NOVEL INNOVATIVE NANOTECHNOLOGY WITH ENDOGENOUS VASCULOPROTECTIVE HEAT SHOCK PROTEIN 70i BY HS OR GGA and FUTURE APPLICATIONS FOR SPINAL CHORD PROTECTION IN AORTIC PATHOLOGY.

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AATS VISION; LEADERSHIP; SCHOLARSHIP

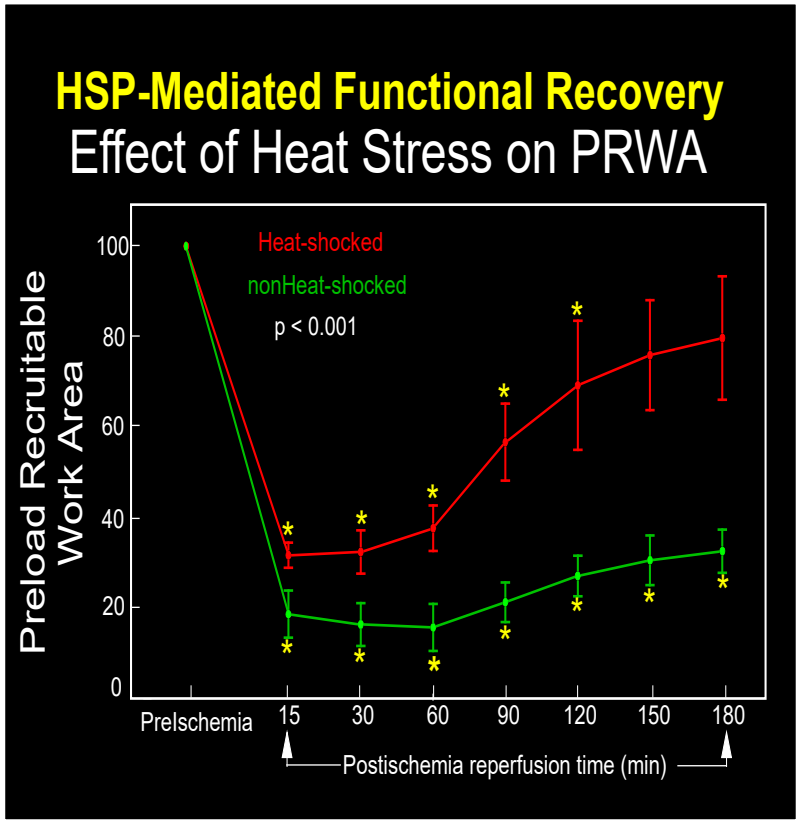
- PROBLEM—PARAPLEGIA, PARAPARESIS,STROKE
  - PATIENTS
  - PERSONAL SIGNIFICANCE---
    - Grandpa
    - Colleague Peter
    - Czarny, Fabio,Cupid,Elio,Baila
      - broke my heart to watch, helped as much as I could

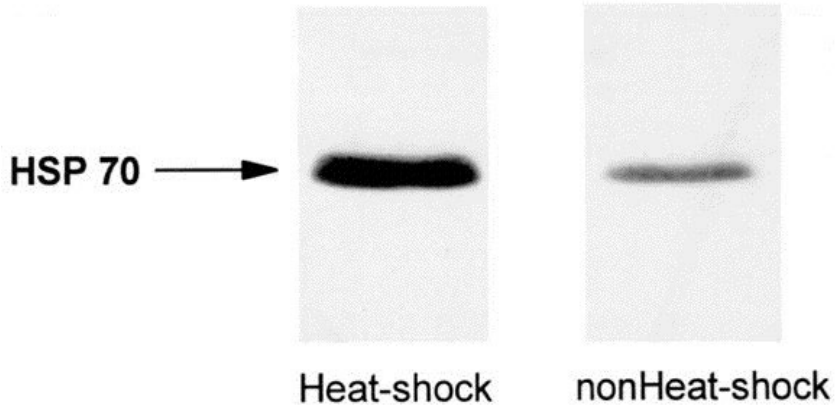
- VISION
  - helping spinal chord problems with endogenous means with heat shock proteins
  - EXOGENOUS TECHNIQUES HELPFUL FOR SPINAL CHORD PROECTION
    COULD BE COMPLEMENTED BY ENDOGENOUS TECHNIQUES of HSP70i
  - Spoke with Dr. Lemaire 2011
  - Neurologic sequelae devastation
  - Thinking about way to improve paraplegia, paraparesis aorta since early 2000s
  - My first patients as a high school student as a phlebotomist at the Veterans hospital behind my highschool in Palo Alto, boyfriend paralyzed when a medical studer German Shepherd dogs degenerative myelitis, grandfather stroke, patients oer career----very devastating, an important problem to improve

