# About OMICS Group

OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

# About OMICS Group Conferences

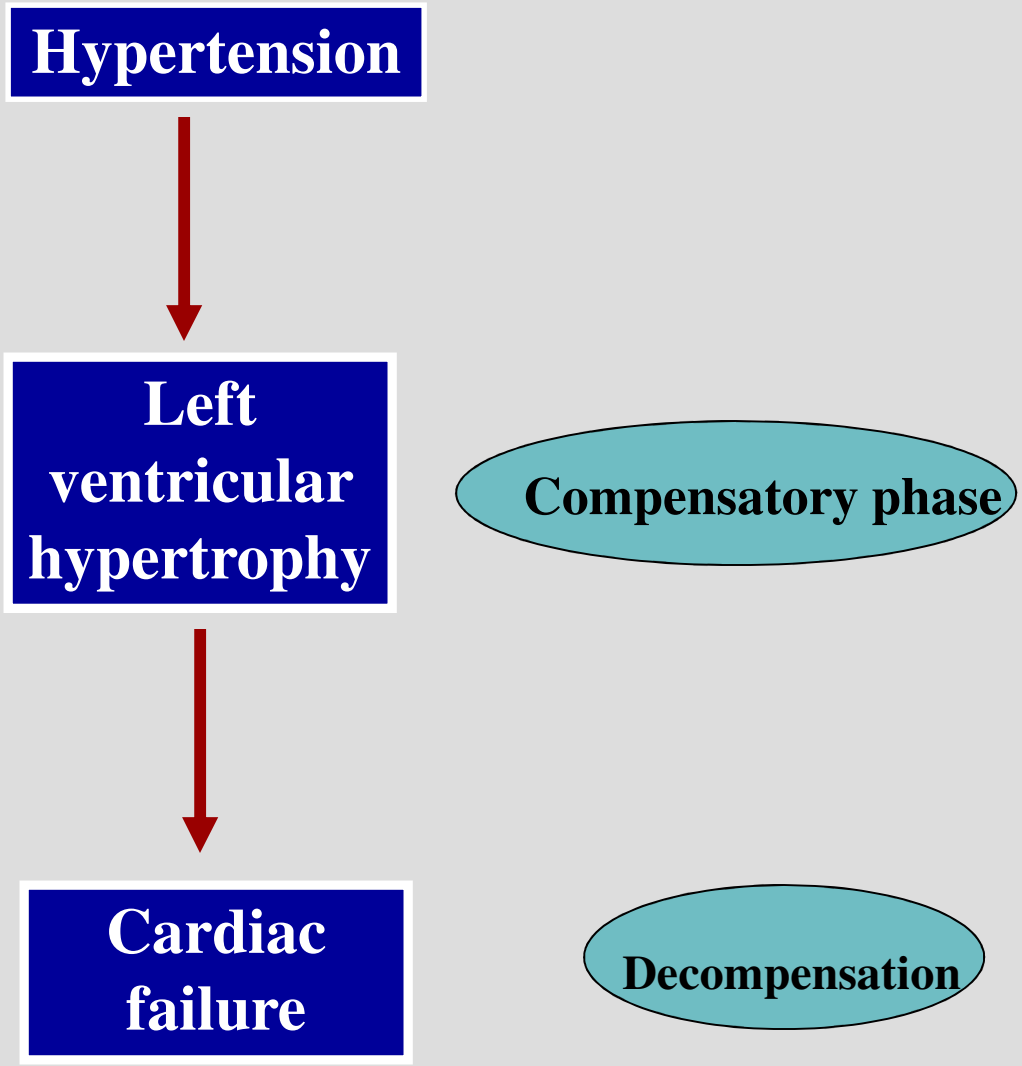
OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

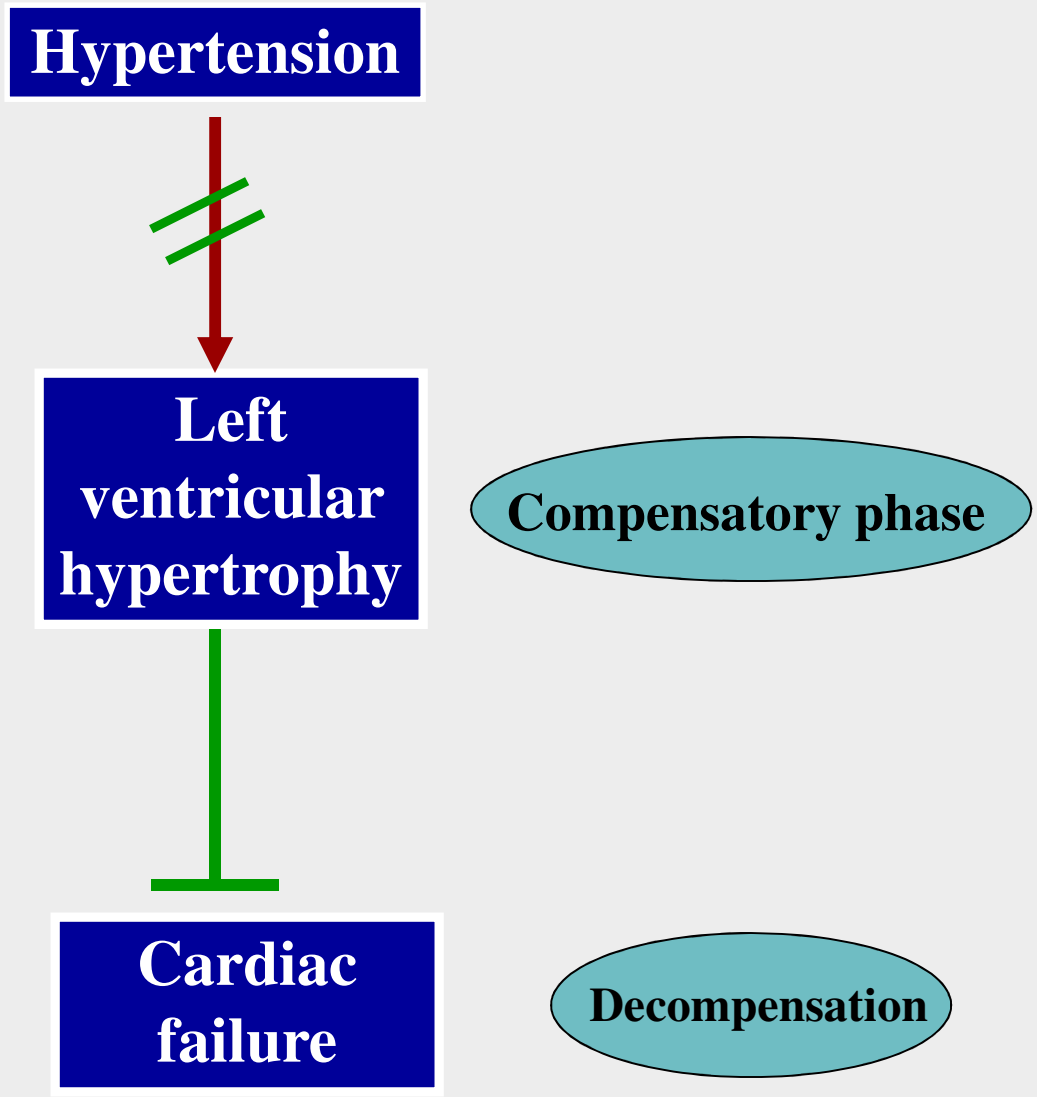
# RELATIONSHIP BETWEEN OXIDATIVE STRESS AND ENERGY METABOLISM IN HYPERTENSION INDUCED CARDIAC REMODELING

**R.Renuka Nair**
**Division of Cellular and Molecular Cardiology**
**Sree Chitra Tirunal Institute for Medical Sciences and Technology**
**INDIA**

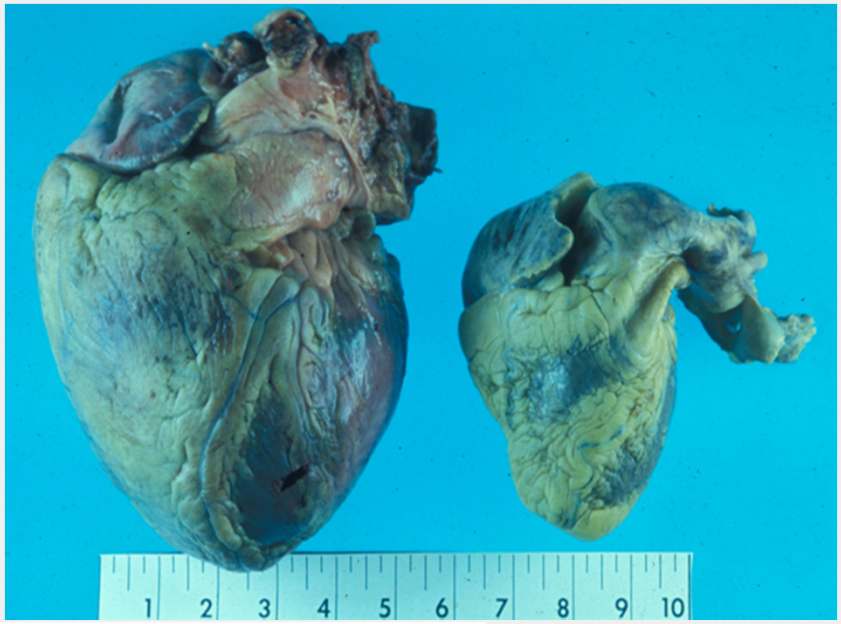
# LEFT VENTRICULAR REMODELING IN CHRONIC PRESSURE OVERLOAD

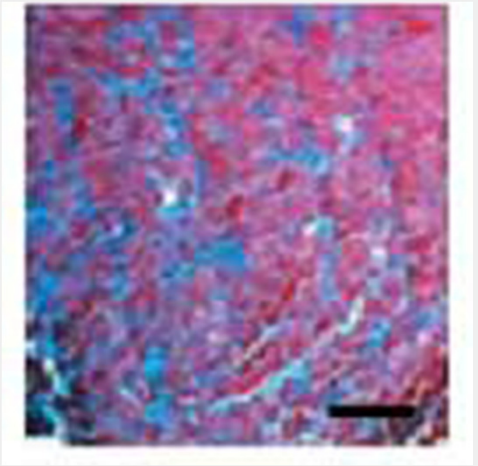


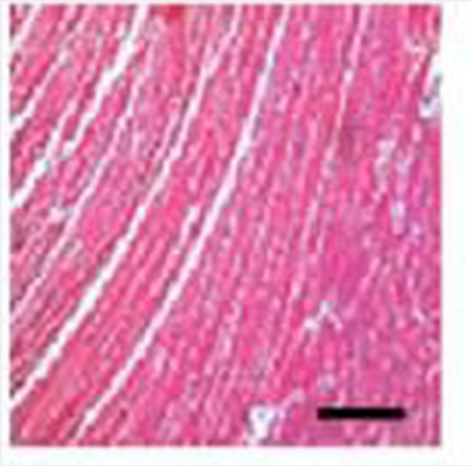
# CARDIAC REMODELING IN CHRONIC PRESSURE OVERLOAD



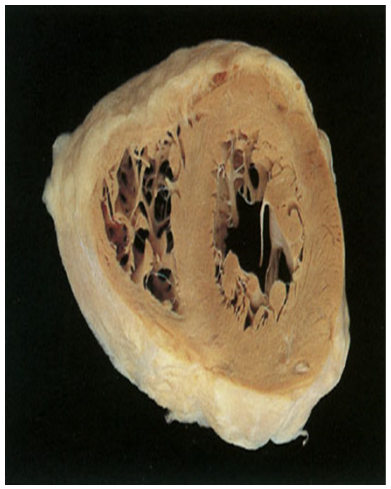
# COMPARISON OF HYPERTROPHIC HEART (LEFT) WITH NORMAL (RIGHT)

