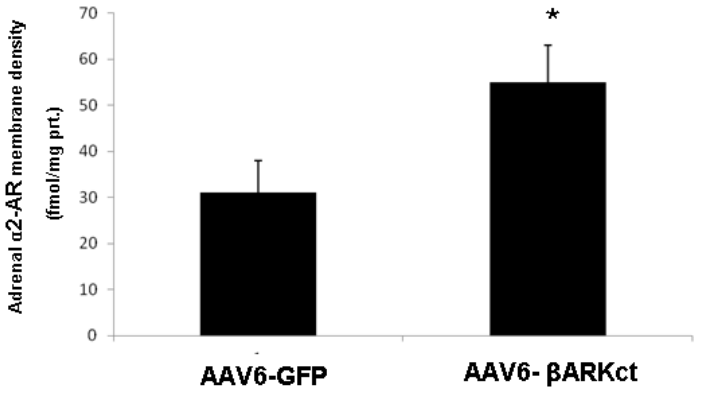
Iperattività simpatica età-correlate associata a disfunzione degli α2-AR surrenalici

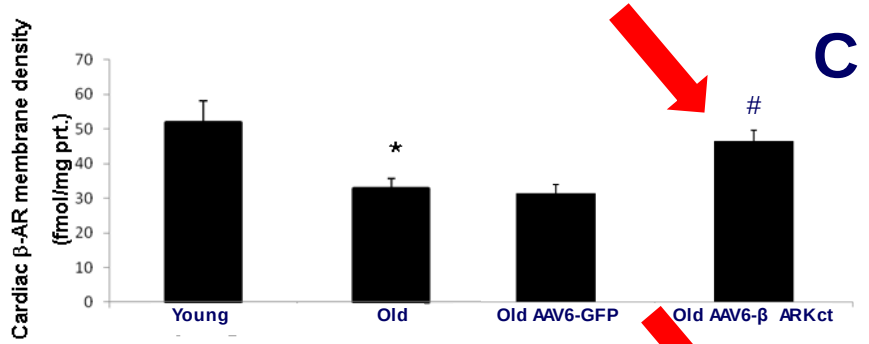


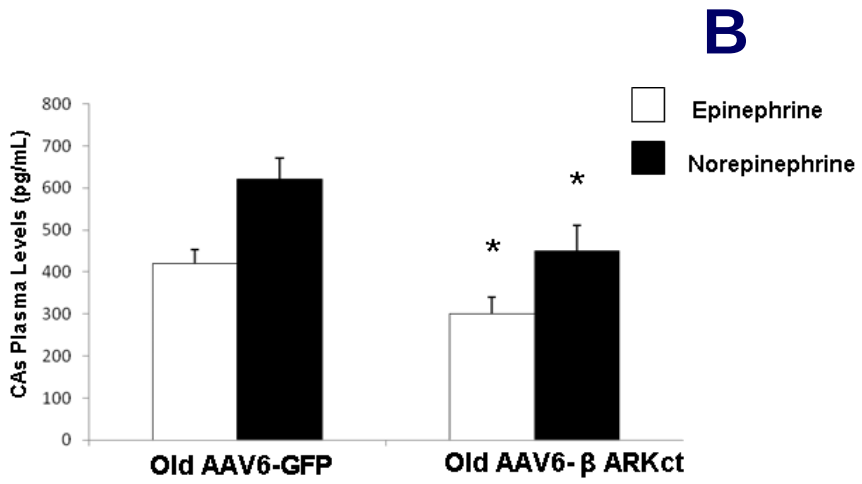


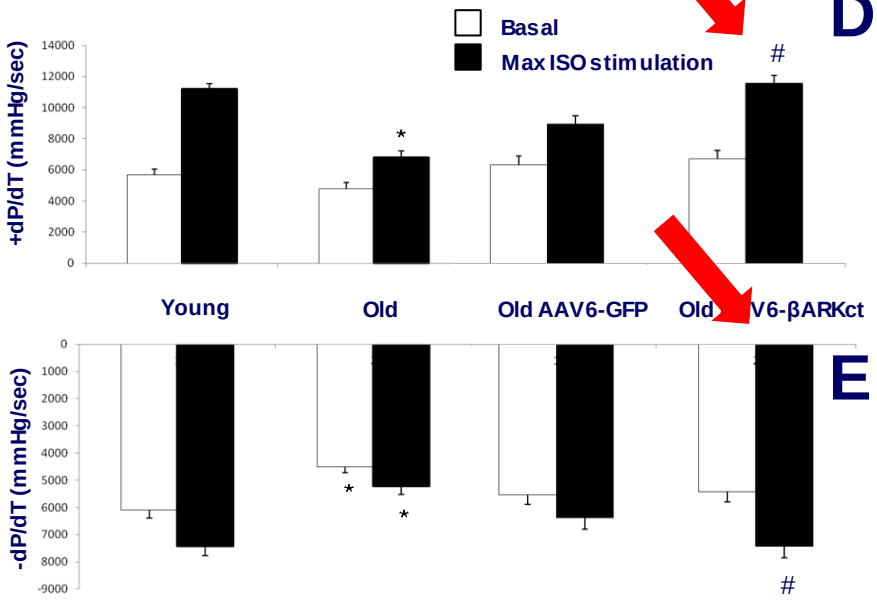
Rengo G et al AHA manuscript in preparation

Inibizione di GRK2 con il trasferimento genico surrenalico dell'iperattività simpatica età-correlata e miglioramento della riserva inotropa cardiaca



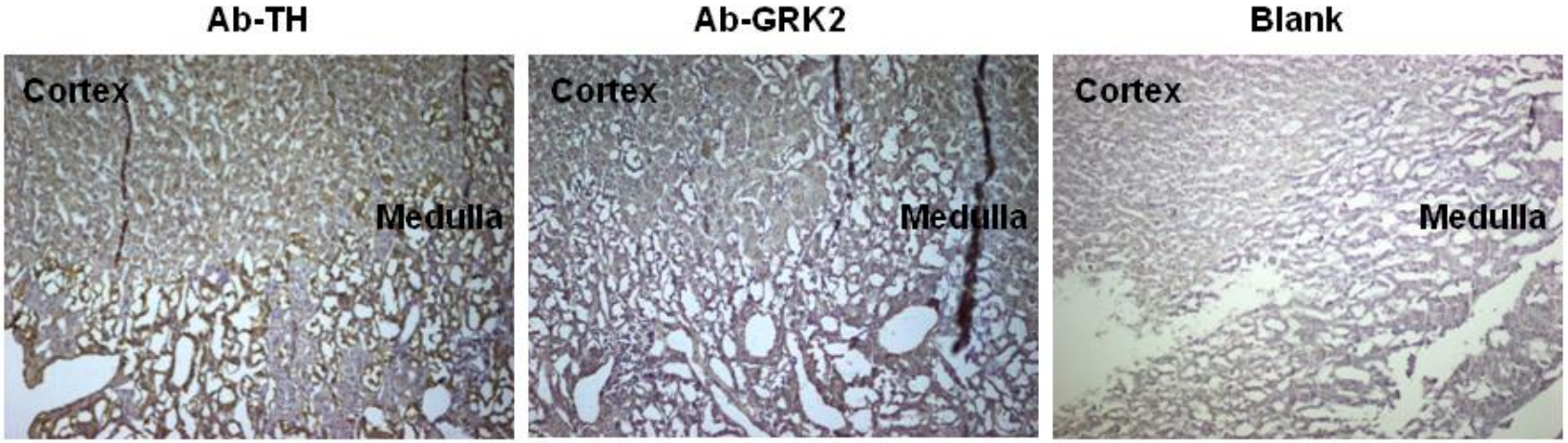


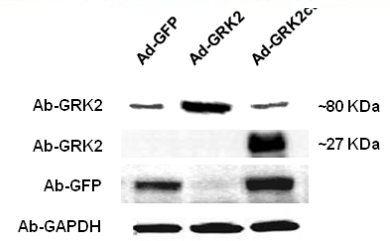


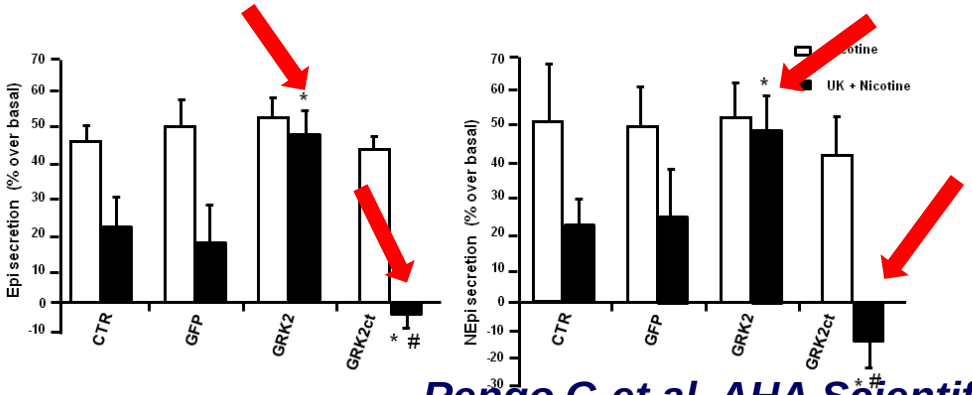


Rengo G et al AHA manuscript in preparation

Modulazione della secrezione surrenalica di catecolamine con manipolazione di GRK2 in cellule cromaffini umane







