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Atrial fibrillation and Metabolic Syndrome

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Disclosure

None!

Topics

- Current status of AF in Japan.
- The association of AF with DM, Mets and Obesity.
- Experimental data on the association of AF with Mets, including PPAR- γ and Leptin.

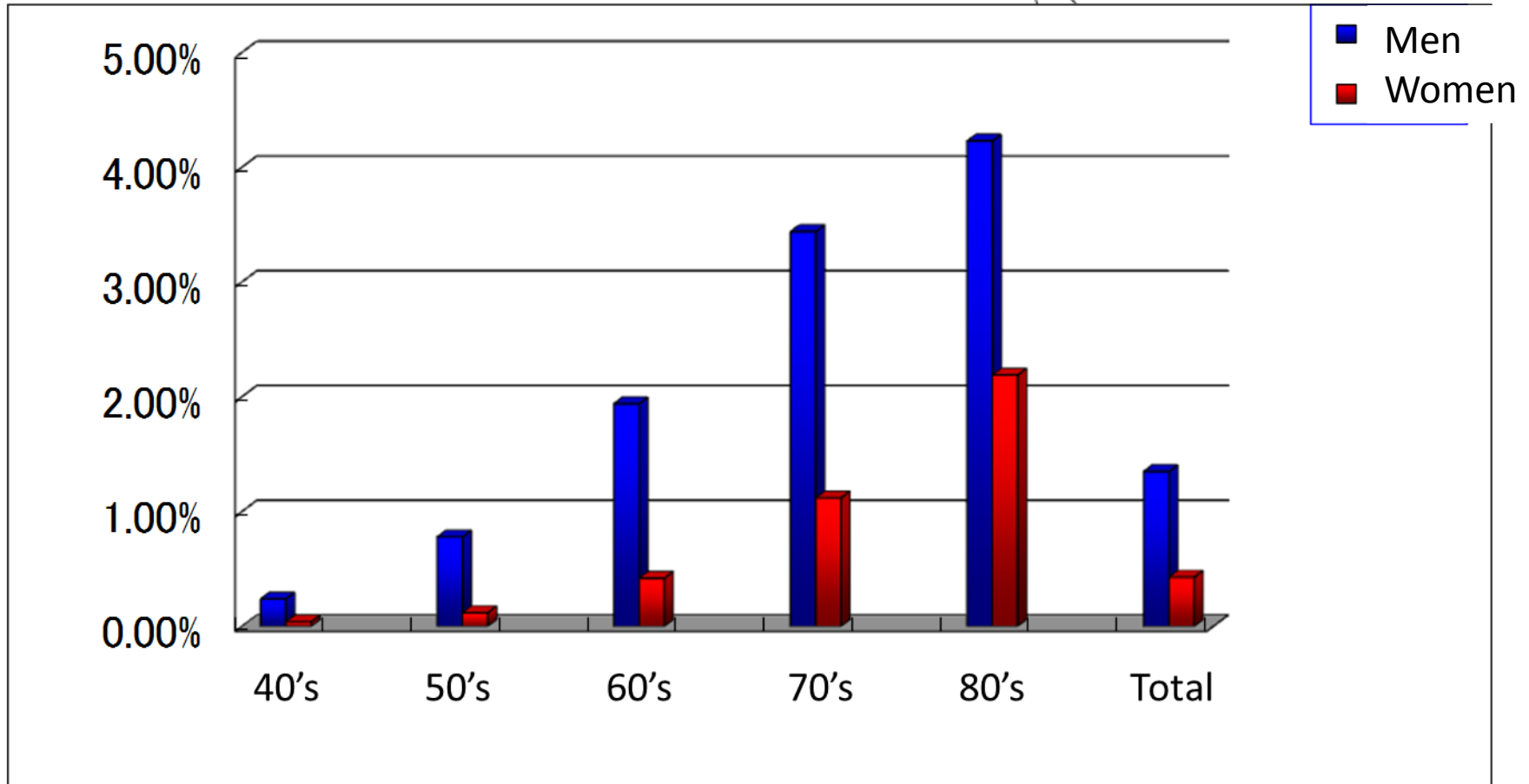
Atrial fibrillation (AF) is one of the most common arrhythmias in humans. In Japan, the population with AF will reach to almost 1 million patients recently. Since the morbidity of AF increases as population becomes older, the Medico-Social burden of AF will increase tremendously unless the appropriate strategy to care those with AF is established.