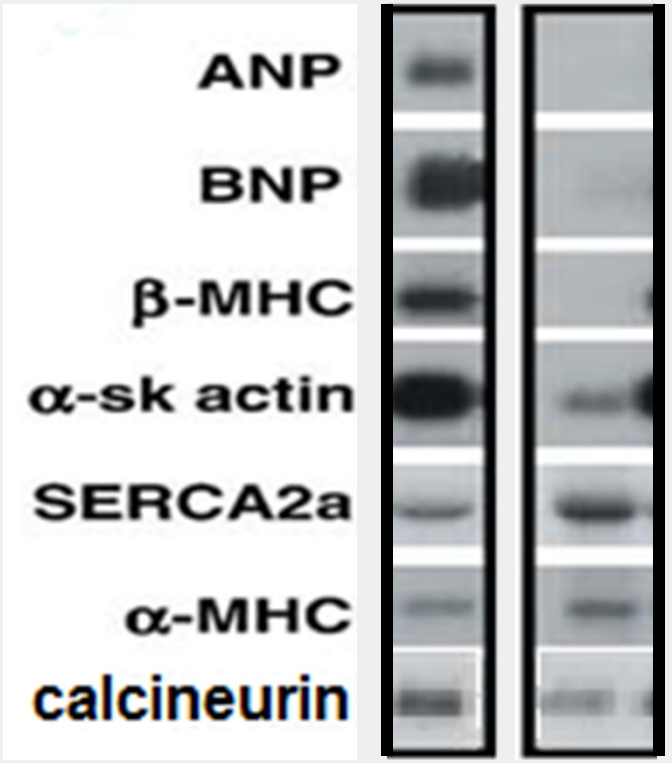






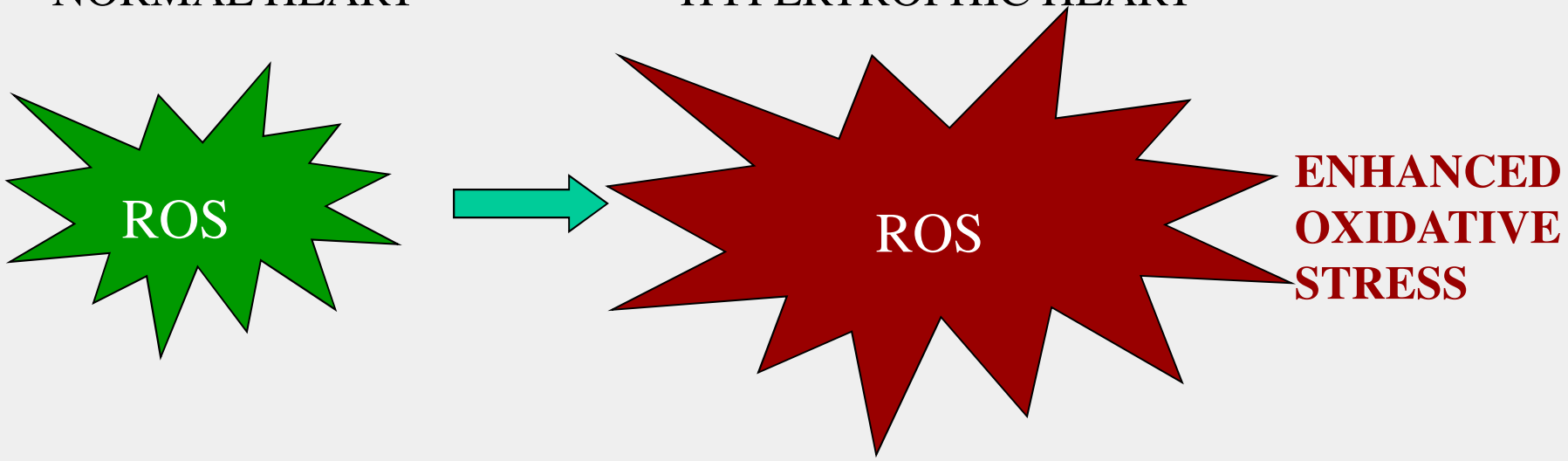



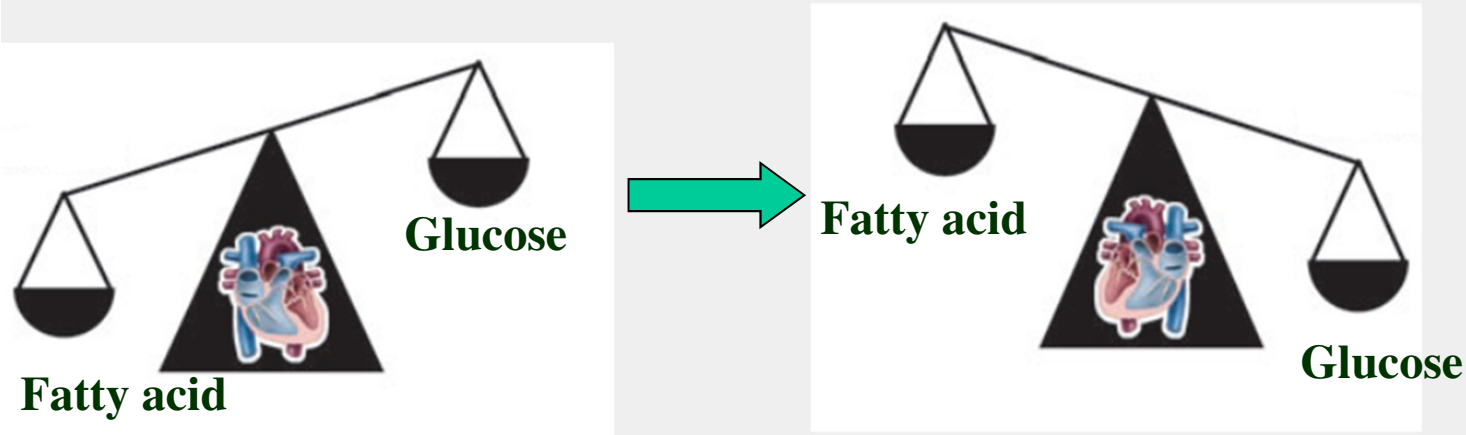


# FEATURES ASSOCIATED WITH HYPERTROPHY

NORMAL HEART

HYPERTROPHIC HEART




**SHIFT IN SUBSTRATE PREFERENCE**

# STRATEGIES TO PREVENT PATHOLOGICAL REMODELING

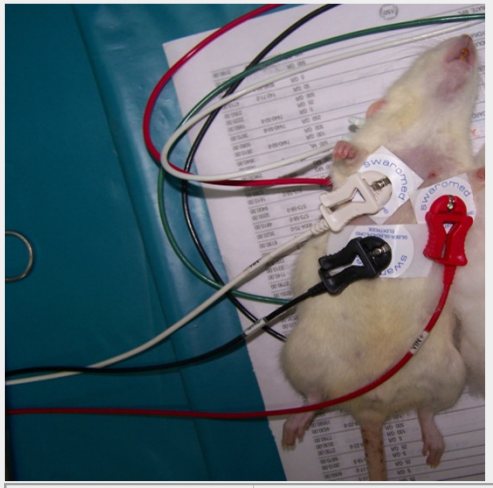
1. **Prevent metabolic shift**
2. **Reduce oxidative stress**

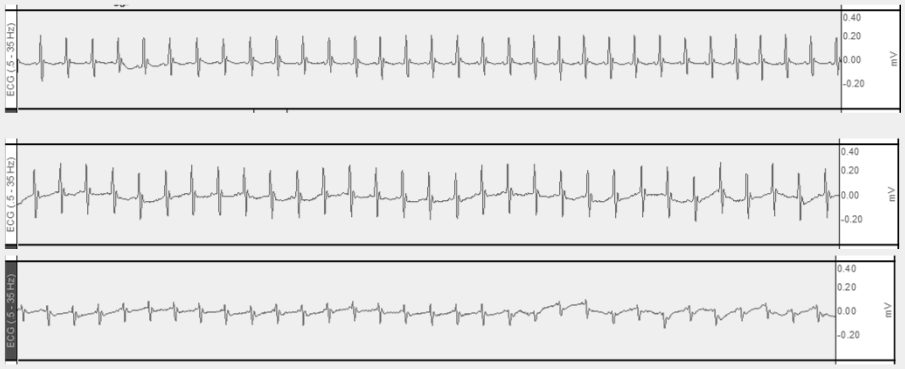
# SPONTANEOUSLY HYPERTENSIVE RAT (6 Months)

|  | SBP (mm/Hg) | DBP (mm/Hg) |
|---|---|---|
| SHR | **197± 1** | **169 ± 5** |
| Wistar | **119 ± 9** | **82 ± 20** |



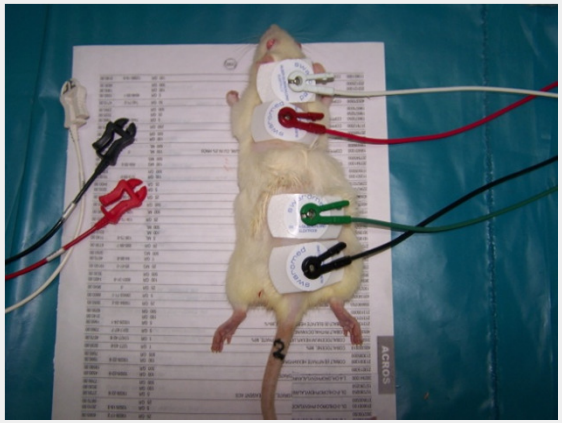

Blood pressure





ECG

| | **Cardiac output (ml/min)** |
|---|---|
| **SHR** | **163.8±3.7** |
| **Wistar** | **168.0±3.3** |