Rengo G et al AHA Scientific Sessions 2012

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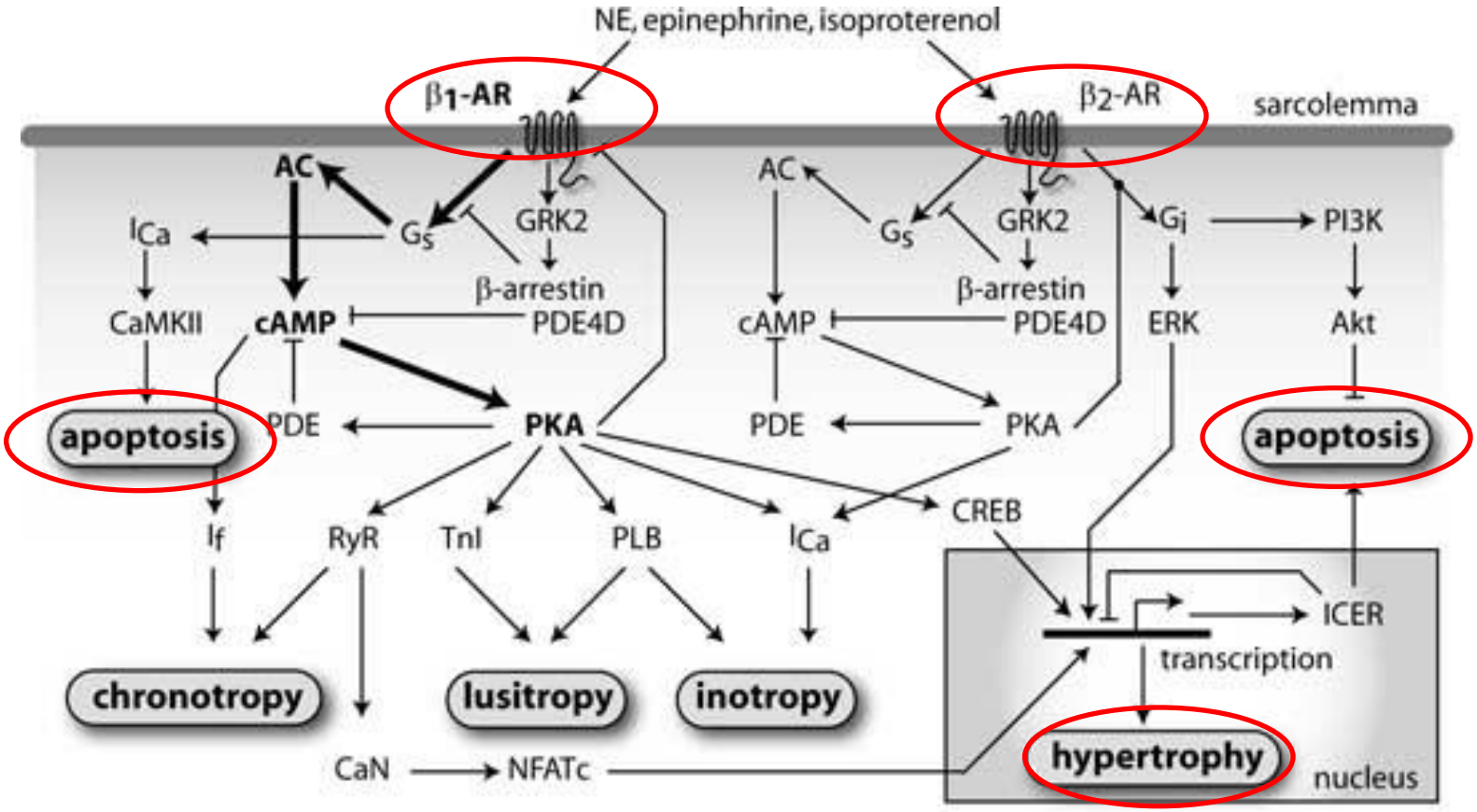
Il signaling e le funzioni dei β-AR nel miocardio

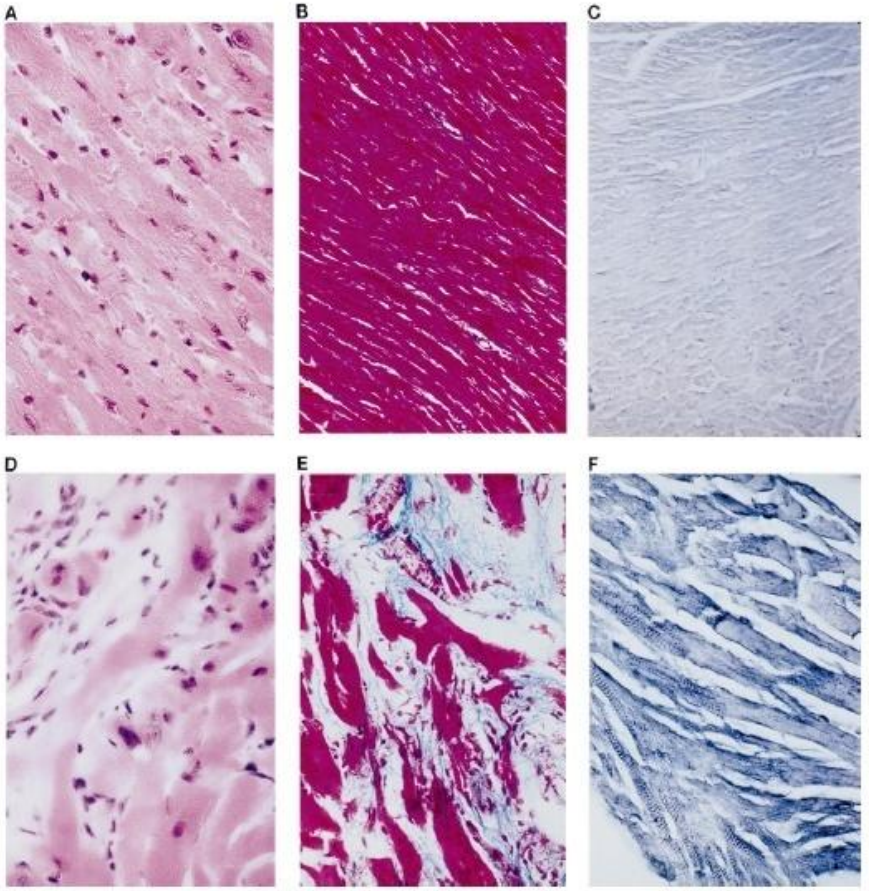


fibrosi **angiogenesi**

Saucerman JJ et al Annals New York Academy Science2006

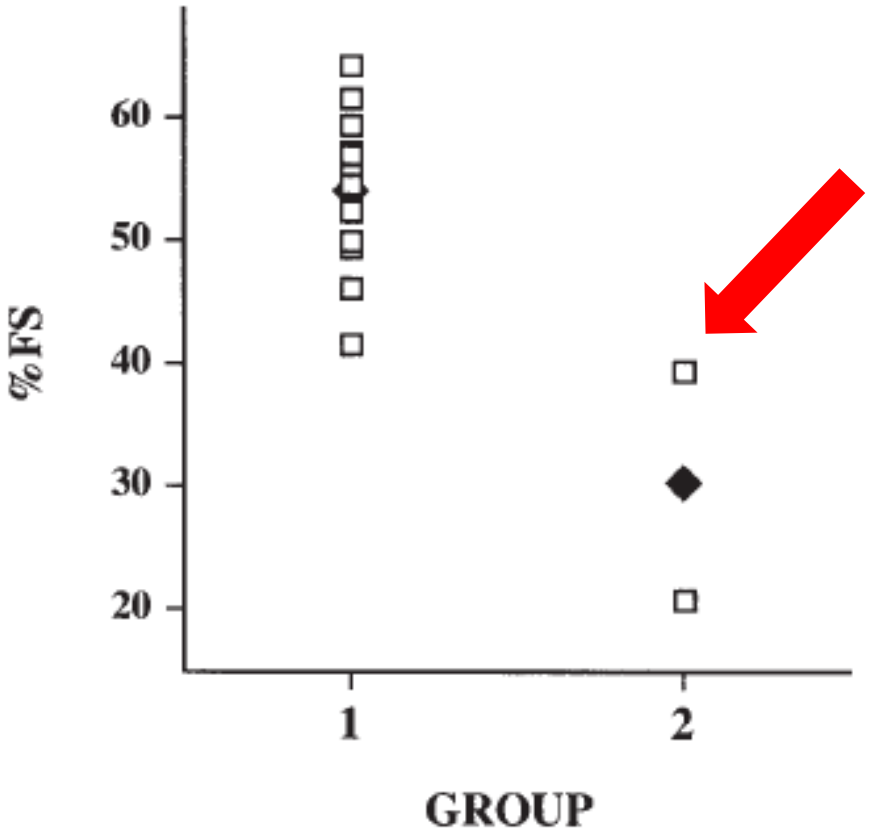
Effetti negativi svolte nel cuore con la over-espressione genica dei β1-AR

Topo normale



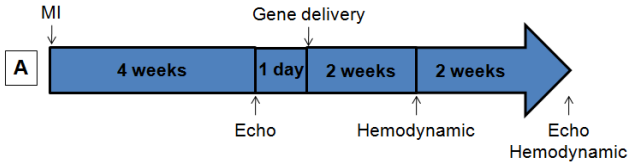
β1 iperinfiltrati

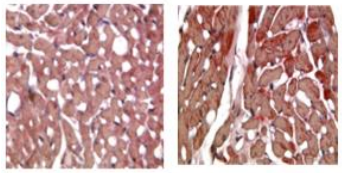
β1 iperfibrosi

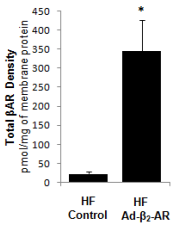


Bisognano JD et al J Mol Cell Cardiol 2000

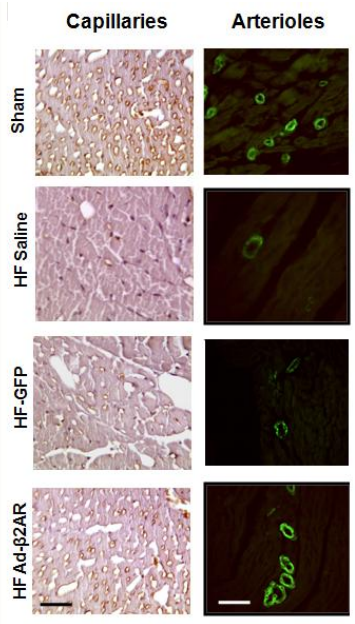
Rimodellamento cardiaco ed angiogenesi indotta dall'over-espressione genica dei β_2-AR nell'IC