Both the epidemiological and experimental data from animal models of AF show that AF is associated with *Aging, Hypertension, Diabetes Mellitus and Obesity*.

Those risk factors of AF constitute the components of Metabolic Syndrome. While recent statistics also disclosed growing increase of those with Metabolic Syndrome. Thus, *Hypertension, Diabetes and Obesity* have caught a great deal of attention in the world of AF. The pathophysiology of the development of AF in metabolic syndrome, however, has been poorly understood.

In the present talk, I will briefly introduce recent progress of the pathophysiology of AF focusing on the roles of above shown components, such as hypertension, DM, and obesity referring to recently reported works including ours.

Morbidity of AF in age, sex in Japan 1

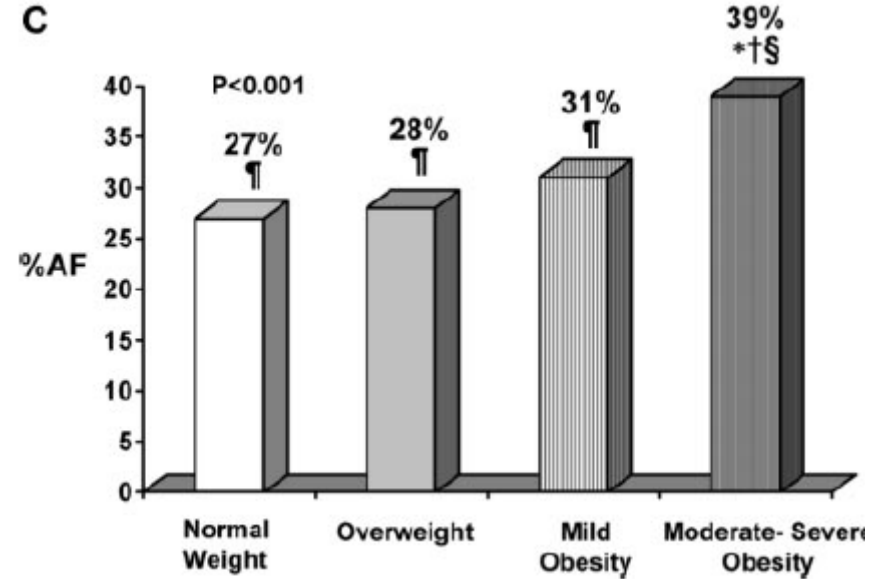
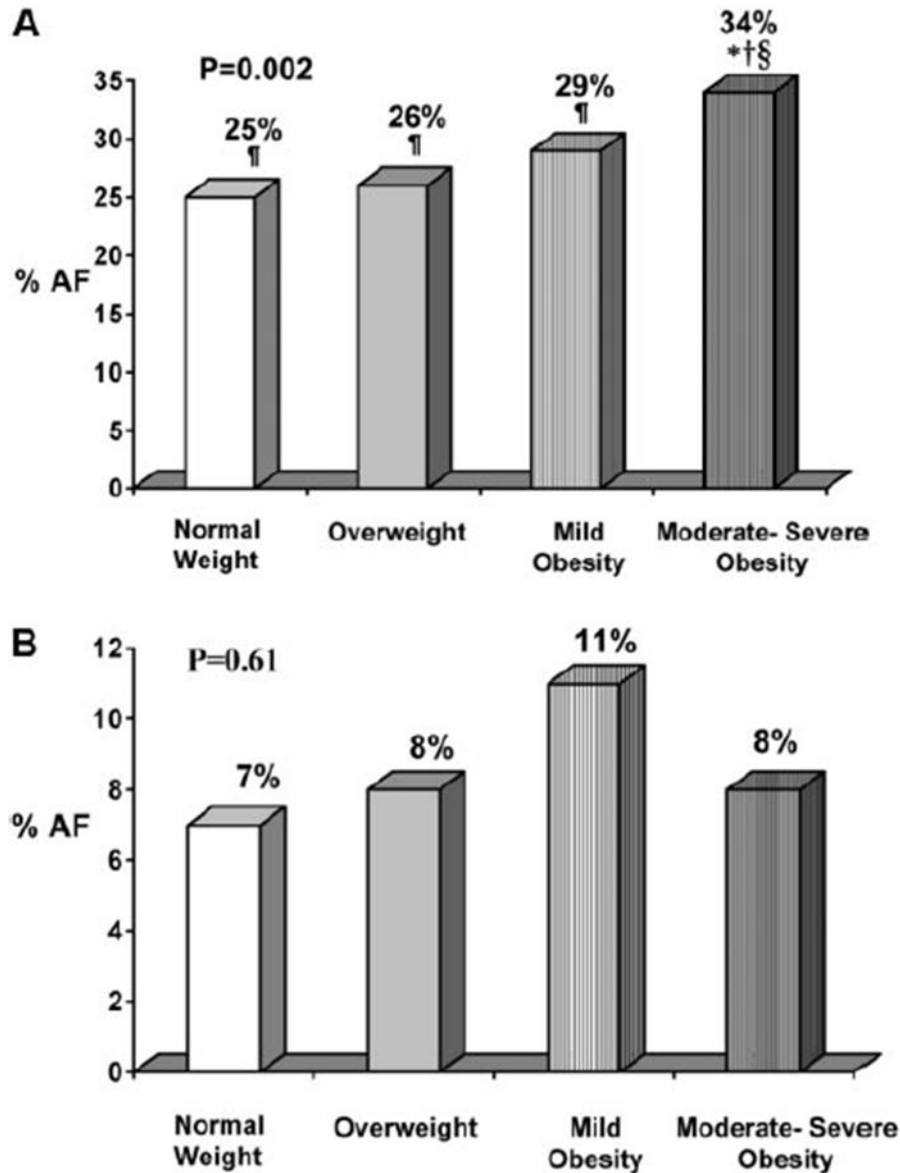