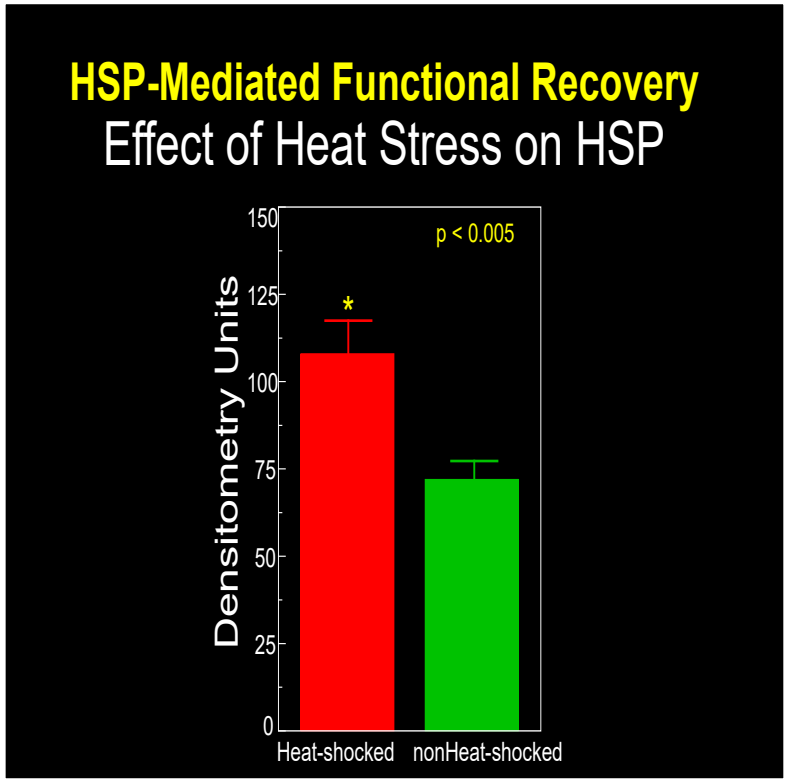
- NOVEL INNOVATION IDEA TO COAT AORTIC STENT WITH GGA AND REDUCE NEUROLOGIC COMPLICATIONS
  - CORONARY STES ARE DRUG ELUTING
  - *Esophageal nor airway stents are not drug eluting*
  - GGA model

- LEADERSHIP
  - Schaff/Morris;Romero;Toft;Tyce Mayo Clinic--Mayo Clinic Scholars Grant
    - Hyperthermia model
  - del Nido Harvard Children Hospital Boston
    - Harvard Gross Grant
    - TSFRE Nina Braunwald Grant