A



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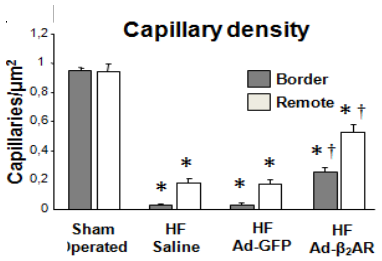

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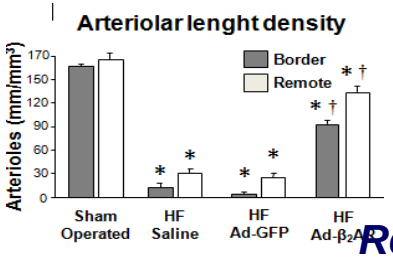
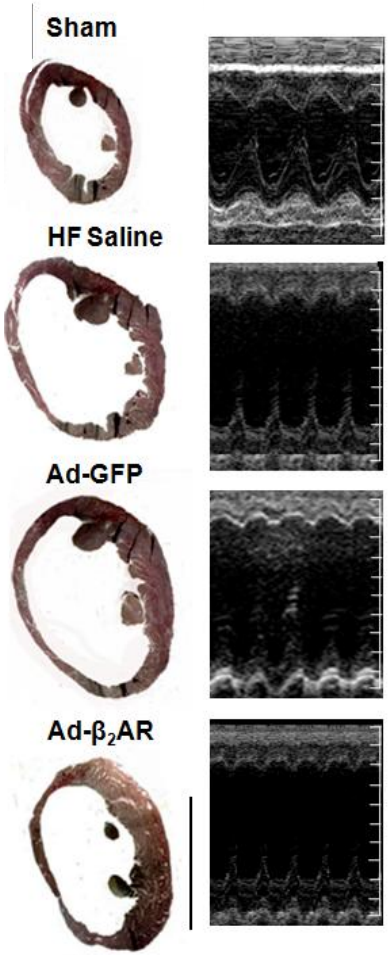
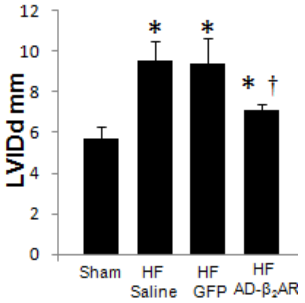
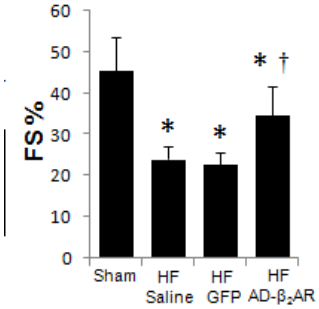


D





E



Rengo G et al British Journal Pharmacology 2012

Differenze farmacologiche di differenti classi di β-bloccanti

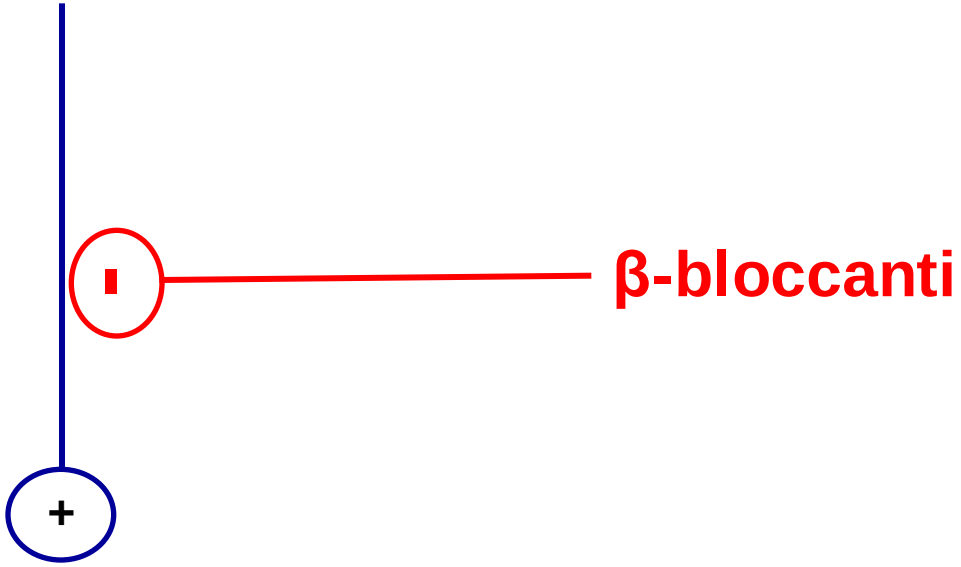
	β_1 blockade	β_2 blockade	α_1 blockade	ISA	Ancillary effects*
Carvedilol	+++	+++	+++	-	+++
Metoprolol	+++	-	-	-	-
Bisoprolol	+++	-	-	-	-
Nebivololo	+++	+++	-	-	-

*anti-oxidant, anti-endothelin, anti-proliferative
lack of β_1 receptor upregulation

Principali trials controllati con β-bloccanti nell'IC

Study	Drug	HF Severity	Pts n.	F.U.	Mortality ↓	Hospital. ↓
US Carvedilol	Carvedilol	Mild/Mod	1094	6.5 mo.	65%	27%
Cibis-II	Bisoprolol	Mod/Sev	2647	1.3 yrs	34%	20%
Merit-HF	Metoprolol	Mild/Mod	3991	1 yr	34%	18%
BEST	Bucindolol	Mod/Sev	2708	2 yr	ns	8%
COPERNICUS	Carvedilol	Severe	2289	10.4 mo.	35%	20%
CIBIS III	Bis vs Enal	Mod/Sev	689	20/18 mo.	32/33%	
SENIOR	Bisoprolol		2128			

Iperattività del SNS



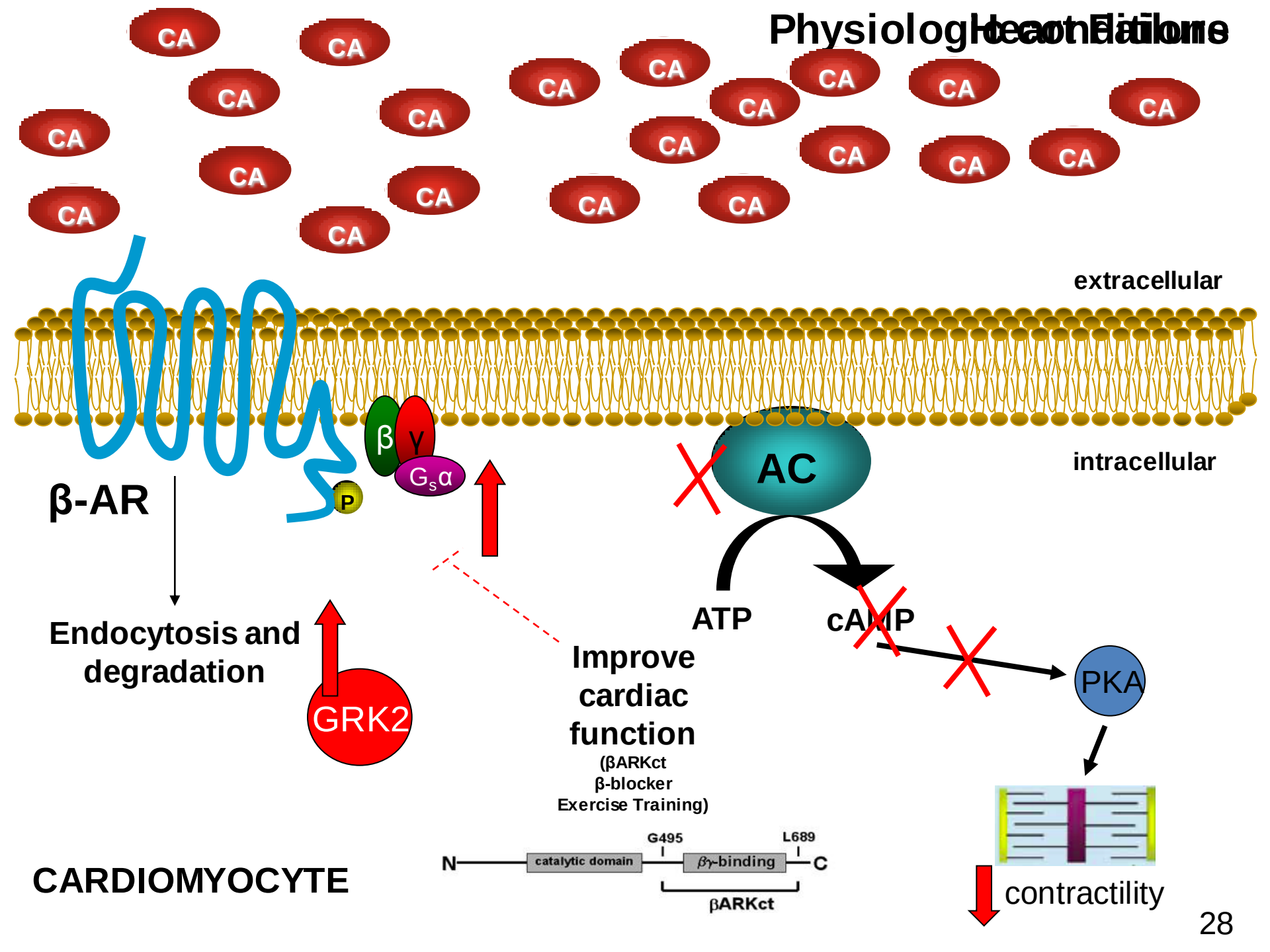
Consumo miocardico O2 *(J Mol Cell Cardiol 1985);*
Fibrosi interstiziale cardiaca *(Eur J Pharmacol 2004);*
Apoptosi dei cardiomiociti *(Cardiovasc Res 2004);*
Rimodellamento avverso *(Am J Physiol Heart Circ Physiol 2007);*
Riduzione della riserva inotropa *(NEJM 1982);*
Produzione miocardica di ROS *(J Cell Mol Med 2007);*
Rischio di aritmie *(NEJM 1991);*
Sistema renina-angiotensina-aldosterone *(Am J Physiol 1992);*
Resistenze vascolari renali and periferiche *(JACC2009);*