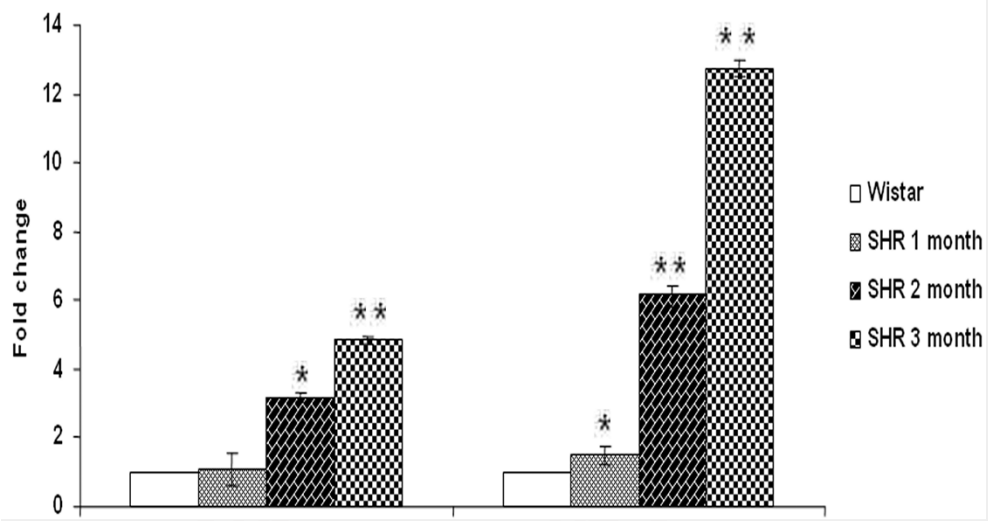
Cardiac output

# HYPERTROPHY INDEX of SHR *vs* WISTAR RATS

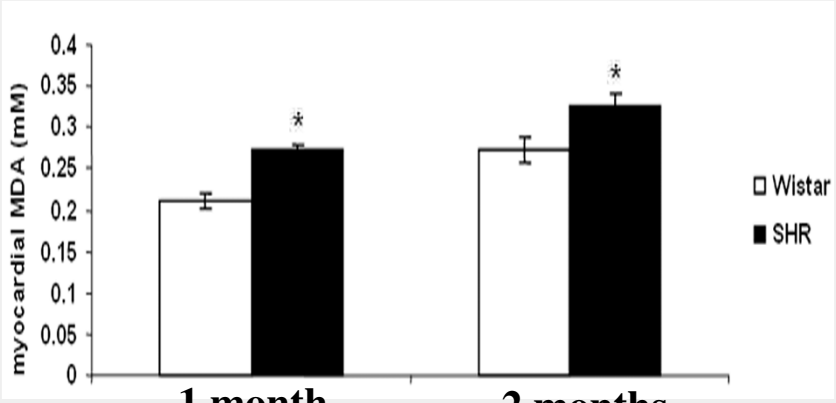
| Age in months | Heart weight(mg) | | Body weight(g) | | Ventricular mass (mg) / body weight (g) | |
|---|---|---|---|---|---|---|
| | *SHR* | *Wistar* | *SHR* | *Wistar* | *SHR* | *Wistar* |
| **1** | 0.3 ±0.04 | 0.28 ±0.03 | 80 ±14 | 75.47 ±8 | 3.75 ±0.08 | 3.71 ±0.09 |
| **2** | 0.6 ±0.04* | 0.47 ±0.03 | 185 ±12 | 171.5 ±12 | 3.24 ±0.08* | 2.74 ±0.09 |
| **4** | 1.04 ±0.03** | 0.6 ±0.07 | 374 ±16* | 245 ±5 | 2.78 ±0.09* | 2.45 ±0.09 |
| **6** | 1.22 ±0.09** | 0.69 ±0.05 | 405 ±9* | 300 ±11 | 3.0 ±0.07** | 2.3 ±0.08 |
| **8** | 1.28 ±0.05** | 0.71 ±0.04 | 400 ±11* | 351 ±9 | 3.2 ± 08** | 2.02 ±0.06 |

* p< 0.05 ** p <0.01

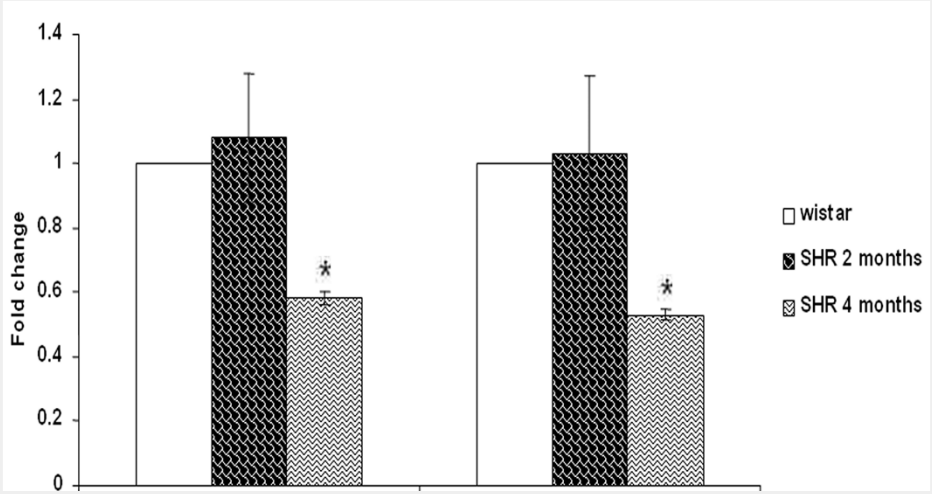
# TEMPORAL VARIATION IN HYPERTROPHY, OXIDATIVE STRESS & FATTY ACID METABOLISM IN SHR



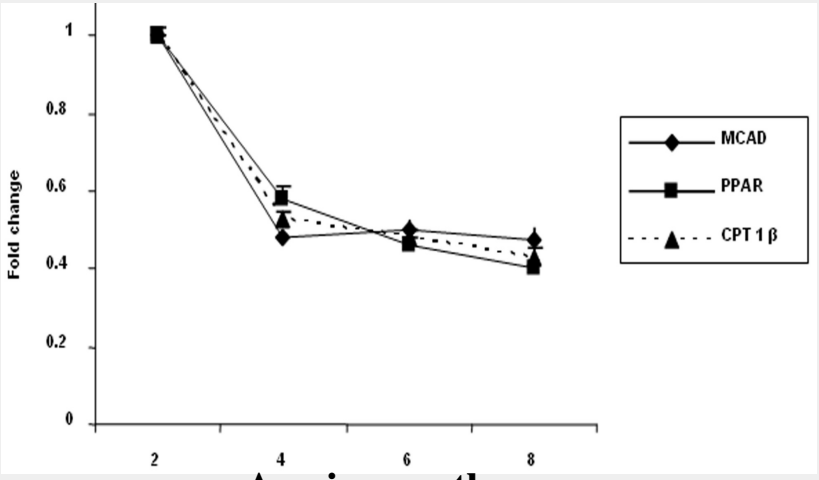

BNP NFκB




LIPID PEROXIDATION




MCAD CPT 1β




AGE DEPENDENT VARIATION IN EXPRESSION OF FAO GENES

* p<0.05 ** p<0.01

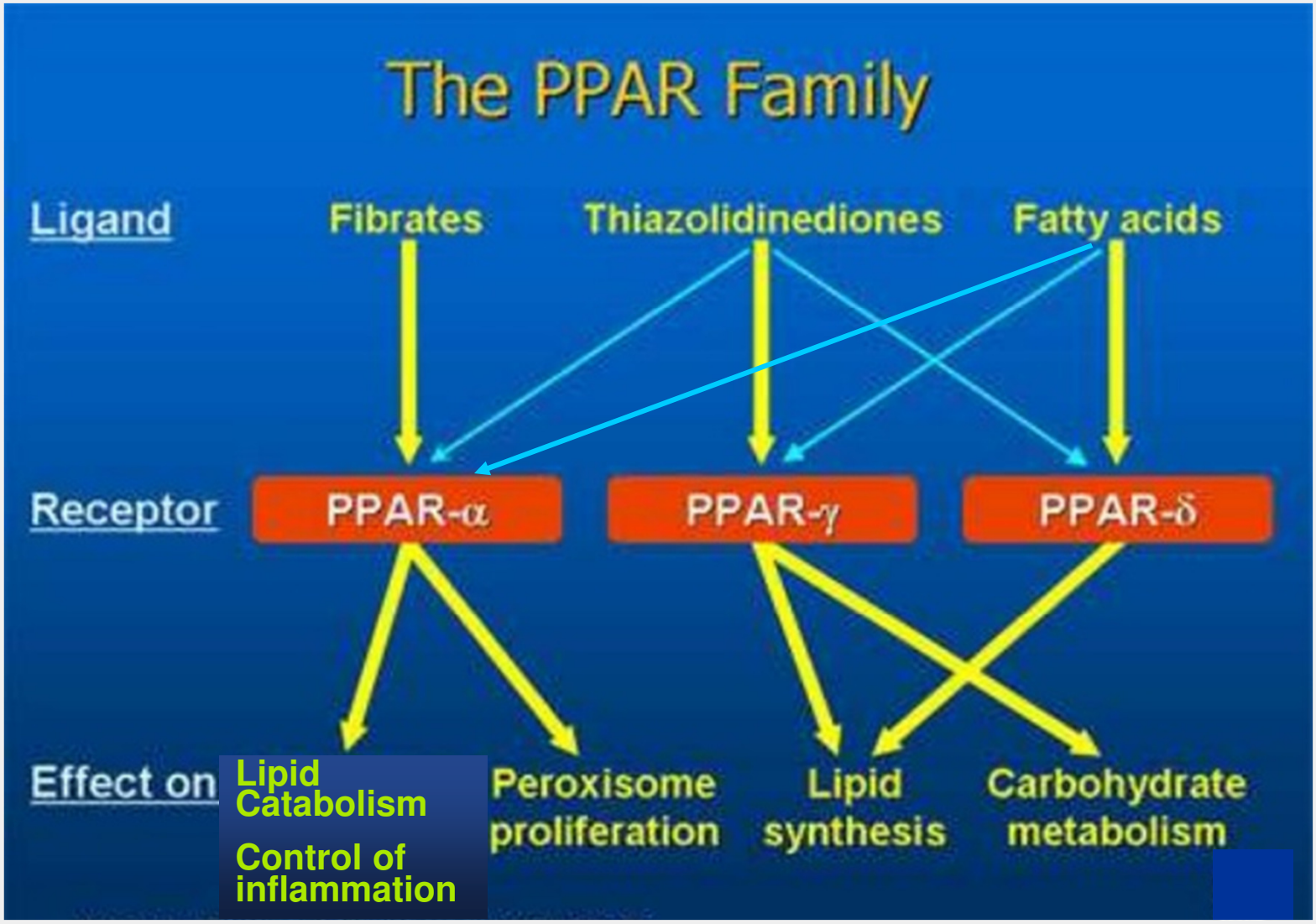
Purushothaman et al. Mol Cell Biochem (2011) 351:59–64

# PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPAR)

**Ligand activated nuclear receptors**

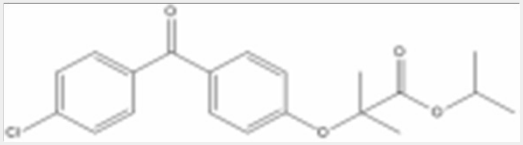
**Regulate cellular processes such as differentiation, development and metabolism (carbohydrate, lipid and protein)**

**Activation initiates transcription of an array of genes involved in energy homeostasis**


The PPAR Family
Ligand
Fibrates
Thiazolidinediones
Fatty acids
Receptor
PPAR-α
PPAR-γ
PPAR-δ
Effect on
Lipid Catabolism
Control of inflammation
Peroxisome proliferation
Lipid synthesis
Carbohydrate metabolism