PROTECTION WITH HSP70i INDUCTION



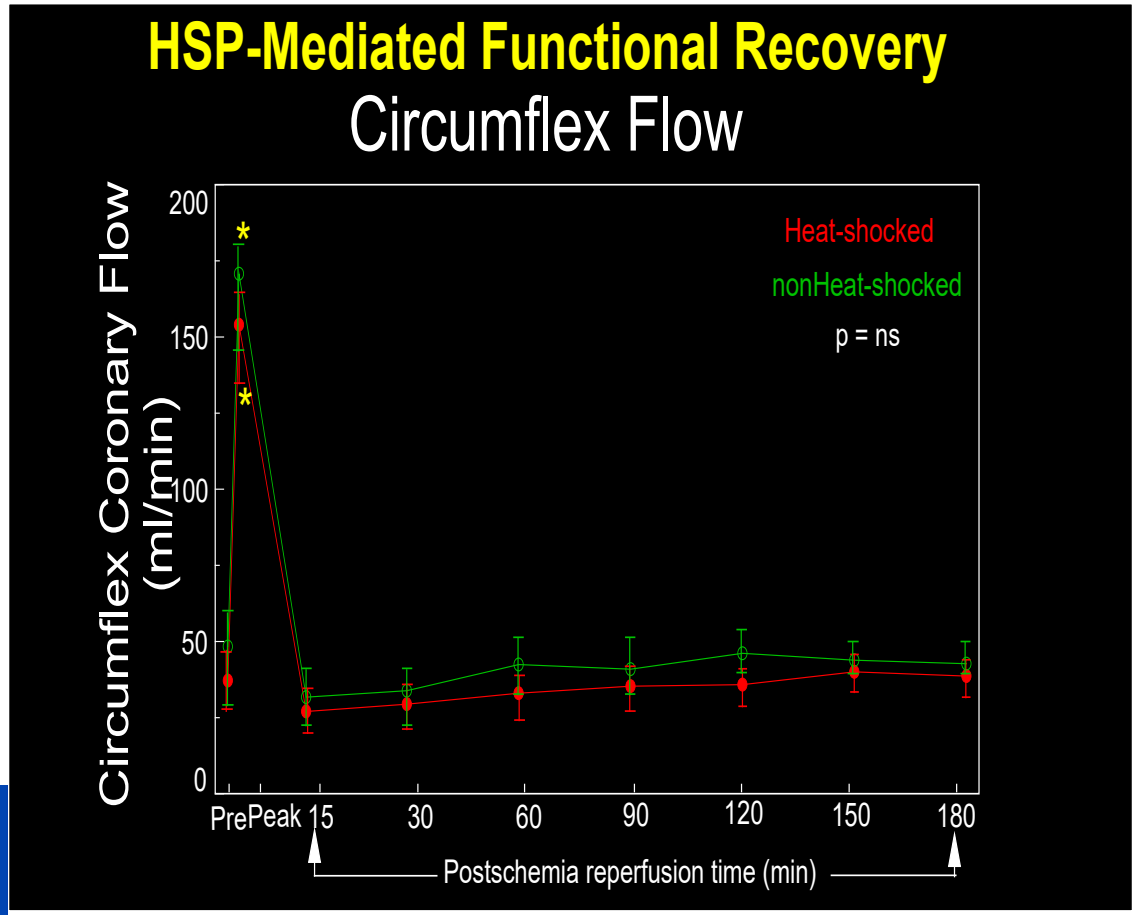




RESULTS

WE DEMONSTRATED PRIOR ENDOGENOUS INDUCTION OF HSP70 HAS CORONARY BENEFITS---

HIGHER PEAK CORONARY FLOW REPERFUSION with CORONARY HSP70I INDUCTION



HS INCREASED CORONARY ARTERY HSP70i (WB)

INCREASED CORONARY VASCUALR HSP70i WAS ALSO ASSOCIATED WITH
IMPROVED ENDOTHELIAL RELAXATION

ENDOTHELIAL DERIVED COR. RELAXATION IMPROVED

HSP70i INDUCED IN AORTA BY GGA

HOWEVER HUMAN HEAT STRESS PROTEIN 70i DECREASES WITH AGE

- HSP70I MOST PREDOMINANT HSP IN HUMANS
- UNFORTUNTELY DECREASED EXPRESION OF HSP70i WITH AGE
- IN AORTIC DISEASE PROBLEMATIC AS AORTIC ENDOTHELIUM WORSENS WITH AGE, INCREASED ANEURYSMAL DISEASE, DISSECTIONS WITH AGE
  ENDOTHELIUM IS ABNORMAL AND WORSENS WITH AGE
  - SIMULTANEOUSLY AORTIC ENDOTHELIUM ABNORMAL IN SMOKING,Diabetes Mellitus, GENDER, HYPERTENSION, HYPERCHOLESTEROLEMIA, MENOPAUSE
  - LIPIDS BAD
  - EXOGENOUS ASPIRIN good
- CORRELATES WITH WHEN AORTIC ANEURYSMS DISSECTIONS ETC INCREASE
- SVENSSON PAPER AORTI NORMALIZATION I SHOULD BE ON THAT PAPER BR EMAIL KHETIN CHICAGO
- CCF AATS AORTIC GUIDELINES---NOTHING ON ENDOGENOUS PROTECTION
- INDEPENDENT NEUROLOGIC PROTECTION OF HSP70i