The NEW ENGLAND JOURNAL of MEDICINE

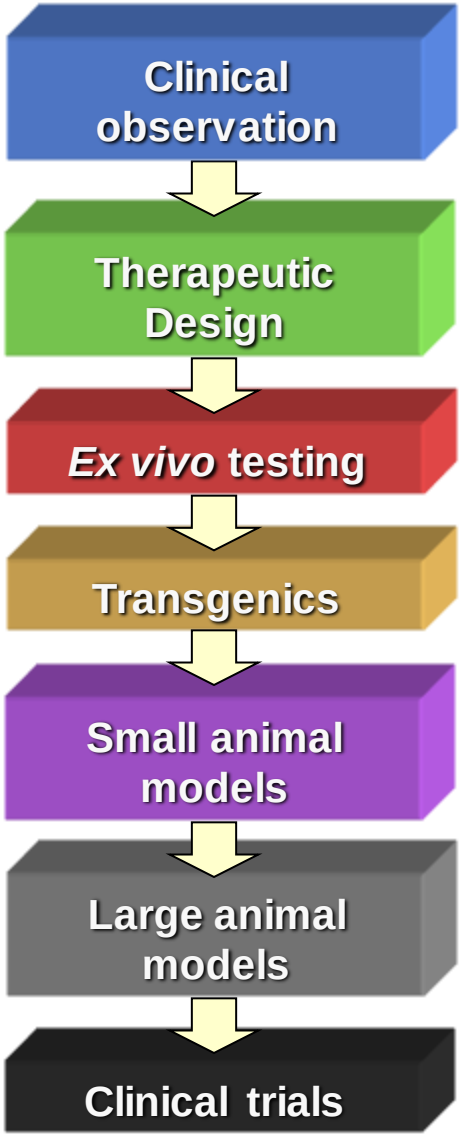
Decreased Catecholamine Sensitivity and β-Adrenergic-Receptor Density in Failing Human Hearts

Michael R. Bristow, M.D., Ph.D., Robert Ginsburg, M.D., Wayne Minobe, B.S., Roger S. Cubicciotti, M.S., W. Scott Sageman, M.S., Keith Lurie, M.D., Margaret E. Billingham, M.D., Donald C. Harrison, M.D., and Edward B. Stinson, M.D.

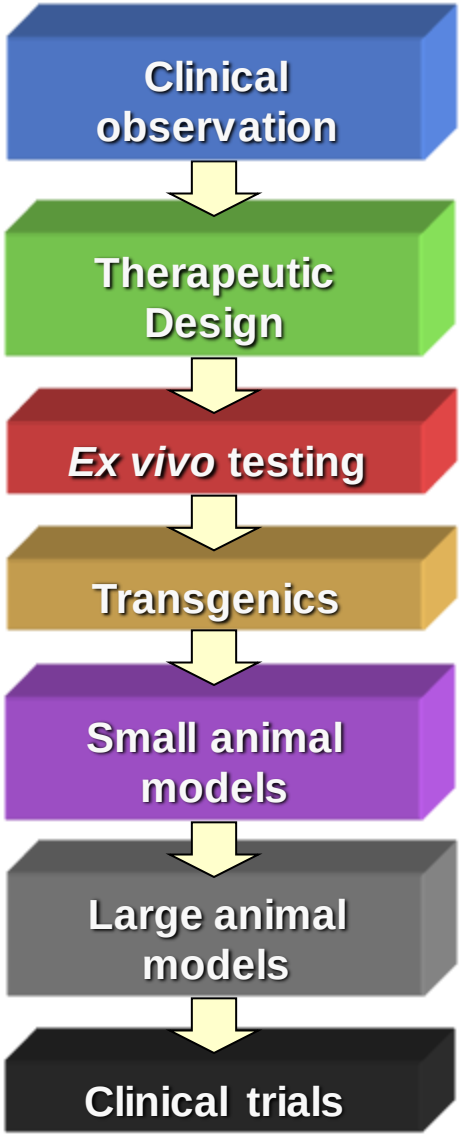
N Engl J Med 1982; 307:205-211 | July 22, 1982


Physiological Homeostasis
CA
extracellular
intracellular
β-AR
P
β
γ
$G_s\alpha$
AC
ATP
cAMP
PKA
Endocytosis and degradation
GRK2
Improve cardiac function
(βARKct
β-blocker
Exercise Training)
G495
L689
N
catalytic domain
βγ-binding
C
βARKct
contractility
CARDIOMYOCYTE