# “REACTIVATION OF PPARα IN CARDIAC HYPERTROPHY CAN PREVENT ADVERSE CARDIAC REMODELING”

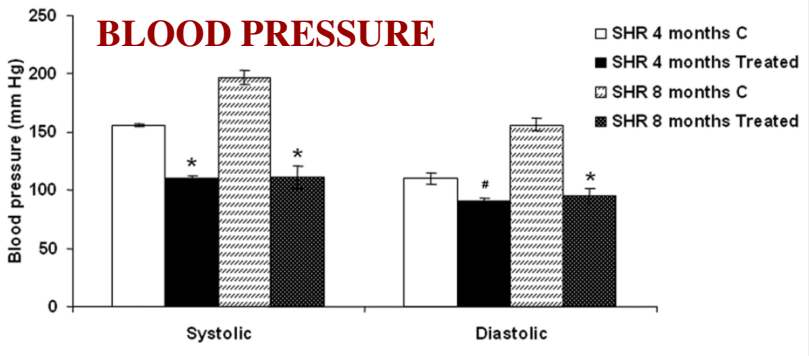
# STIMULATION OF FATTY ACID OXIDATION BY ACTIVATION OF PPARα

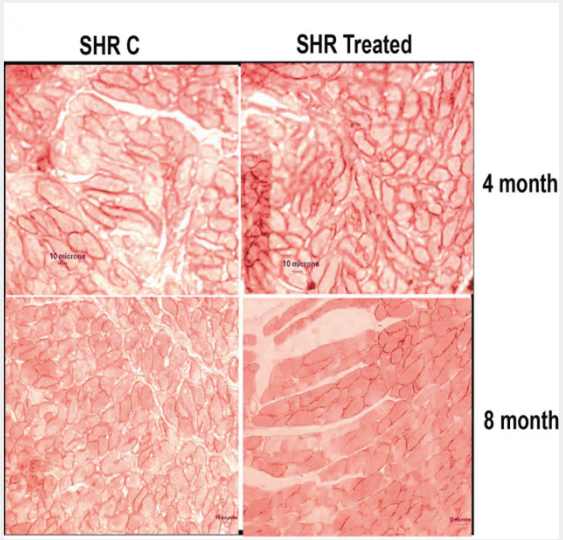
**PPARα agonist- Fenofibrate**  **100mg/kg/day**

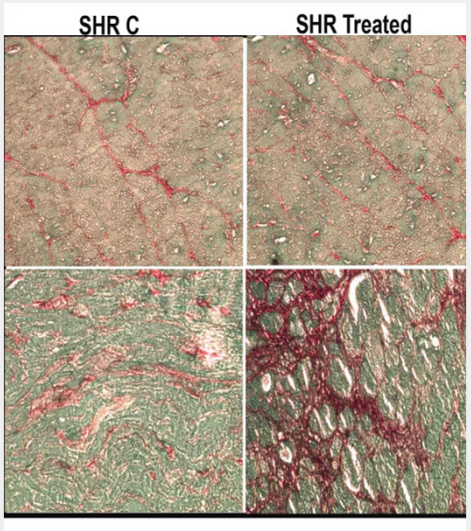
**Spontaneously Hypertensive Rat**

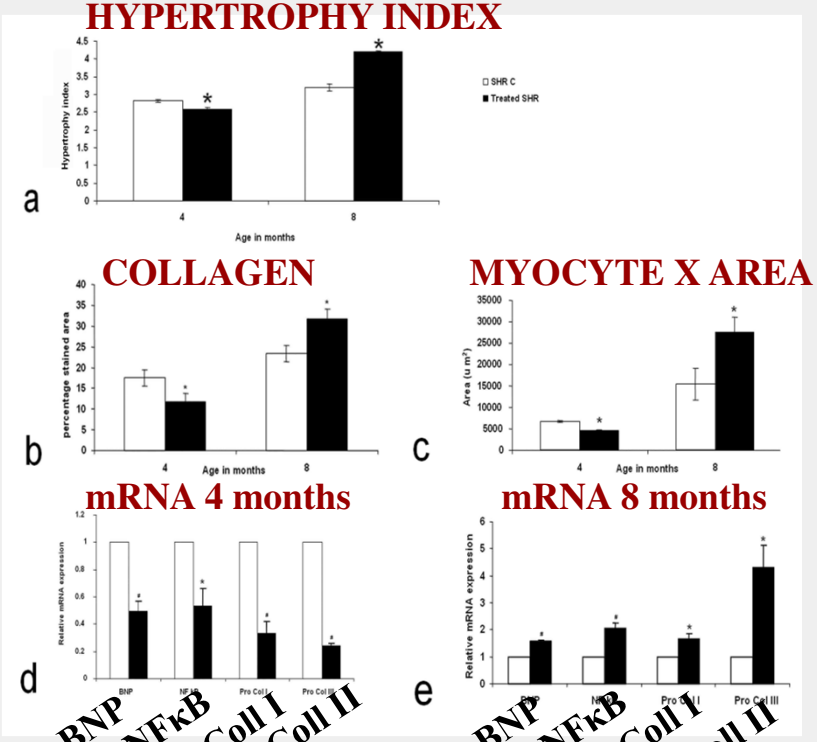
| | 2-month-old | 6-month-old |
|---|---|---|
| Hypertrophy | + | + |
| Metabolic shift | − | + |
| Restore energy homeostasis | Prevent metabolic switch | Reverse metabolic switch |
| Goal | Prevention of cardiac remodeling | Reverse remodeling |

# CARDIOVASCULAR RESPONSE TO PPARα AGONIST FENOFIBRATE : Treatment time – 60 days

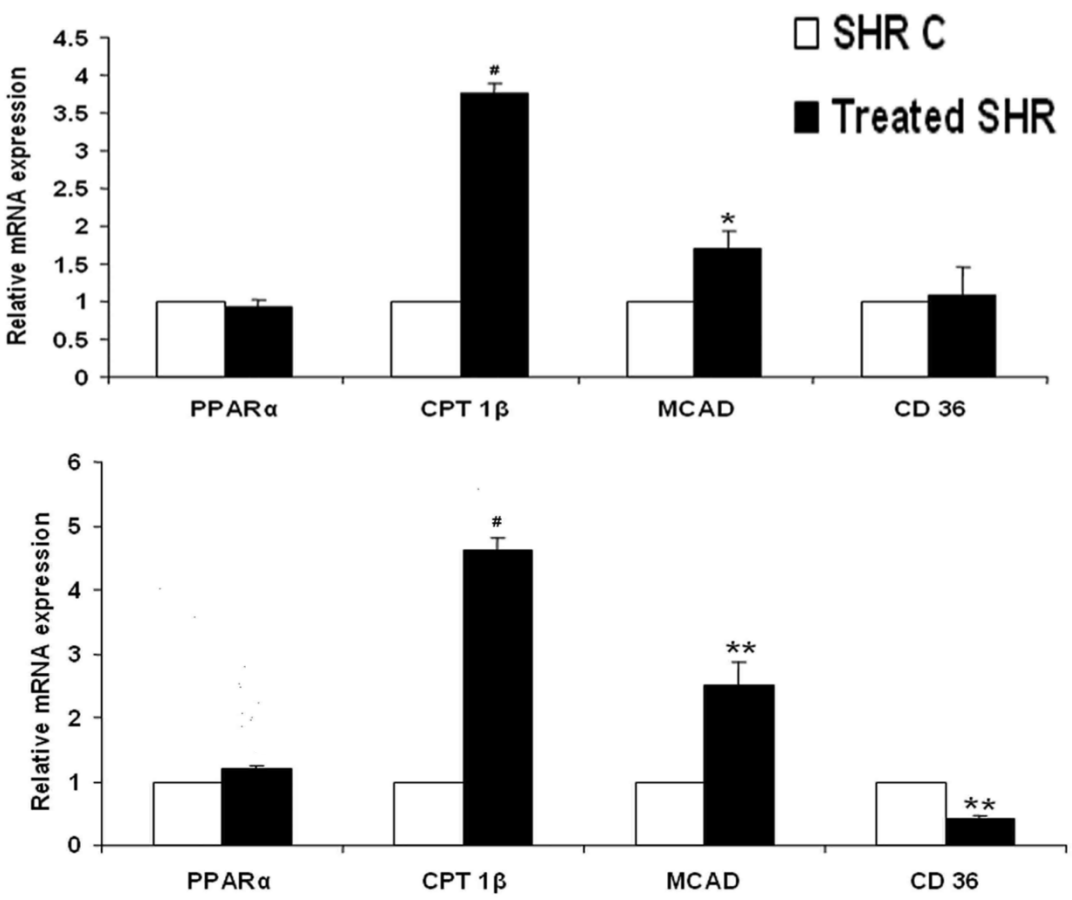


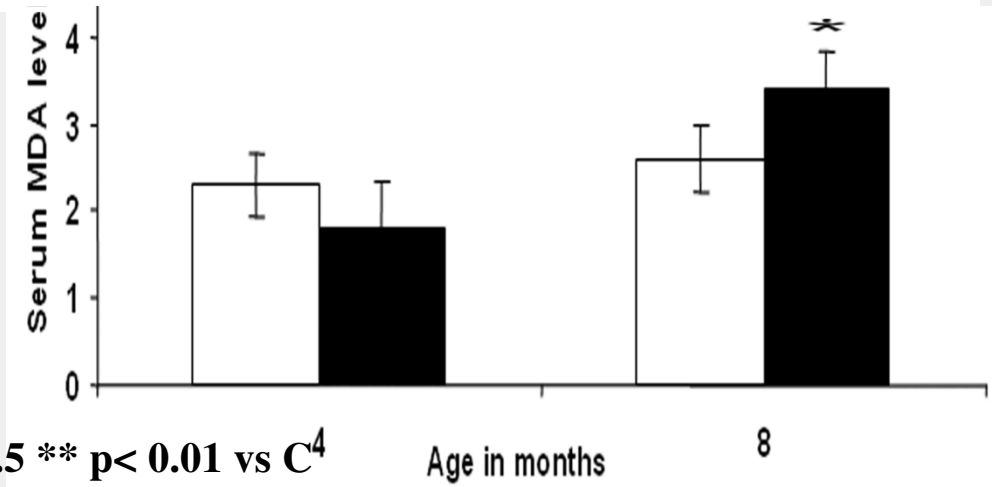




| Variable | 4mths | 8 mths |
|---|---|---|
| Blood pressure | ↓ | ↓ |
| Hypertrophy index | ↓ | ↑ |
| Myocyte area | ↓ | ↑ |
| Collagen | ↓ | ↑ |
| BNP expression | ↓ | ↑ |
| NFκB expression | ↓ | ↑ |




* p< 0.5 ** p< 0.01 vs C[4]

| Variable | 4 mths | 8 mths |
|---|---|---|
| PPARα | — | — |
| CPT1 β | ↑ | ↑ |
| MCAD | ↑ | ↑ |
| CD36 | — | ↓ |
| MDA | ↓ | ↑ |