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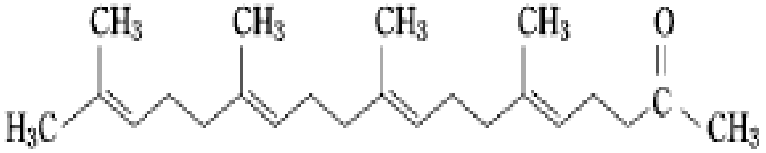
IV GGA: $C_{23}H_{38}O$

Structural formula:

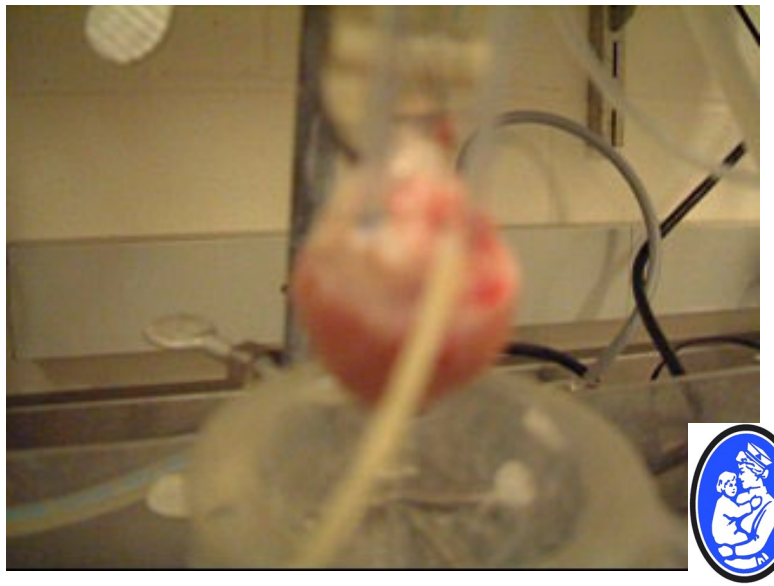


- antiulcer drug—Japan x 20 yrs
- increases hsp70
- Antiaptotic
- Neuro protection—only po
- Hepatic protection
  - Nuclear hsf1 translocation---inc hsp70i
  - Decreased caspase 3, 9
- Cardiac protection; po, decreased CPK

Cardioplegia composition

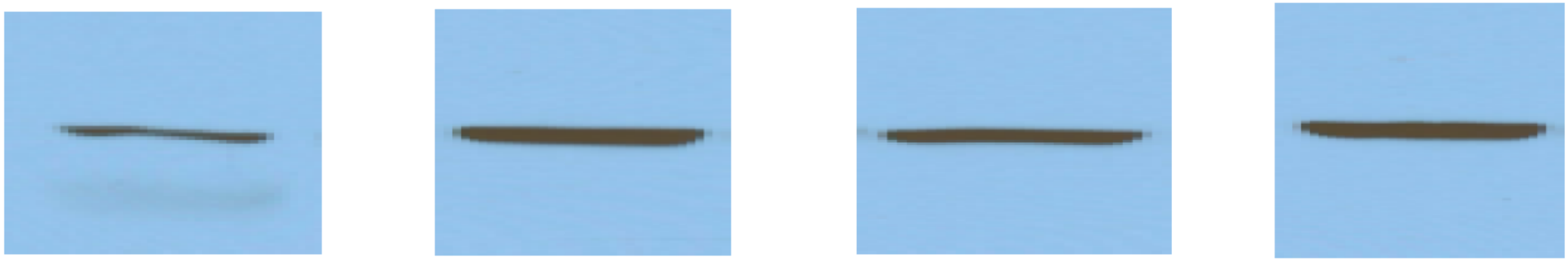
	4L
Glucose (sigma G-8270)	8.3g
NaCl (sigma S-9888)	27.6g
$NaHCO_3$ (sigma S-6014)	7.9g
$MgSO_4$ (sigma M-1880)	1.17g
KH_2PO_4 (sigma P-0662)	0.66g
KCl (sigma P-4504)	0.99g
Insulin (sigma I-5500) 25u/ml	1.6ml
10%$CaCl_2$ (sigma C-5080)	7.4ml