Modello di ricerca traslazionale



La ricerca traslazionale di GRK2



Circulation 1993

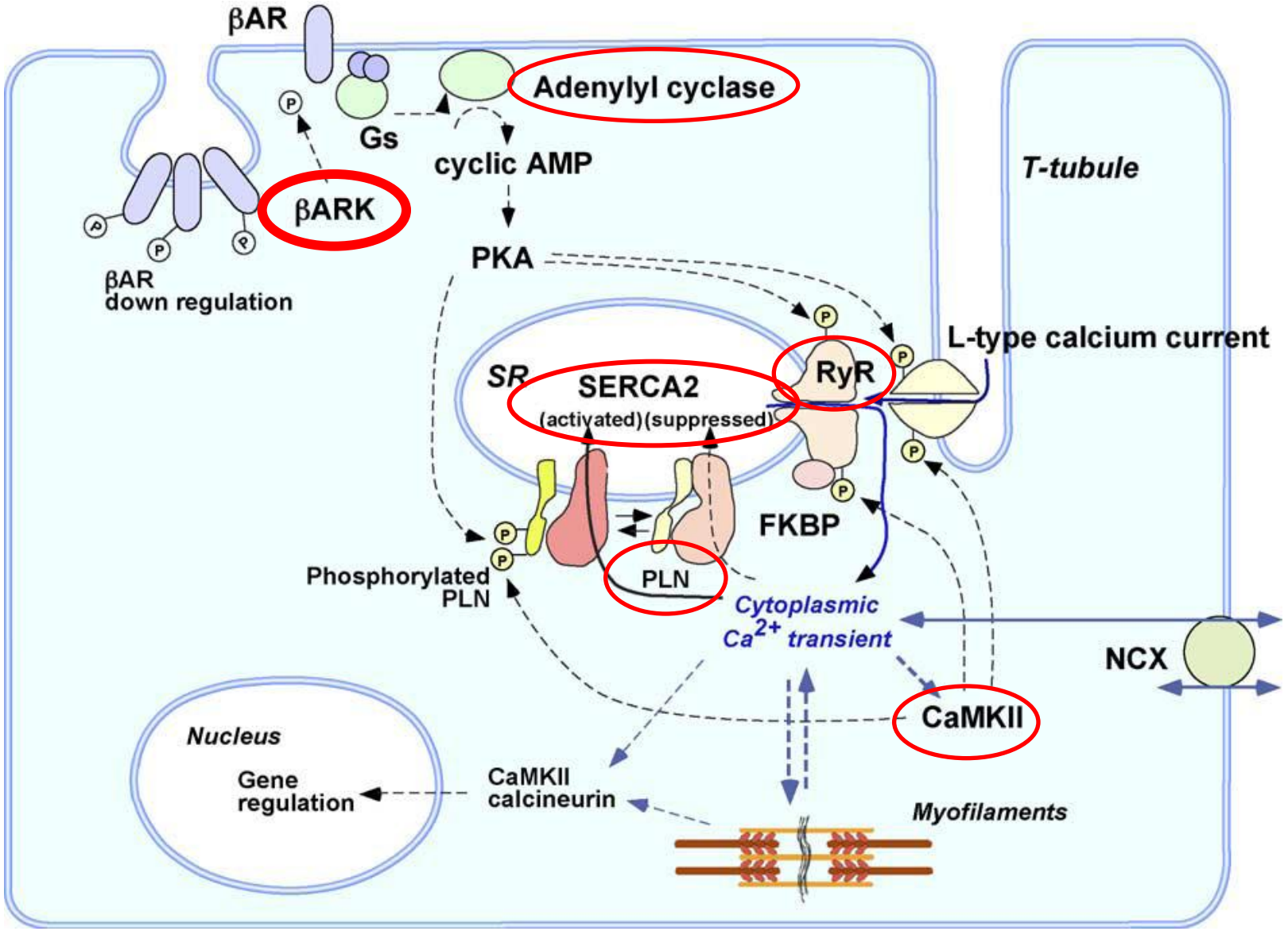
Circulation 2004

Science 1995, PNAS 1998, 2001, JACC 2002, Circ. Res 2008

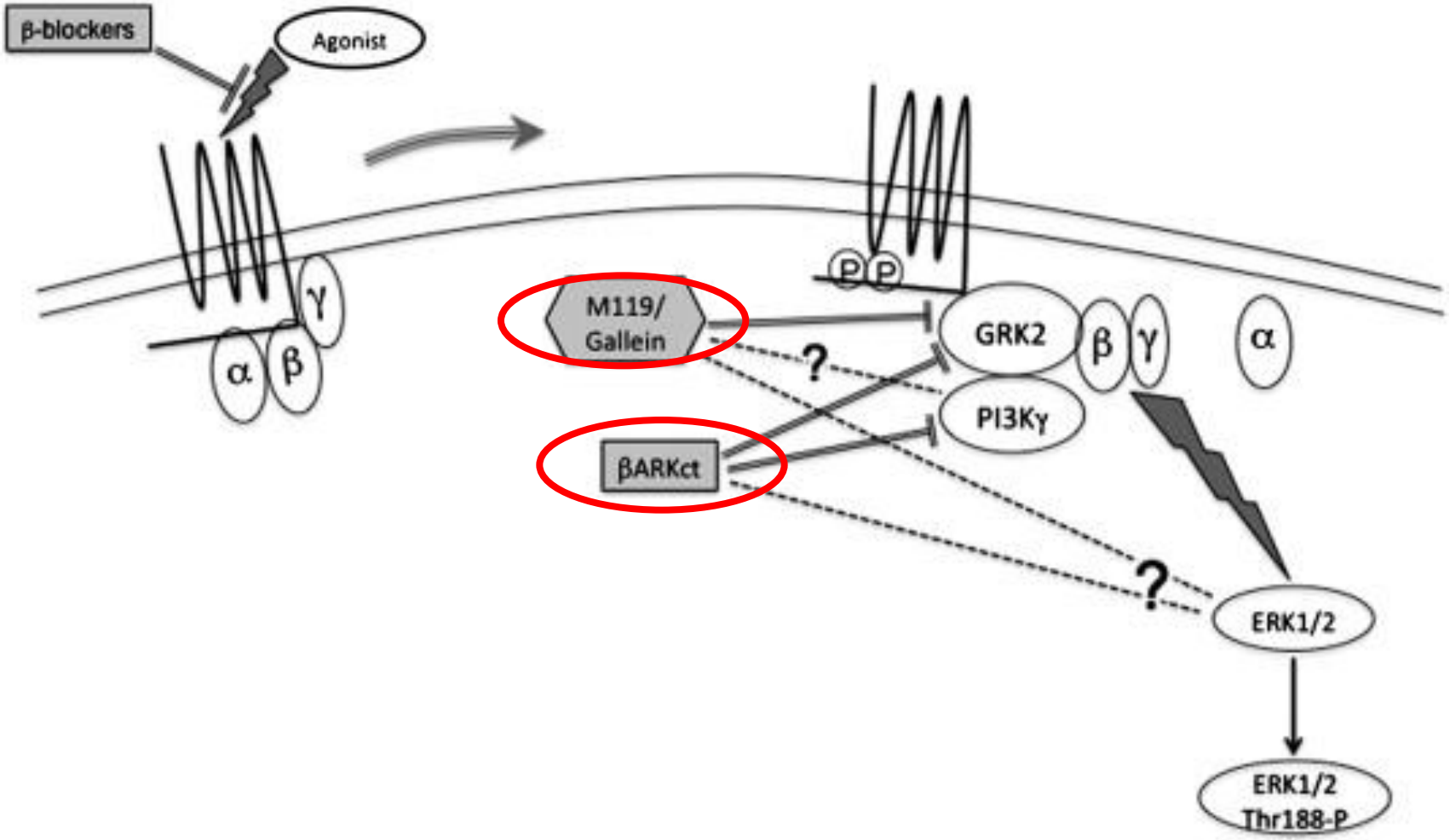
Circulation 2000, 2001, 2009

Eur Heart J. 2012

Molecole sperimentate in terapia genica dell'IC



Inibizione di GRK2 mediante piccole molecole capaci di sequestrare le subunità Gβγ



Kamal et al J Mol Cell Cardiol 2011

Seven-transmembrane-spanning receptors and heart function

Howard A. Rockman, Walter J. Koch* & Robert J. Lefkowitz†‡

*Departments of Medicine and Cell Biology, *Surgery, †Biochemistry, and ‡The Howard Hughes Medical Institute, Duke University Medical Center, Durham, North Carolina 27710, USA (e-mail: h.rockman@duke.edu)*

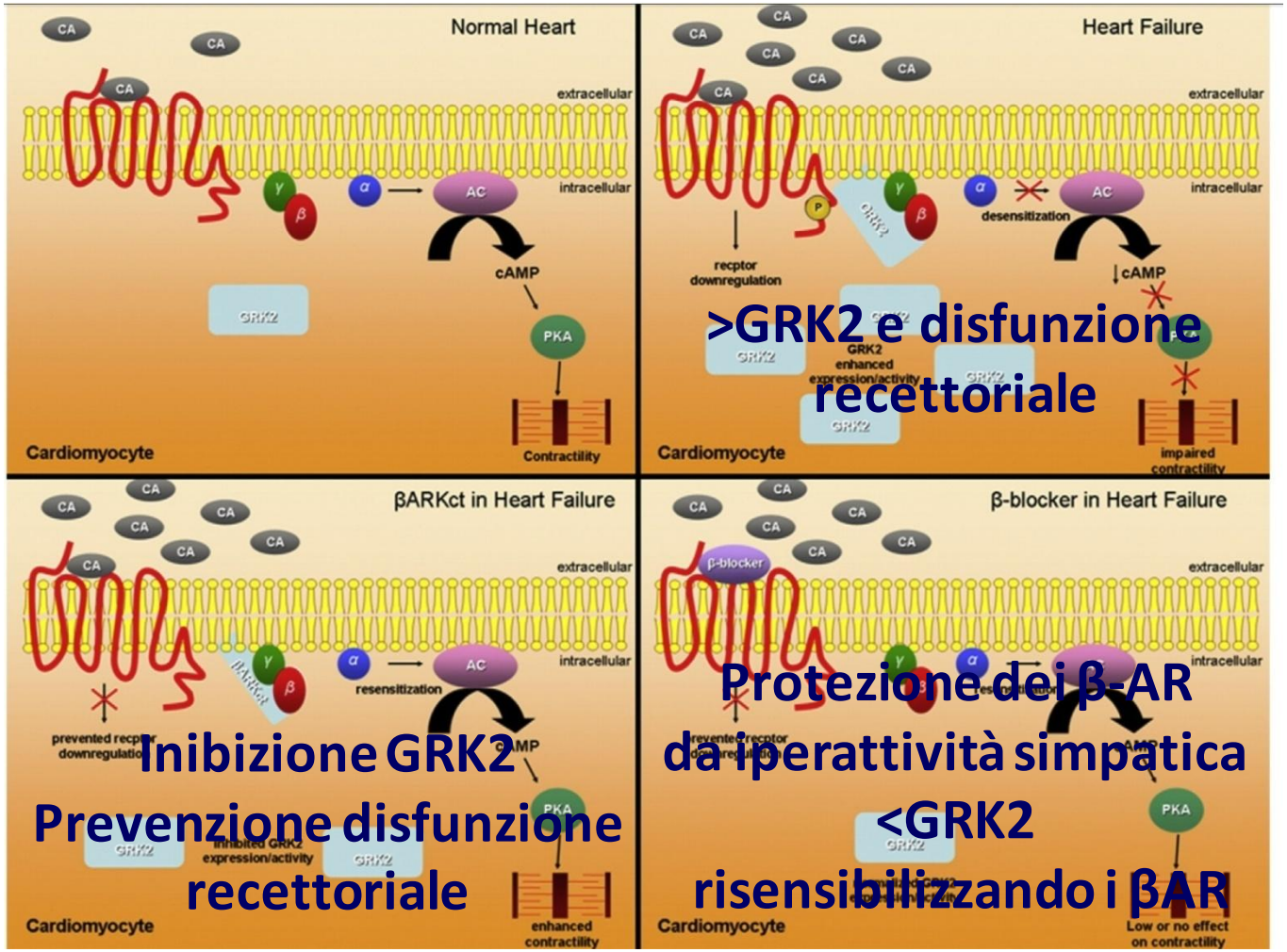
Understanding precisely how the heart can recognize and respond to many different extracellular signalling molecules, such as neurotransmitters, hormones and growth factors, will aid the identification of new therapeutic targets through which cardiovascular diseases can be combated. In recent years, we have learned more about the complex interactions that occur between the receptors and the signalling pathways of the heart and its environment. Most of these discoveries have focused on the most common type of cardiac receptor — the seven-transmembrane-spanning receptor or G-protein-coupled receptor.

NATURE | VOL 415 | 10 JANUARY 2002 | www.nature.com

The paradox of β-AR blockade and β-ARK1 inhibition

An important issue raised by the above findings is how to rationalize the seemingly protective effect of interrupting β-AR signalling with β-AR blockers and the beneficial effect of inhibiting β-ARK1 in heart failure. In fact, inhibiting β-ARK1 activity would be expected to facilitate β-AR signalling — much like β-agonists, which are poorly tolerated when administered chronically to individuals with heart failure[75]. In this context, we need to address several points that may aid our understanding of this apparent paradox.

Rimodellamento inverso del signaling dei β-AR indotto dai β-bloccanti



>GRK2 e disfunzione recettoriale

Inibizione GRK2
Prevenzione disfunzione recettoriale

Protezione dei β-AR da iperattività simpatica
<GRK2
risensibilizzando i βAR

Rengo G et al J Mol Cell Cardiol 2011

Effetto preventivo dell'esercizio fisico e del metoprololo sulla disfunzione dei β-AR nell'invecchiamento

Ageing is associated to β-AR downregulation

Table II. β-Adrenoceptor Radioligand Binding Properties in Left Ventricular Membranes Isolated from Rat Hearts of Varying Ages

Age	Bmax (fmole per mg membrane protein)	Percent β2ARs
2 mo	55.0±4.2	39.7±3.7
8 mo	45.2±2.9*	34.9±4.1
24 mo	39.4±2.2‡	36.3±4.1

n = 14 hearts for each age group; *$P < 0.05$ compared to 2 mo (one way ANOVA); ‡$P < 0.01$ compared to 2 mo (one way ANOVA). IC_{50}s for ICI 118,551 competition binding are not different among three age groups. 2 mo: $\beta_2 = 1.50 \times 10^{-8}$ M, $\beta_1 = 2.78 \times 10^{-6}$ M; 8 mo: $\beta_2 = 1.48 \times 10^{-8}$ M, $\beta_1 = 3.58 \times 10^{-6}$ M; 24 mo: $\beta_2 = 1.33 \times 10^{-8}$ M, $\beta_1 = 3.86 \times 10^{-6}$ M.