Purushothaman et al.
J Cardiovasc Pharmacol 011;58:254–262

# CARDIAC RESPONSE TO ACTIVATION OF PPARα USING FENOFIBRATE IN YOUNG AND OLD SHR

## 2 MONTH OLD SHR

No metabolic shift

Prevention of metabolic shift



Reduction of blood pressure

Enhanced FAO

Regression of hypertrophy

Reduction of oxidative stress

No change in CD36 expression

## 6 MONTH OLD SHR

Metabolic shift +



Reactivation of FAO

Reduction of blood pressure

Enhanced FAO

Exacerbation of hypertrophy

Increase in oxidative stress

Further reduction of CD36

Purushothaman et al.
J Cardiovasc Pharmacol 011;58:254–262

**Possible cause for age dependent variation in response to fenofibrate** ***and ways to prevent adverse remodeling***

1. **Reactivation of FAO after metabolic shift can be detrimental**

***Can prevention of metabolic shift at the initial stage prevent adverse remodeling?***

**2. Defective CD36 may prevent FA transport**

***A substrate that bypasses CD36 may be appropriate***

# EXPERIMENTAL DESIGN

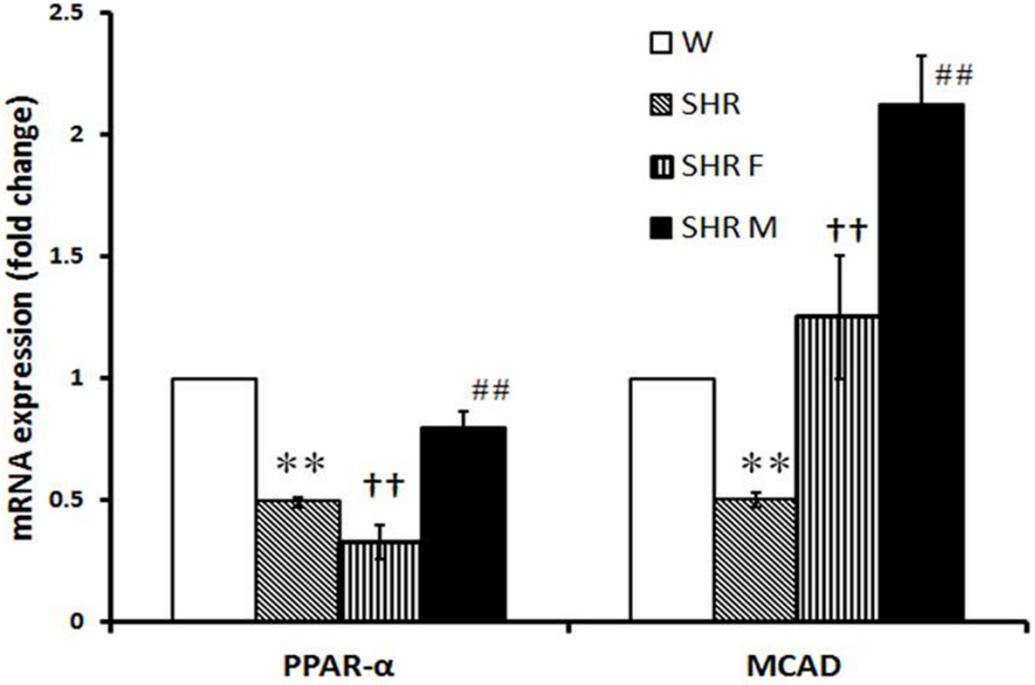
**Two month old male SHR**

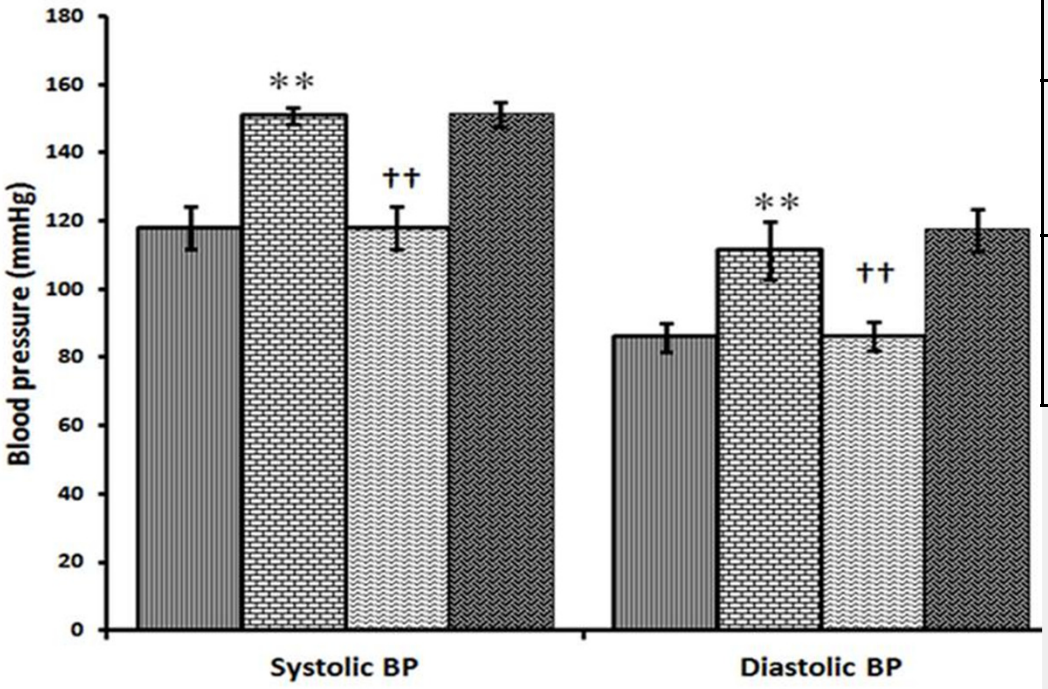
**Treatment period- 120 days**
**(2 – 6 months of age)**

**Stimulation of PPARα**

**Agonist mediated stimulation**
**Fenofibrate**
**(100mg/kg/day)**

**Fatty acid substrate mediated stimulation**
**Medium chain triglyceride**
**Tricaprylin (5% of diet)**



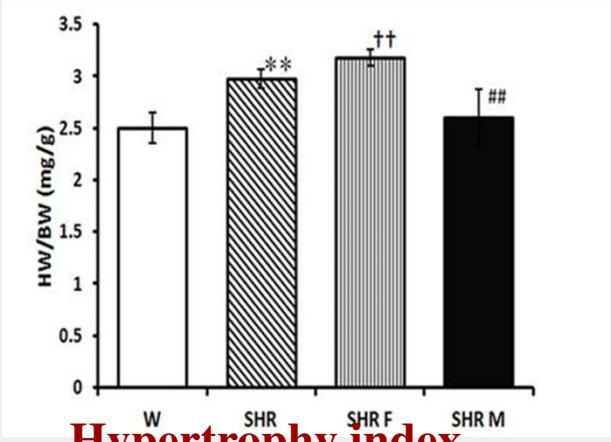




## CARDIOVASCULAR RESPONSE TO TREATMENT

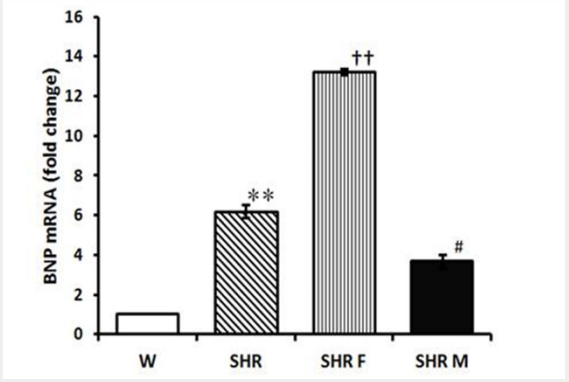
| Variable | Fenofibrate | MCT |
|---|---|---|
| **PPARα** Expression | ↓ | ↑ |
| **MCAD** Expression | ↑ | ↑ |
| **Systolic BP** | ↓ | — |
| **Diastolic BP** | ↓ | — |