Langendorf model of ischemia/reperfusion



SIMILAR HSP70i INDUCTION at 24 HRS AFTER HS as 24 HRS AFTER 60MG/KG GGA

Cardiac Expression of HSP72 with Heat Stress



C 24HS 24GGA30 24GG60

HSP70i level 24 hours after GGA administration at 30 or 60mg/kg		
	Raw data	Normalized to C
C	6842.054	1.00
HS24	17946.024	2.62
GGA30	14643.953	2.14
GGA60	17576.246	2.57

SUMMARY

-Hyperthermia in the rabbit induces hsp70i *and not hsc70,* like other species.

-Hyperthermia stimulates hsp70i at 24 hrs but also earlier as soon as 2 hrs.

-Increased hsp70i at 24 hours is associated with better cardiac and coronary function than at 12 hours.
-and is associated with nuclear translocation

-Aortic hsp70i is also greater at 24 han 12 hours
-also associated with increased nuclear translocation

-Single dose of GGA induces significant, specific, early and sustained expression of myocardial inducible HSP70i
-as early as 2 hours after injection
-while not induce expression of constituitive HSP70 at 24 hrs.

-GGA induces similar to gold standard *HSC70 and* Hsp70i induction as hyperthermic stress at 24hrs.

GGA administration results in improved cardiac function particularly at 60min reperfusion,
separate from that of cardioplegia

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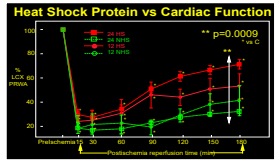
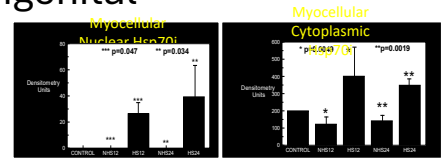
DISCUSSION---

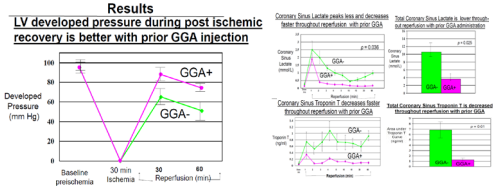
VASCULAR MECHANISMS OF PROTECTION OF HEAT SHOCK PROTEIN 70i





- MECHANISM OF PROTECTION OF HEAT SHOCK PROTEIN 70–
- Decrease free radical production, Decreased inflammation, Mitochondrial protection
- THUS MANEUVERS T IMPROVE AORTIC ENDOTHELIAL FUNCTION ARE IMPERATIVE---Covid, adult congenital
- FUTURE TEMPORAL TRENDS OF IMPROVED FUNCTION AT 24 VS. 12 HRS AFTER HS
- NUCLEAR TRANSLOCATION AS SEEN IN MYOCARDIUM AS WELL AS AORTA
  - FUTURE MECHanism of protection nuclear translocation

- BIOCHEMICAL ANALYSIS
- PROTECTION FROM CATECHOLAMINES
- UNDERSTAND GENDER, RACE,AGE,DISEASE DIFFERENCES IN HSP70i EXPRESSON TO COMPLEMENET EACH OTHER RATHER THAN COMPLTW
- NOVEL AGENTS PROTECTING VIA HSP70I; eg GGA



- ADJUCTS TO CARDIOPLEGIA
- early induction for better post reperfusion protection
  - Looking for agent can protect WITHIN 2 HOURS HEART PRVED Q AORTA

- Future Collaborate and Innovaton for coating stents

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FUTURE ENDEAVORS and DIRECTIONS---- LIMITATIONS

- HYPERTHERMIA NOT CLINICALLY APPLICABLE
  - OTHER STIMULI
- All animals male adults
  - at Mayo Clinic and Children Hospital Boston, Harvard
  - GENDER DIFFERENCES?
    - In aortic dissection, AS,AR
  - RACIAL DIFFERENCES?
    - Valvar heart disease, not included in guidelines
  - AGE DIFFERENCES---was preliminary purpose of Nina Braunwald Grant

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