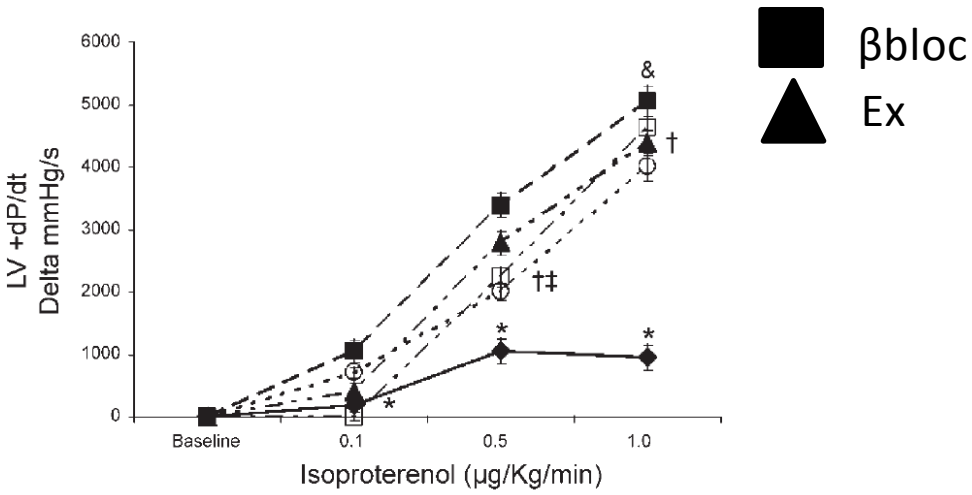
Rui-Ping Xiao et al J Clin Ivest 1998

Exercise Training and Metoprolol prevent age-related β-AR downregulation

Table 4. *Effects of training, metoprolol treatment, and training plus metoprolol treatment on cardiac membrane β-AR density and adenylyl cyclase activity*

	β-AR Density, fmol/mg membrane protein					
	Old Untrained	Young Untrained	Old Trained	Old Metoprolol	Old Trained Plus Metoprolol	*P*
	29.6±2.4	53.1±5.1	48.8±4.9	47.5±6.0	51.4±7.4	<0.01 OU vs. all
	Rate of cAMP production, pmol·mg^{-1}·min^{-1}					
No addition	14.8±3.7	40.5±2.8	34.3±2.8	35.6±2.2	38.6±3.1	<0.001 OU vs. all
Iso (10 μM) + GTP (100 μM)	12.6±3.6	54.8±3.3	61.8±3.2	56.5±4.5	59.6±4.2	<0.001 OU vs. all
Gpp(NH)p (10 μM)	24.2±5.4	50.4±6.0	52.4±9.1	58.1±6.5	49.8±7.2	<0.01 OU vs. all
Forskolin (100 μM)	41.2±6.1	95.6±12	53.4±9.0	55.6±11	50.8±10	<0.01 YU vs. all

Values are means ± SE. Gpp(NH)p, β-γ-imidoguanosine 5′-triphosphate; Iso, isoproterenol.



Leosco D, Rengo G et al Am J Physiol 2007

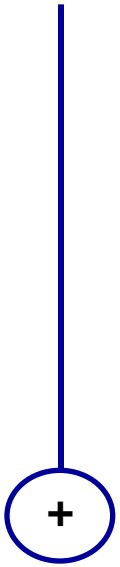
La regolazione del sistema nervoso simpatico

1. Meccanismi molecolari dell'iperattività simpatica nel surrene

2. Signaling β-adrenergico cardiaco e meccanismi molecolari della terapia con β-bloccanti e con inibizione di GRK2

3. **GRK2 nuovo biomarker di iperattività simpatica**

Iperattività del SNS



Consumo miocardico O2 *(J Mol Cell Cardiol 1985);*
Fibrosi interstiziale cardiaca *(Eur J Pharmacol 2004);* Apoptosi dei cardiomiociti *(Cardiovasc Res 2004);*
Rimodellamento inverso *(Am J Physiol Heart Circ Physiol 2007);*
Riduzione della riserva inotropa *(NEJM 1982);*
Produzione miocardica di ROS *(J Cell Mol Med 2007);*
Rischio di aritmie *(NEJM 1991);*
Sistema renina-angiotensina-aldosterone *(Am J Physiol 1992);*
Resistenze vascolari renali and periferiche (*JACC2009);*

Aumento livelli di GRK2 e disfunzione del signaling dei recettori beta-adrenergici cardiaci

European Heart Journal (2001) **22**, 1136–1143
doi:10.1053/euhj.2000.2407, available online at http://www.idealibrary.com on IDEAL®

Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure

H. P. Brunner-La Rocca, M. D. Esler, G. L. Jennings and D. M. Kaye

Alfred and Baker Medical Unit, Baker Medical Research Institute, Alfred Hospital, Melbourne, Australia

PLASMA NOREPINEPHRINE AS A GUIDE TO PROGNOSIS IN PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE

JAY N. COHN, M.D., T. BARRY LEVINE, M.D., MARIA TERESA OLIVARI, M.D., VICTORIA GARBERG, R.N., DENNIS LURA, B.S., GARY S. FRANCIS, M.D., ADA B. SIMON, PH.D., AND THOMAS RECTOR, PH.D.

JACC Vol. 26, No. 5
November 1, 1995:1257–63

Adverse Consequences of High Sympathetic Nervous Activity in the Failing Human Heart

DAVID M. KAYE, MBBS, PHD, FRACP,* JEFFREY LEFKOVITS, MBBS, FRACP,
GARRY L. JENNINGS, MDBS, FRACP, PETER BERGIN, MBBS, FRACP,
ARCHER BROUGHTON, MBBS, PHD, FRACP, MURRAY D. ESLER, MBBS, PHD, FRACP

Come si misura l'iperattività del SNS nell'IC

Method	Advantages	Limitations
Plasma Norepinephrine	• Easily measurable;	• High variability; • Overestimation due to reduced renal clearance in HF; • Systemic NE does not reflect organ-specific concentrations;
Norepinephrine Cardiac/Renal spillover	• Information on organ-specific sympathetic activity; • Indipendent from HF severity;	• Invasive tecniques; • Available in specialized centres;
Heart rate variability	• Easily and non-invasively performable;	• HRV reflects sinoatrial response to sympathetic/vagal stimulation; • No individual HR spectral component is specific for sympathetic cardiac modulation;
^{123}I-MIBG	• Information on cardiac-specific sympathetic dysregulation; • Non invasive;	• Expensive tecnique; • Patients exposition to radionuclides;

Reciprocal In Vivo Regulation of Myocardial G Protein–Coupled Receptor Kinase Expression by β-Adrenergic Receptor Stimulation and Blockade

Guido Iaccarino, MD; Eric D. Tomhave, BS; Robert J. Lefkowitz, MD; Walter J. Koch, PhD

Background—Impaired myocardial β-adrenergic receptor (βAR) signaling, including desensitization and functional uncoupling, is a characteristic of congestive heart failure. A contributing mechanism for this impairment may involve enhanced myocardial β-adrenergic receptor kinase (βARK1) activity because levels of this βAR-desensitizing G protein–coupled receptor kinase (GRK) are increased in heart failure. An hypothesis has emerged that increased sympathetic nervous system activity associated with heart failure might be the initial stimulus for βAR signaling alterations, including desensitization. We have chronically treated mice with drugs that either activate or antagonize βARs to study the dynamic relationship between βAR activation and myocardial levels of βARK1.

Methods and Results—Long-term in vivo stimulation of βARs results in the impairment of cardiac βAR signaling and increases the level of expression (mRNA and protein) and activity of βARK1 but not that of GRK5, a second GRK abundantly expressed in the myocardium. Long-term β-blocker treatment, including the use of carvedilol, improves myocardial βAR signaling and reduces βARK1 levels in a specific and dose-dependent manner. Identical results were obtained in vitro in cultured cells, demonstrating that the regulation of GRK expression is directly linked to βAR signaling.

Conclusions—This report demonstrates, for the first time, that βAR stimulation can significantly increase the expression of βARK1, whereas β-blockade decreases expression. This reciprocal regulation of βARK1 documents a novel mechanism of ligand-induced βAR regulation and provides important insights into the potential mechanisms responsible for the effectiveness of β-blockers, such as carvedilol, in the treatment of heart failure. (***Circulation.*** **1998;98:1783-1789.)**

Key Words: heart failure ■ receptors, adrenergic, beta ■ myocardium ■ catecholamines

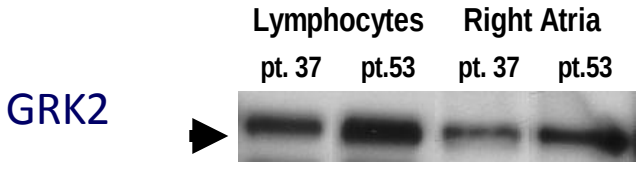
Iaccarino G et al Circulation 1998

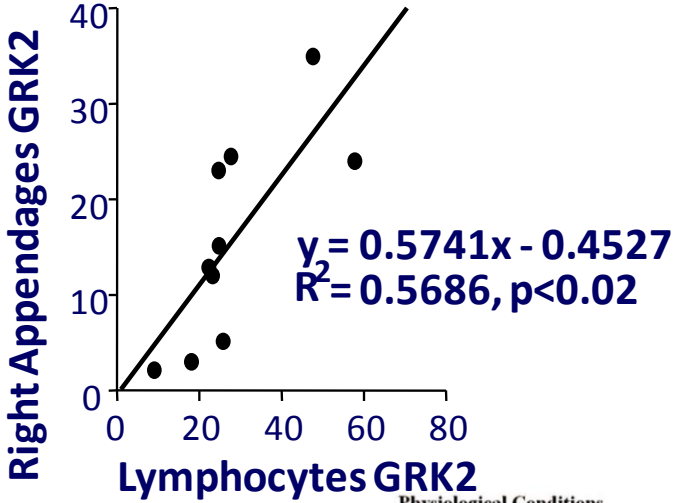
L’iperattività simpatica correla con la disfunzione dei βAR e quest’ultima è dovuta all’aumentata attività di GRK2