** p< 0.01 SHR Vs W
†† p< 0.01 SHR F Vs SHR
## p< 0.01 SHR F Vs SHR

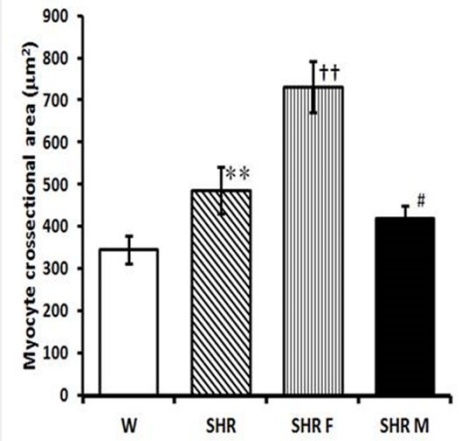
# EFFECT OF FENOFIBRATE AND MCT ON CARDIAC HYPERTROPHY

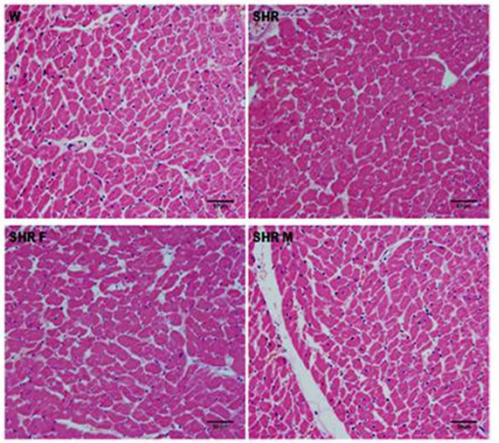



Hypertrophy index

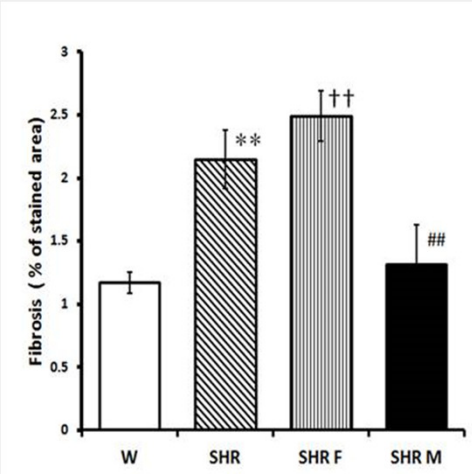


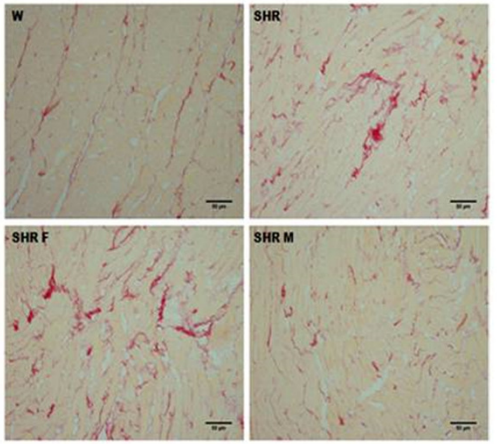

BNP expression




Myocyte cross sectional area



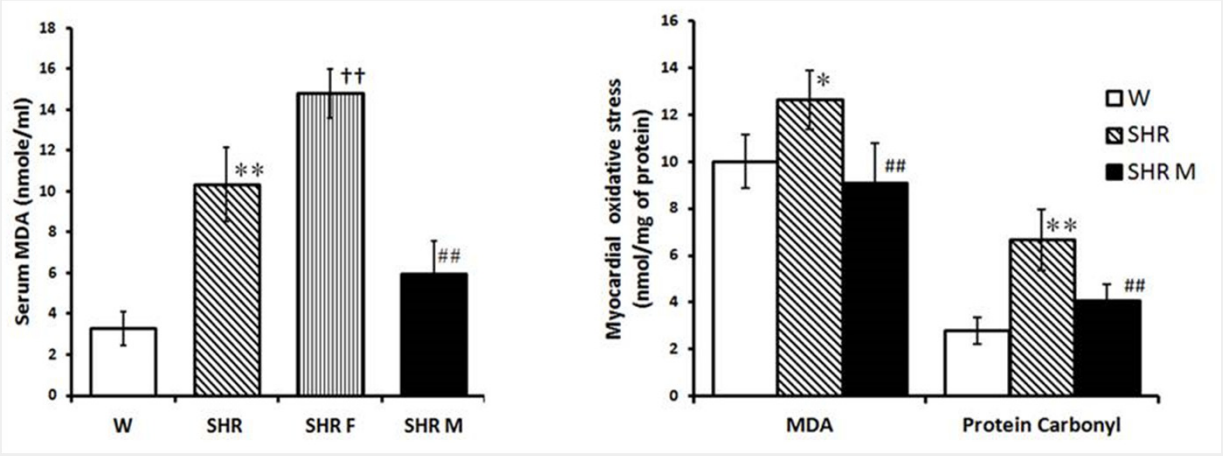

Ventricular wall fibrosis

** p< 0.01 SHR Vs W

†† p< 0.01 SHR F Vs SHR

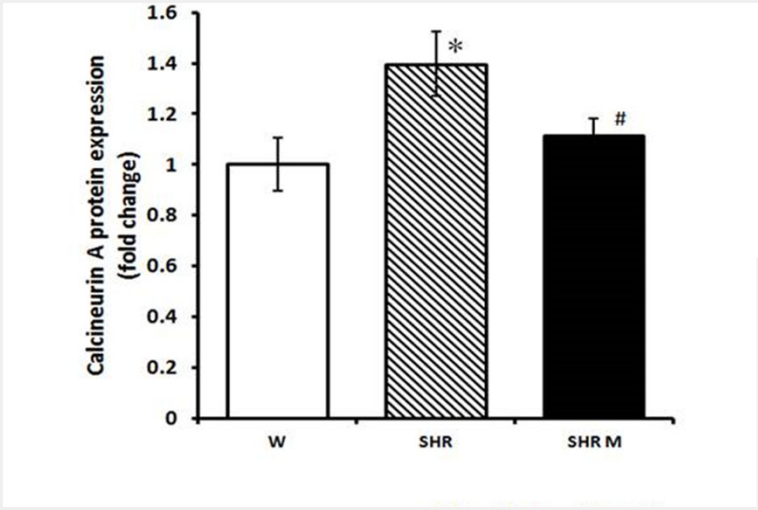
## p< 0.01 SHR F Vs SHR

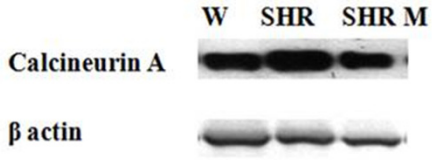
# OXIDATIVE STRESS IN RESPONSE TO TREATMENT




** p <0.01 W vs SHR
* p <0.030 W vs SHR
†† p < 0.01 SHR vs SHR F
##p < 0.01 SHR vs SHR M

# CALCINEURIN EXPRESSION IN RESPONSE TO MCT

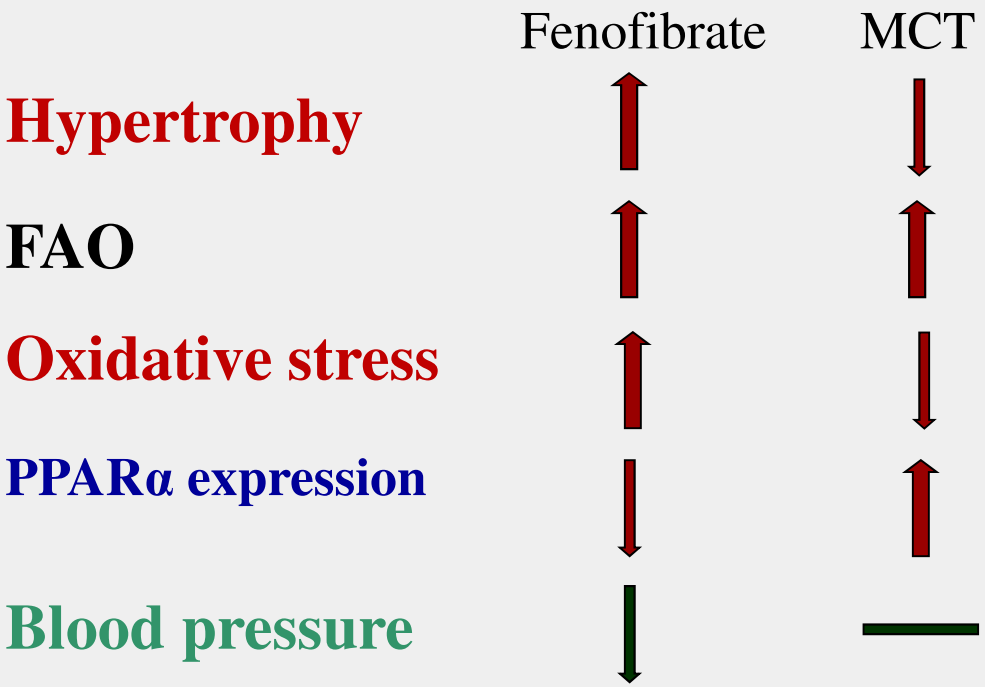



*p <0.03 SHR vs W
#p < 0.046 SHR M vs SHR

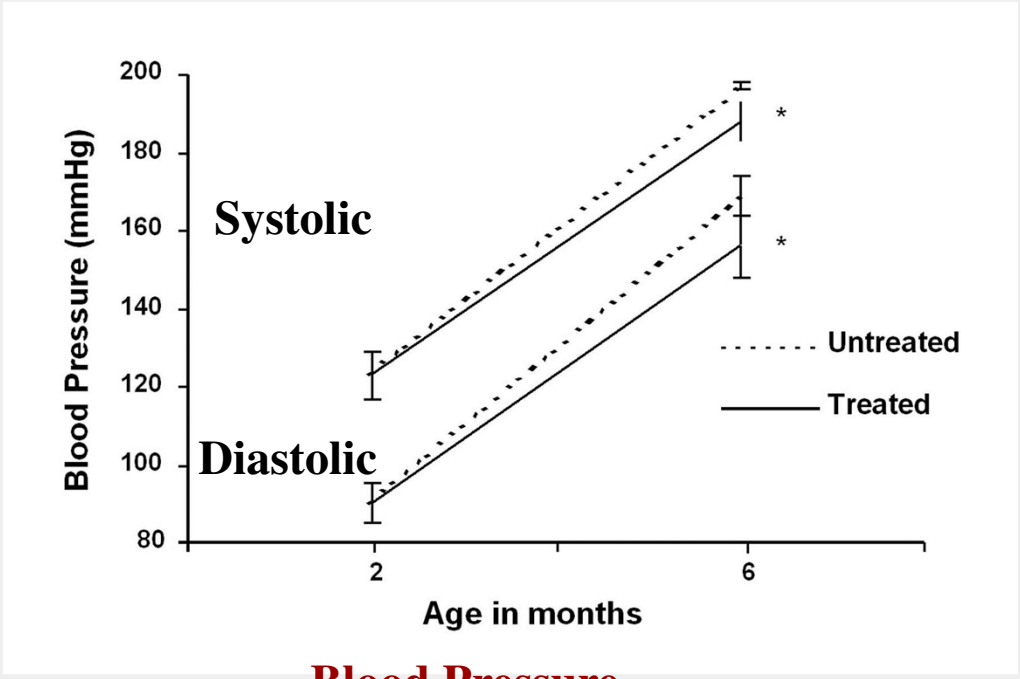
# Lipid profile unaffected by MCT

# Variable response to agonist and substrate mediated stimulation of FAO

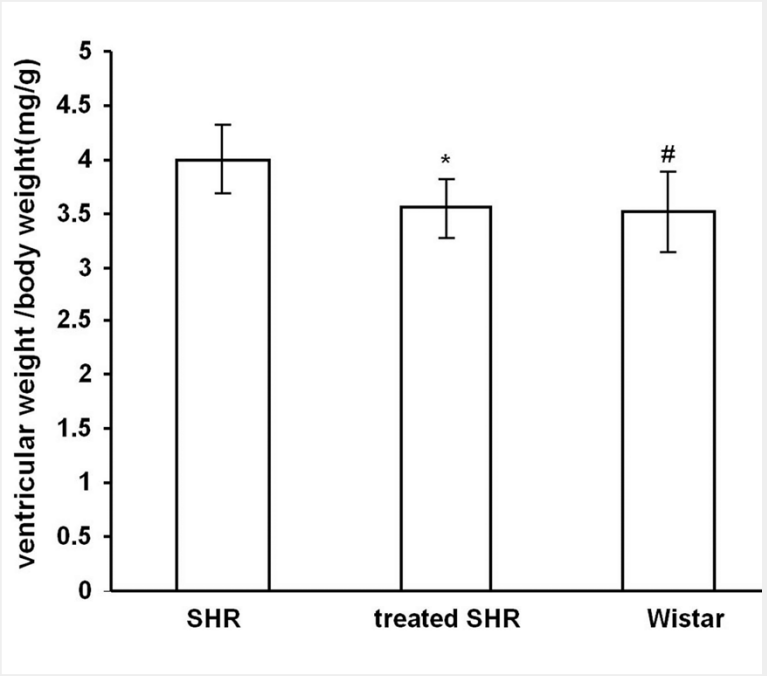



**Substrate mediated stimulation of Fatty acid metabolism prevents adverse cardiac remodeling**

# EFFECT OF *CARDOGUARD* ON CARDIAC REMODELING IN SHR




**Blood Pressure**



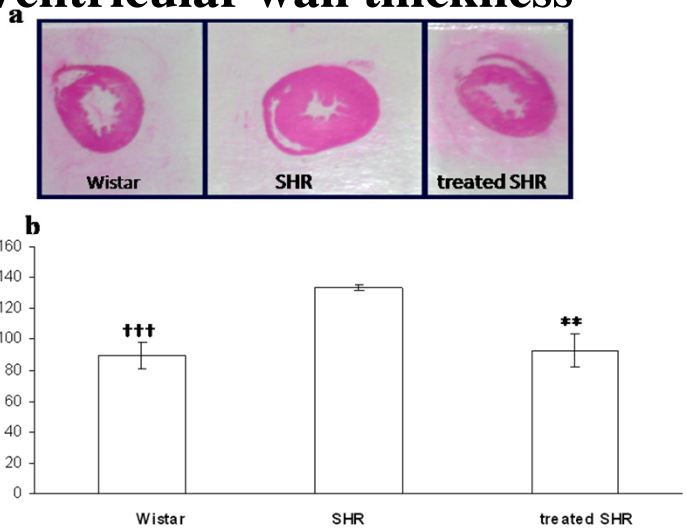

**Hypertrophy index**

***CARDOGUARD:***

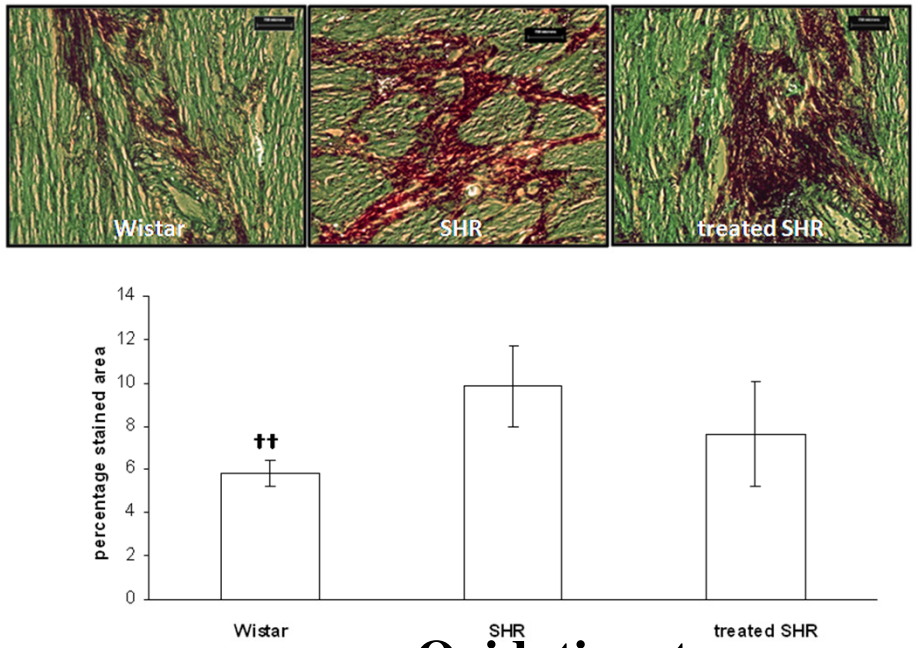