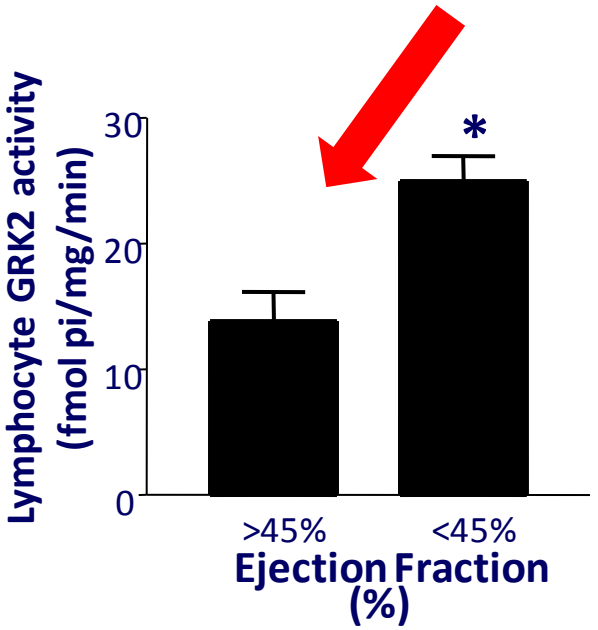
Si può ipotizzare che

GRK2 potrebbe quindi rappresentare un nuovo bio-marker di IC in grado di dare informazioni sul grado di iperattività simpatica e quanto quest’ultima danneggi il βAR

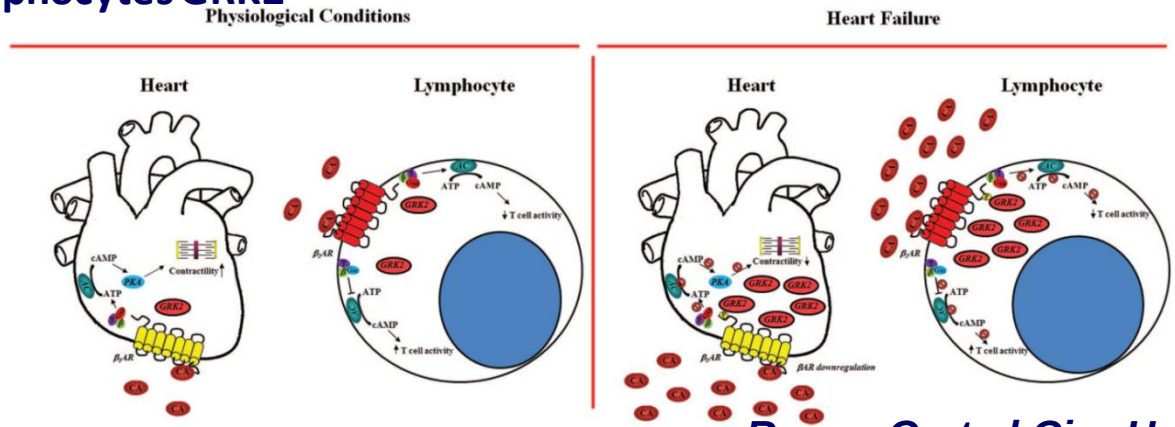
Elevata espressione di GRK2 nel miocardio e nei linfociti nell'IC







Iaccarino G et al Eur Heart J 2005

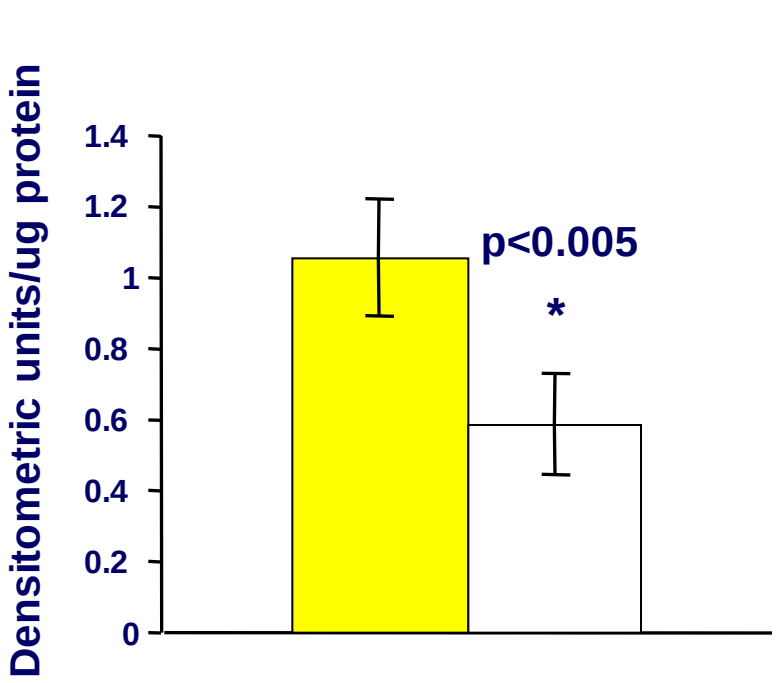


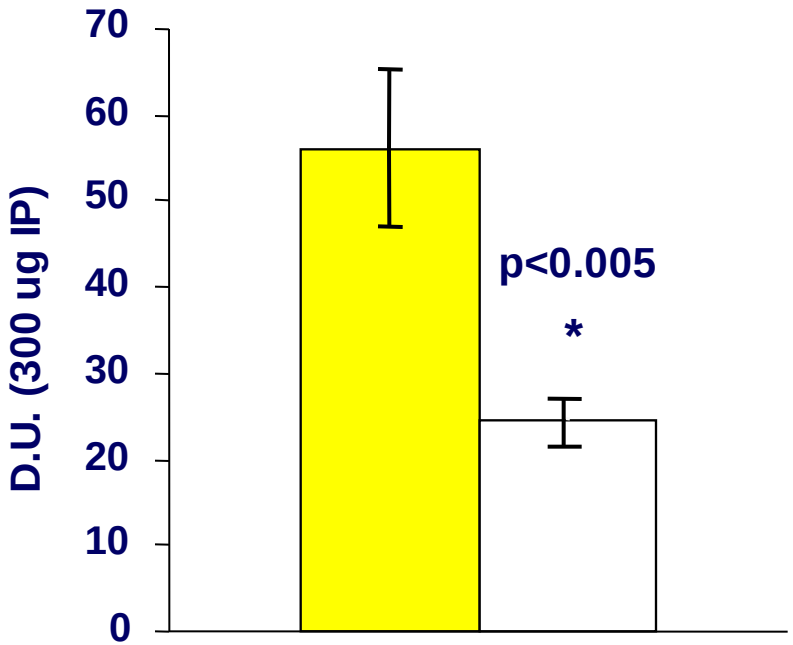
Rengo G et al Circ Heart Fail 2012

Livelli di βARK dopo LVAD nella IC

Myocardial GRK2 protein

Human Pre/Post LVAD Lymphocyte GRK2





Pre-LVAD (n=12)

Post- LVAD (n=12)

Hata G et al J Card Fail 2006

Valutazione prognostica dei livelli di GRK2 nei linfociti in pz con IC

Table 1. Characteristic of patients in the overall study population and in patients stratified in survivors and non survivors

	All (n=282)	Survivors (n=142)	Non Survivors (n=140)	p value
Age, y	70.74±10.68	67.7±10.5	73.8±10	<0.0001
Gender, % Male (n)	70.2% (198)	73.9% (105)	66.4% (93)	0.193
LVEF, %	32±9.2	35.2±8.65	28.9±8.7	<0.0001
NYHA class	II = 21.3% (60) III = 78.7% (222)	II = 30.9% (44) III = 68.1% (98)	II = 11.4% (16) III = 88.6% (124)	<0.0001
Hypertension, % (n)	76.2% (215)	78.2% (111)	74.3% (104)	0.486
Diabetes, % (n)	44.7% (126)	41.5% (59)	47.9% (67)	0.338
Hypercolesterolemia, % (n)	33.7% (95)	33.8% (48)	33.6% (47)	1.000
AF, % (n)	18.8% (53)	18.3% (26)	19.3% (27)	0.880
COPD, % (n)	28.7% (81)	26.8% (38)	30.7% (43)	0.511
GFR <60 ml/mg, % (n)	37.2% (105)	28.9% (41)	45.7% (64)	0.005
Medication				
ACE I / ARBs, % (n)	83.7% (236)	84.5% (120)	82.9% (116)	0.749
BetaBlockers, % (n)	52.8% (149)	57% (81)	48.6% (68)	0.189
Diuretics, % (n)	69.9% (197)	66.9% (95)	72.9% (102)	0.301
CaChannelAnt, % (n)	24.5% (69)	26.8% (38)	22.1% (31)	0.407
Biochemical determinations				
Serum NT-proBNP, pg/dl	1851.4±1177.6	1357.4±988.3	2352.5±1114.8	<0.0001
Plasma Norepinephrine, pg/dl	607.3±241.5	553.8±221.5	661.5±249.4	<0.0001
Lymphocyte GRK2, D.U.	1.39±0.69	1.15±0.59	1.65±0.69	<0.0001

Data are expressed as mean±1 standard deviation or percentage.
LVEF= left ventricular ejection fraction; NYHA= New York Heart Association; AF= Atrial fibrillation; COPD= chronic obstructive pulmonary disease; GFR= Glomerural Filtration Rate; ACE I= angiotensin-converting-enzyme inhibitor; ARBs= angiotensin receptor blockers; NT-proBNP= N-terminal pro-brain natriuretic peptide; GRK2= G coupled-receptor Kinase 2

Rengo G et al JACC Heart Failure submitted

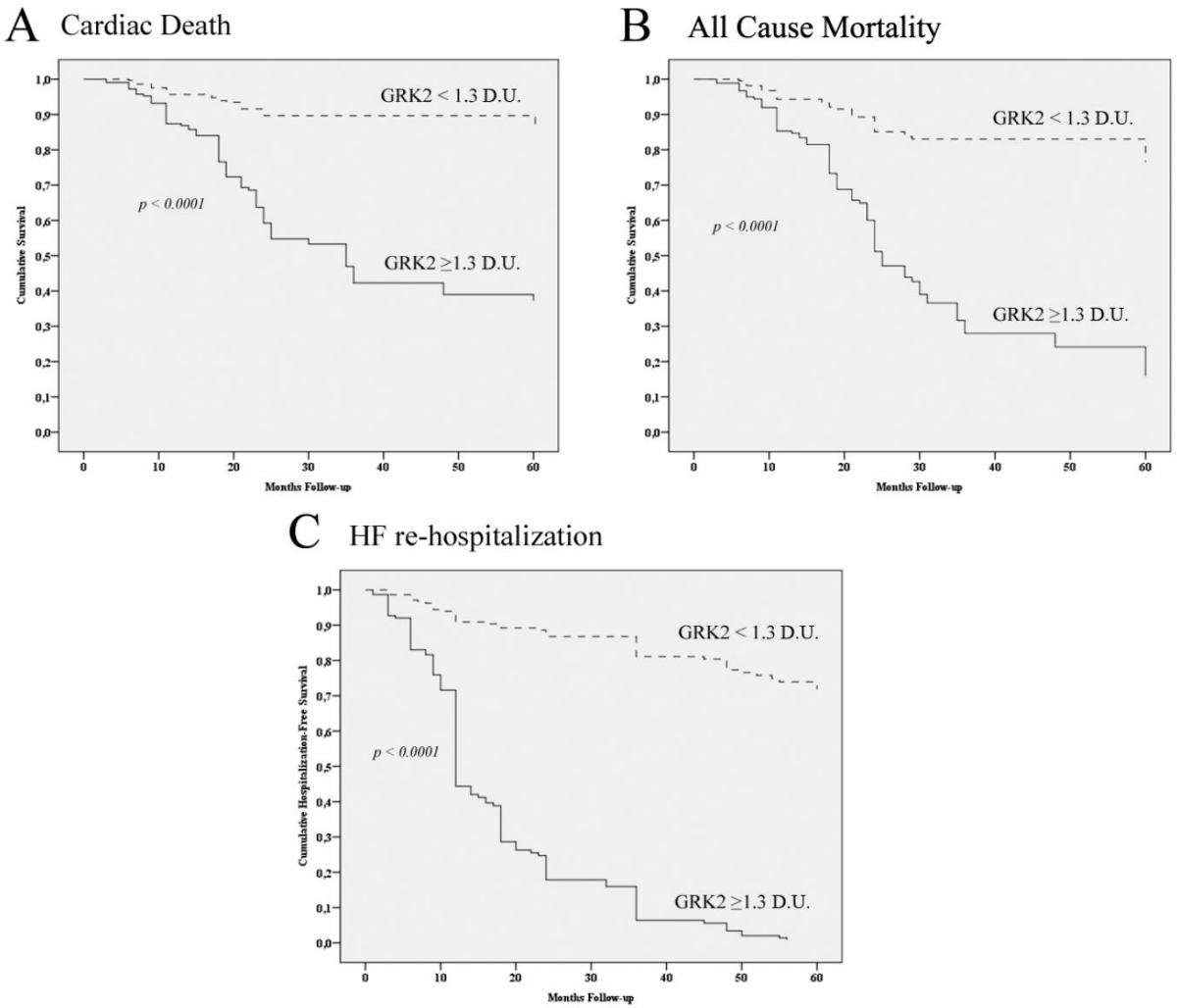
Predittori di morte cardiaca, morte per tutte le cause e riospedalizzazione per IC

	Table 2A. Cardiac Death					Tab 2B. All Cause Death					Tab 2C. HF re-hospitalization				
	Univariate		Multivariate analysis			Univariate		Multivariate analysis			Univariate analysis		Multivariate analysis		
	Wald	p value	Wald	Hazard ratio	p value	Wald	p value	Wald	Hazard ratio	p value	Wald	p value	Wald	Hazard ratio	p value
Age	25.381	<0.0001	6.713	1.034	0.010	24.218	<0.0001	7.913	1.031	0.005	11.662	0.001	6.925	1.029	0.008
Gender	2.903	0.088	0.056	0.950	0.813	1.259	0.262	0.213	0.914	0.645	4.175	0.041	0.302	1.105	0.583
LVEF	36.520	<0.0001	3.936	0.973	0.047	33.291	<0.0001	4.678	0.975	0.031	45.618	<0.0001	11.139	0.968	0.001
NYHA class	17.949	<0.0001	5.513	0.277	0.019	12.221	<0.0001	0.408	0.821	0.523	5.280	0.022	1.625	1.382	0.202
Hypertension	0.373	0.541	-	-	-	0.164	0.686	-	-	-	1.767	0.184	-	-	-
Diabetes	3.276	0.070	0.125	0.932	0.724	1.555	0.212	-	-	-	16.335	<0.0001	8.454	0.622	0.004
Hypercolesterolemia	1.101	0.294	-	-	-	0.012	0.914	-	-	-	7.033	0.008	3.309	0.722	0.069
AF	0.369	0.544	-	-	-	0.320	0.572	-	-	-	0.148	0.701	-	-	-
COPD	0.831	0.362	-	-	-	1.162	0.281	-	-	-	0.009	0.923	-	-	-
GFR <60 ml/mg	19.821	<0.0001	6.143	0.593	0.013	12.206	<0.0001	4.848	0.658	0.028	9.770	0.002	0.117	0.944	0.732
NT-proBNP	78.497	<0.0001	8.102	1.000	0.004	70.719	<0.0001	8.156	1.000	0.004	65.345	<0.0001	12.274	1.000	<0.0001
Norepinephrine	16.918	<0.0001	0.358	1.000	0.550	21.586	<0.0001	1.343	1.000	0.246	9.523	0.002	1.392	1.000	0.238
Lymphocyte GRK2	47.03	<0.0001	10.648	1.614	0.001	58.013	<0.0001	16.157	1.626	<0.0001	125.374	<0.0001	53.344	2.067	<0.0001

LVEF= left ventricular ejection fraction; NYHA= New York Heart Association; AF= Atrial fibrillation; COPD= chronic obstructive pulmonary disease; GFR= Glomerural Filtration Rate; NT-proBNP= N-terminal pro-brain natriuretic peptide; GRK2= G-coupled Receptor Kinase 2

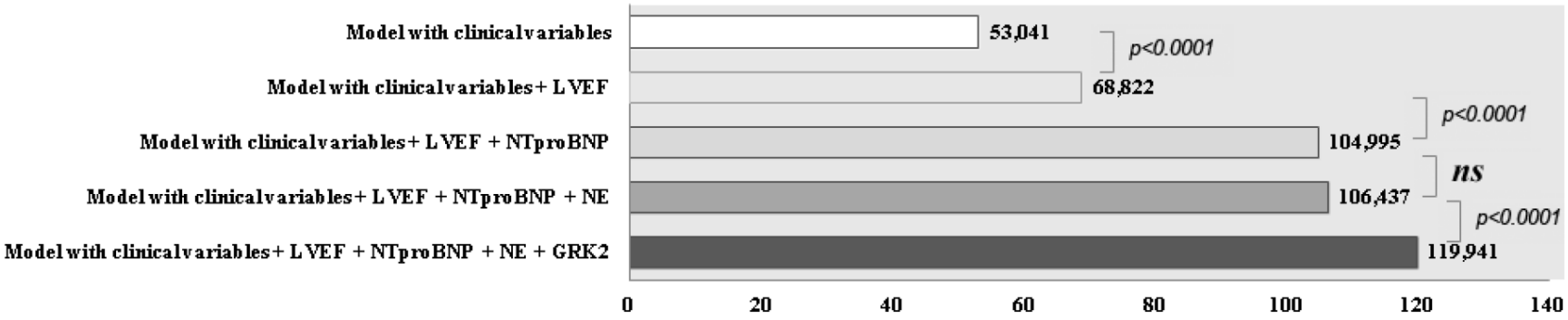
Rengo G et al JACC Heart Failure submitted

Sopravvivenza in pz con GRK2 sopra e sotto la mediana



Rengo G et al JACC Heart Failure submitted

Valore prognostico incrementale di GRK2 rispetto alle variabili cliniche e ad altri biomarker



Rengo G et al JACC Heart Failure submitted

Conclusioni

- L'aumento di GRK2 nel surrene svolge un ruolo fondamentale nell'induzione dell'iperattività simpatica nell'IC
- L'inibizione di GRK2 nel cuore mediante terapia genica o farmacologica (paroxetina, galleina) ripristina le alterazioni del signaling adrenergico e migliora la contrattilità nell'IC
- GRK2 linfocitario si propone come nuovo biomarker di iperattività simpatica per la stratificazione prognostica dei pz con IC

Graditudine al mio Maestro, a tutti i Colleghi e Ricercatori incontrati nel corso della mia carriera accademica

1960 - 1980

Prof. Mario Condorelli
Prof. Giuseppe Giuffrida
Prof. Giuseppe Critelli
Prof. FrancescoTrimarchi
Prof. Ferraù
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Dott. Giuseppe Rengo
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Dott.ssa Daniela Liccardo
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Ing. Alessandro De Nunzio

Il testimone ora passa a…

Università degli Studi di Napoli Federico II
Dpt Scienze Mediche Translazionali
Cattedra e Scuola di Specializzazione di Geriatria
Direttore prof. Nicola Ferrara

Nicola Ferrara
Carlo Vigorito
Pasquale Abete
Dario Leosco
Vincenzo Canonico
Giusto Gerundo
Giuseppe Rengo

"Tristo è quel discepolo che non supera lo suo maestro"

Leonardo da Vinci

Un particolare voto augurale va al **“Laboratorio di Geriatria Traslazionale”**

Università degli Studi di Napoli Federico II
Dpt Scienze Mediche Translazionali
Cattedra e Scuola di Specializzazione di Geriatria
Direttore prof. Nicola Ferrara

Dario Leosco & Giuseppe Rengo

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Collaborazioni:

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Anastasios Lymperopoulos,
Nova Southeastern University, Fort Lauderdale, FL

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