***Rauwolfia serpentina*** **(Sarpagandha/Indian Snakeroot) (120mg)**
***Terminalia arjuna*** **(Arjuna/Myrobalan) (40mg)**
***Boerhavia diffusa*** **(Punarnava/Spreading Hogweed) (40mg)**
***Terminalia chebula*** **(Hareethaki/Chebulic myrobalan) (40mg)**
***Terminalia belerica*** **(Vibheetaki/Beleric myrobalan) (40mg)**
***Emblica officinalis (*****Amlaki/Indian gooseberry) (40mg)**

# EFFECT OF *CARDOGUARD* ON CARDIAC HYPERTROPHY AND OXIDATIVE STRESS

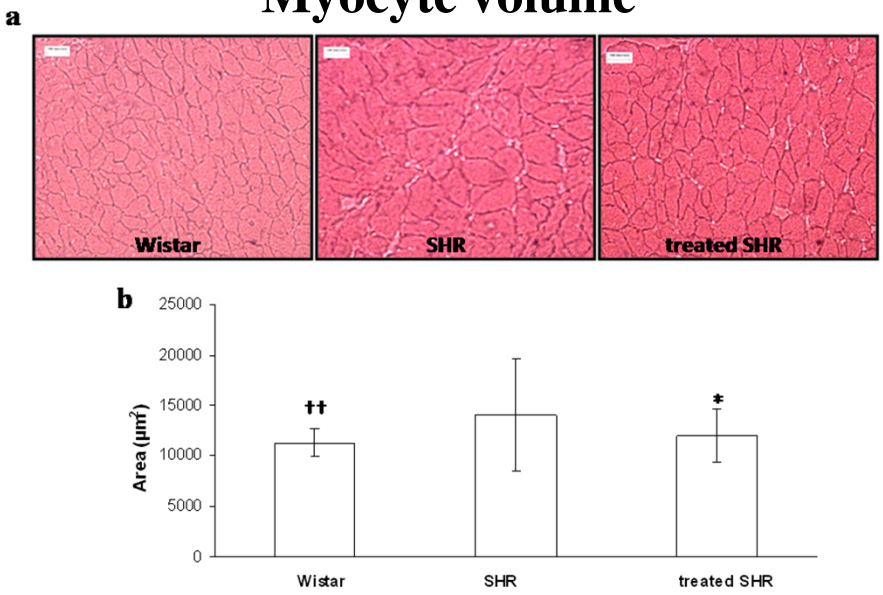
## Ventricular wall thickness



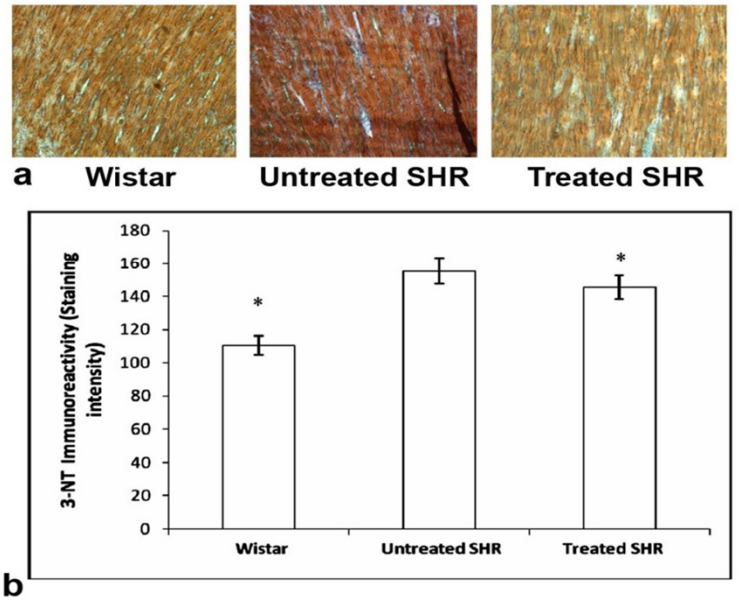

## Fibrosis




## Myocyte volume




## Oxidative stress



## RESPONSE OF SHR TO TREATMENT WITH *CARDOGUARD*

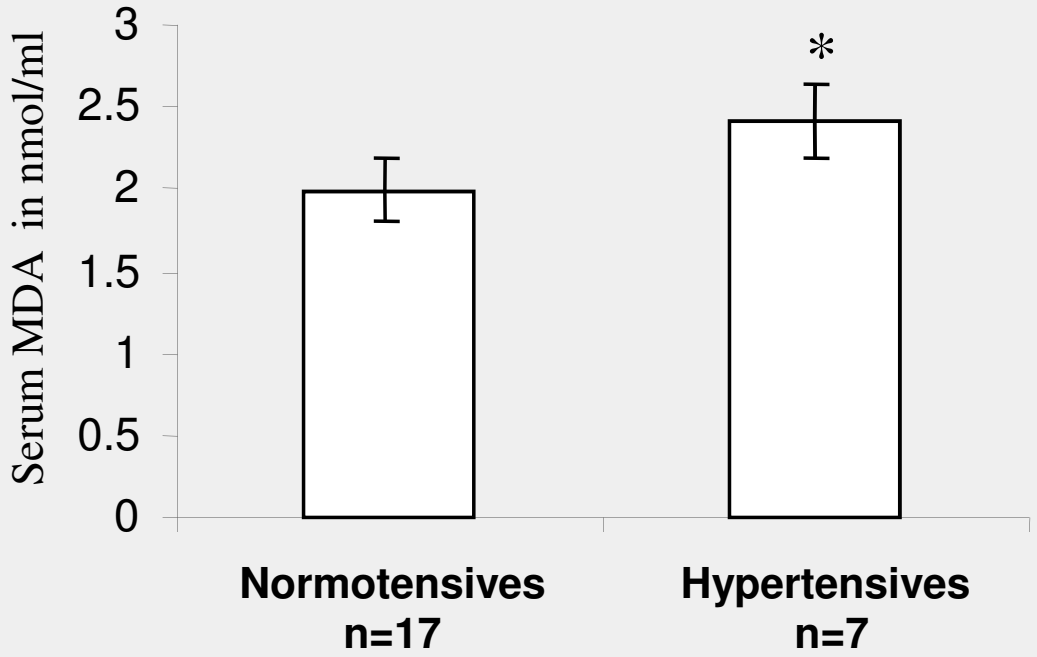
**1. Reduction of blood pressure**

**2. Reduction of cardiac hypertrophy**

**3. Reduction of oxidative stress**

**Sankar et al. *Canadian J Physiol Pharmacol*. 2012; 90: 627-35**

# Oxidative stress in normotensive and hypertensive individuals as measured by serum MDA level



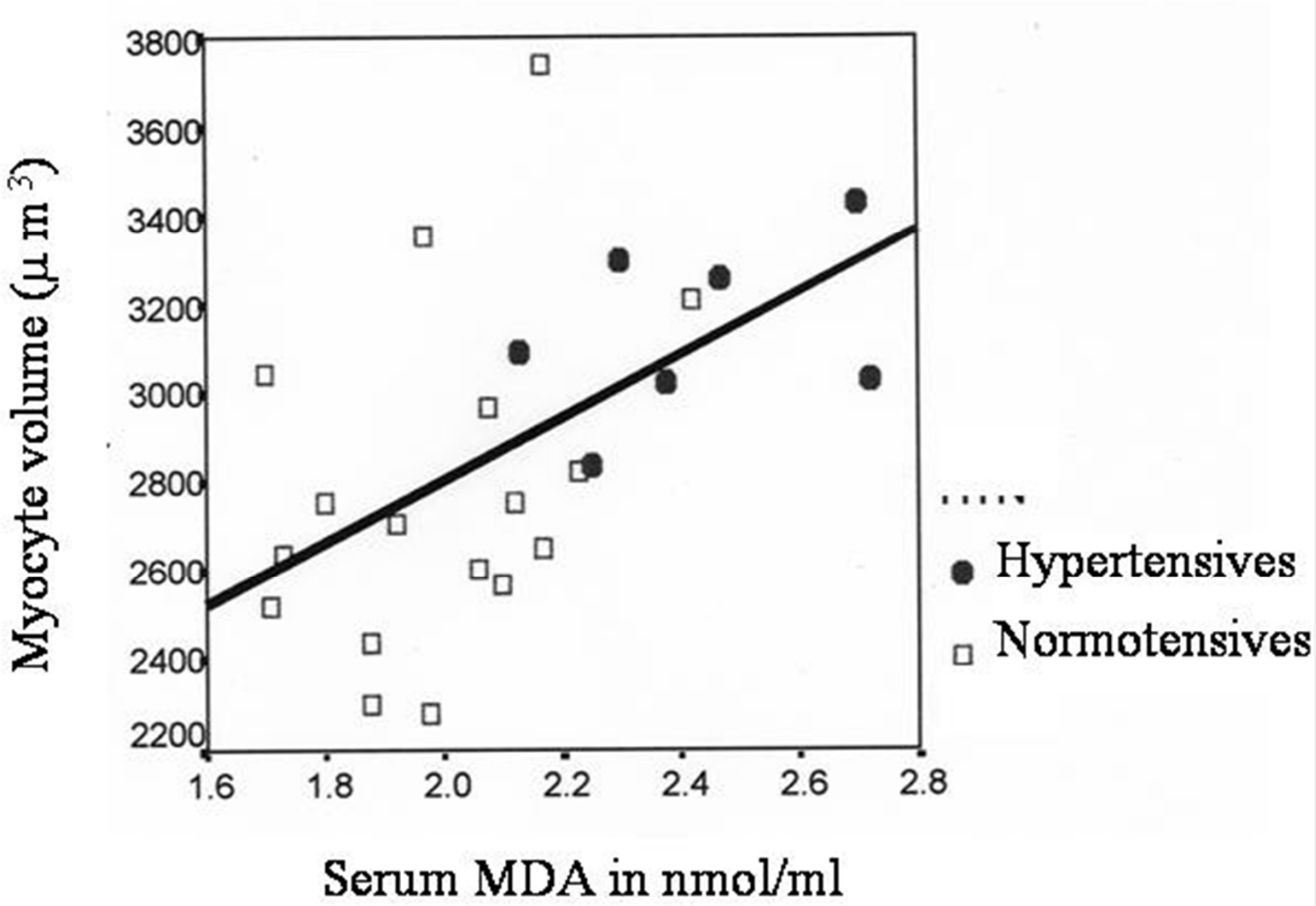

**Enhanced oxidative stress in hypertensive individuals**

* p< 0.001 Vs Normotensives

## Influence of oxidative stress on myocyte volume

- 10 ml of fasting blood sample
- Serum Lipid Peroxidation using TBA assay
- FBS, TC, HDL, TAG using Randox kits
- LDL using Friedwald formulae
- Synchronized myocyte culture treated with 5% human serum for 72 hours
- Myocyte volume using image analysis

## Association between Serum MDA level and Cell volume



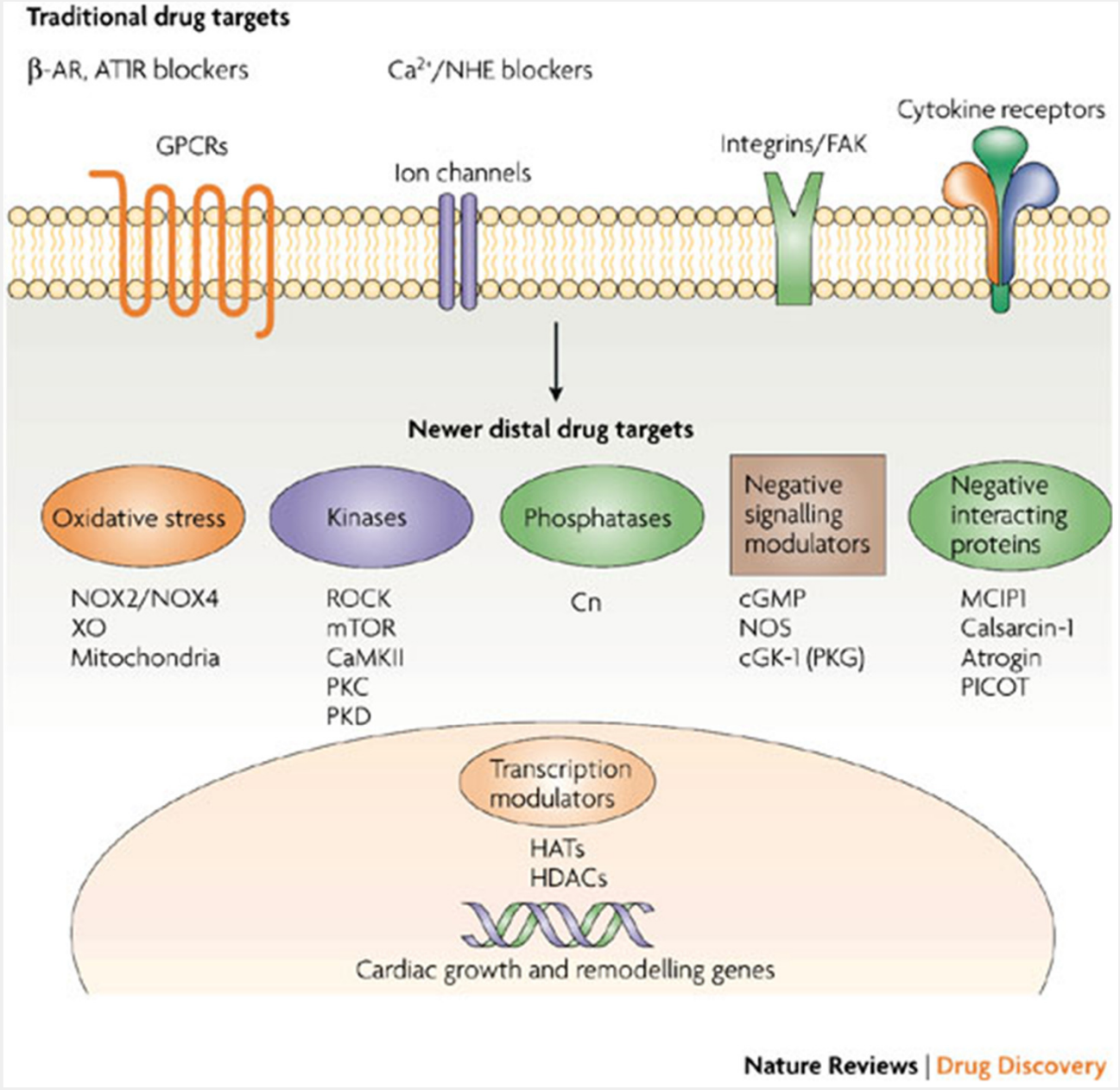

**Adiga et al *Int J Cardiol* 2007; 115: 246-248**

## CONCLUSION:

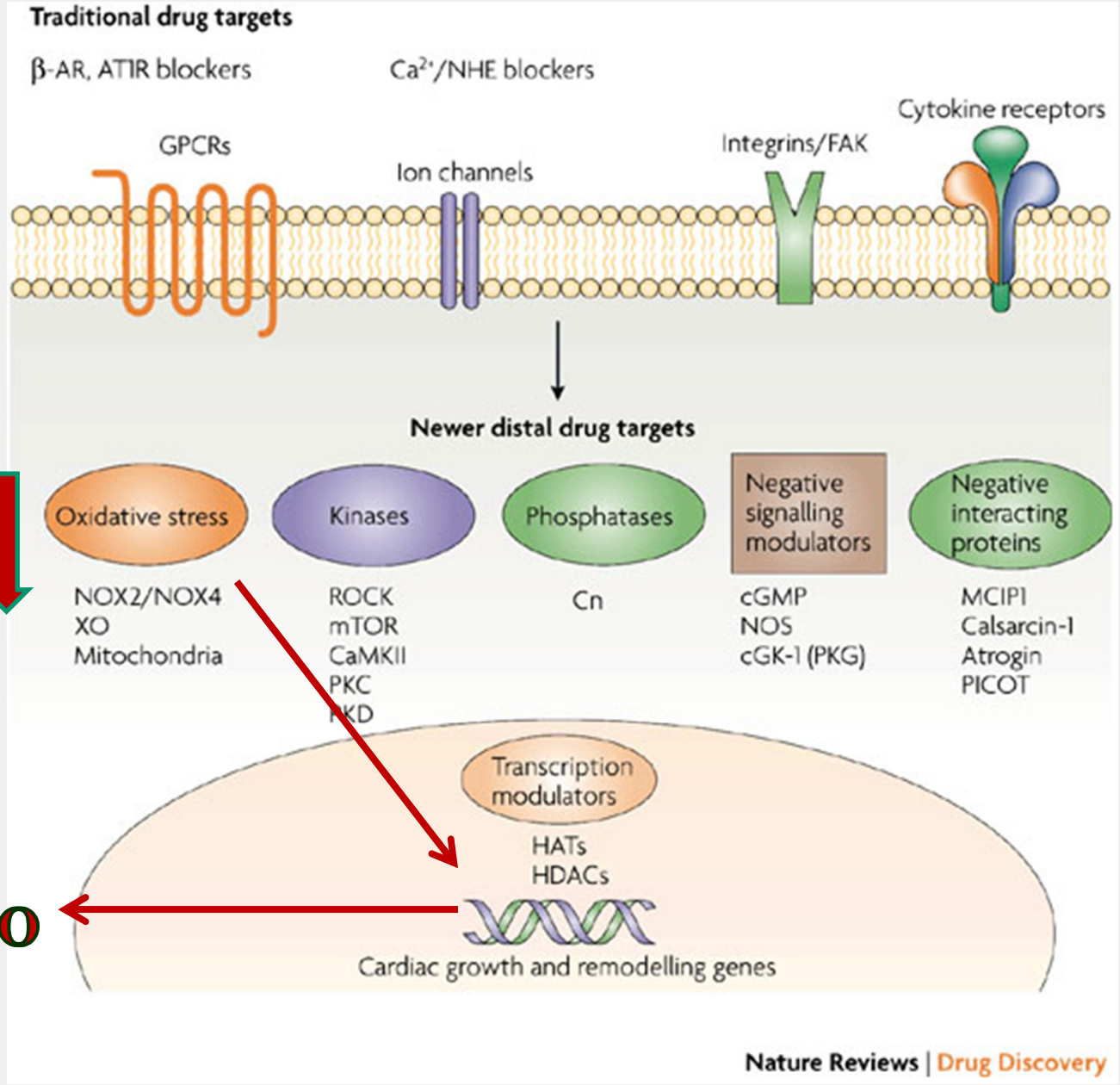
- ❖Reduction of oxidative stress promotes reverse remodeling
- ❖No positive association between blood pressure and cardiac remodeling
- ❖Reactivation of FAO is beneficial if linked with decrease in oxidative stress

**Therapeutic implications:**

- •Fenofibrate can be harmful in individuals with hypertrophy
- •Supplementation with MCT can prevent pathological cardiac remodeling in chronic pressure overload


Traditional drug targets
β-AR, ATIR blockers
Ca2+/NHE blockers
GPCRs
Ion channels
Integrins/FAK
Cytokine receptors
Newer distal drug targets
Oxidative stress
Kinases
Phosphatases
Negative signalling modulators
Negative interacting proteins
NOX2/NOX4
XO
Mitochondria
ROCK
mTOR
CaMKII
PKC
PKD
Cn
cGMP
NOS
cGK-1 (PKG)
MCIP1
Calsarcin-1
Atrogin
PICOT
Transcription modulators
HATs
HDACs
Cardiac growth and remodelling genes
Nature Reviews | Drug Discovery

# FUTURE RESEARCH




**CAN REDUCTION OF OXIDATIVE STRESS PREVENT METABOLIC SHIFT ?**



Sreeja Purushothaman M.Sc., Ph.D.- Temporal variation in oxidative stress, FAO and hypertrophy in SHR, treatment with fenofibrate for activation of PPARα



Saifudeen Ismael M.Sc.- Supplementation with medium chain triglycerides for reactivation of PPARα and prevention of adverse cardiac remodeling



Vandana Sankar M.Sc. Ph.D.- Treatment of SHR with *Cardoguard* for prevention of adverse cardiac remodeling



Indira Adiga M.Sc., Ph.D. - Correlation of human serum lipid peroxidation with cardiomyocyte volume

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**Kerala State Council for Science, Technology and Environment**

# Thanks' for your kind attention!!!!!!



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