- Morbidity: 0.56 %
- Number of patients: 716,000, ;
(nearly reaching to 1 million)

Previous reports on the association between Metabolic syndrome and Atrial fibrillation

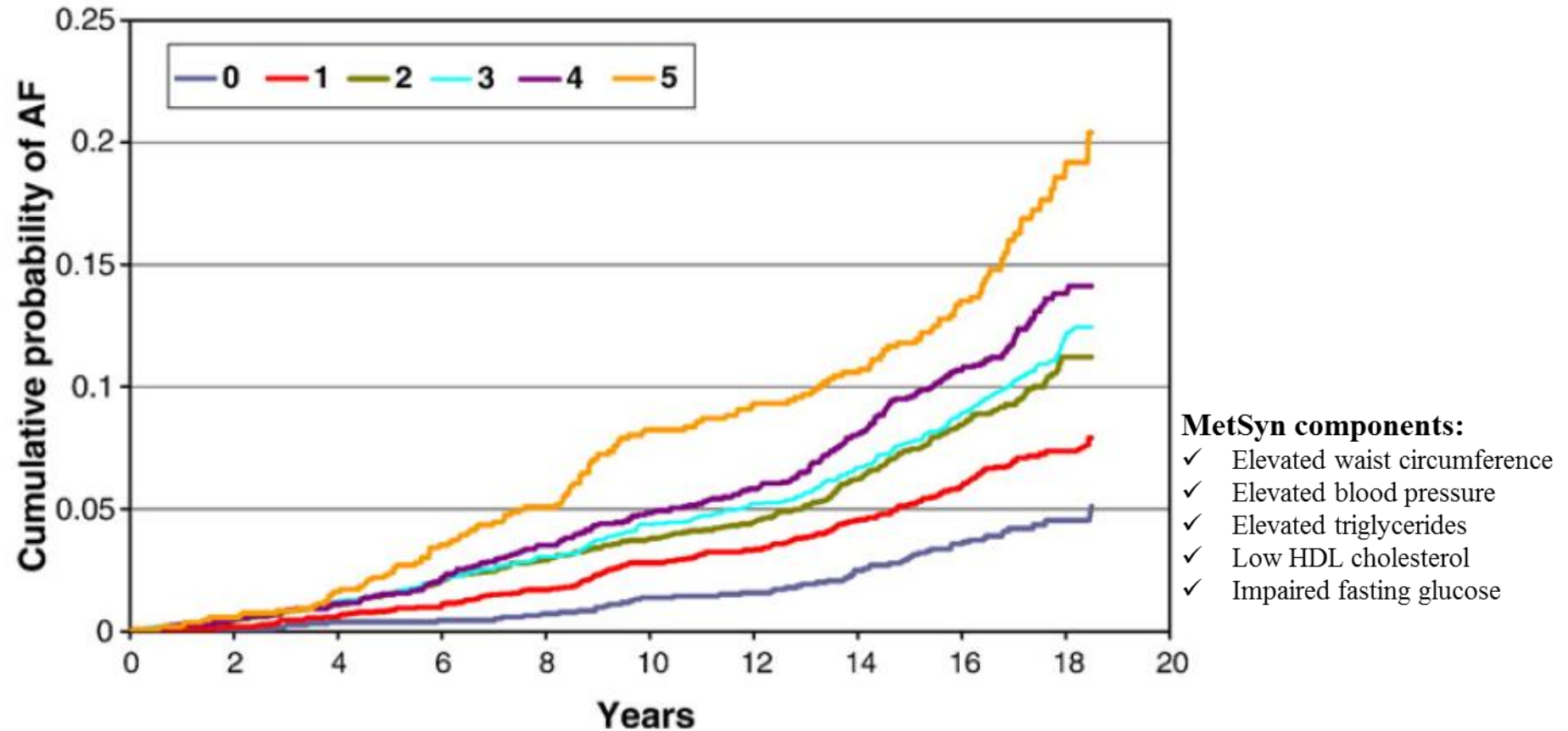
1. **Obesity and Metabolic Syndrome Are Independent Risk Factors for Atrial Fibrillation After Coronary Artery Bypass Graft Surgery**
Echahidi et al *Circulation*. 2007;116[suppl I]:I-213–I-219
2. **Metabolic Syndrome and Risk of Development of Atrial Fibrillation. The Niigata Preventive Medicine Study**
Watanabe et al *Circulation*. 2008;117:1255-1260.
3. **A Twin Study of Metabolic Syndrome and Autonomic Tone.**
GEHI et al *J Cardiovasc Electrophysiol*, 2009; 20: 422-428
4. **Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study**
Chamberlain et al *Am Heart J* 2010;159:850-6.
5. **Association of the Metabolic Syndrome With Atrial Fibrillation Among United States Adults (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study)**
Tanner et al *Am J Cardiol* 2011;108:227–232
6. **Impact of Metabolic Syndrome on Procedural Outcomes in Patients With Atrial Fibrillation Undergoing Catheter Ablation**
Mohanty et al *J Am Coll Cardiol* 2012;59:1295–301

Metabolic Syndrome is an Independent Risk Factors for Atrial Fibrillation After Coronary Artery Bypass Graft Surgery; Analysis of Obesity



Incidence of postoperative atrial fibrillation according to BMI (kg/m²): Normal weight: BMI 25; overweight: 25 BMI 30; mild obesity (obese 1): 30 BMI 35; moderate-severe obesity (obese 2): BMI 35. A, All patients; (B) patients 50 years old; (C) patients 50 years old. The probability value corresponds to the overall comparison of the 4 groups. The symbols indicate the significant ($P<0.05$) differences within the different groups. *Significant difference versus normal weight; †significant difference versus overweight; ‡ significant difference versus mild obesity; § significant difference versus moderate-severe obesity; ¶ significant difference versus moderate-severe obesity.

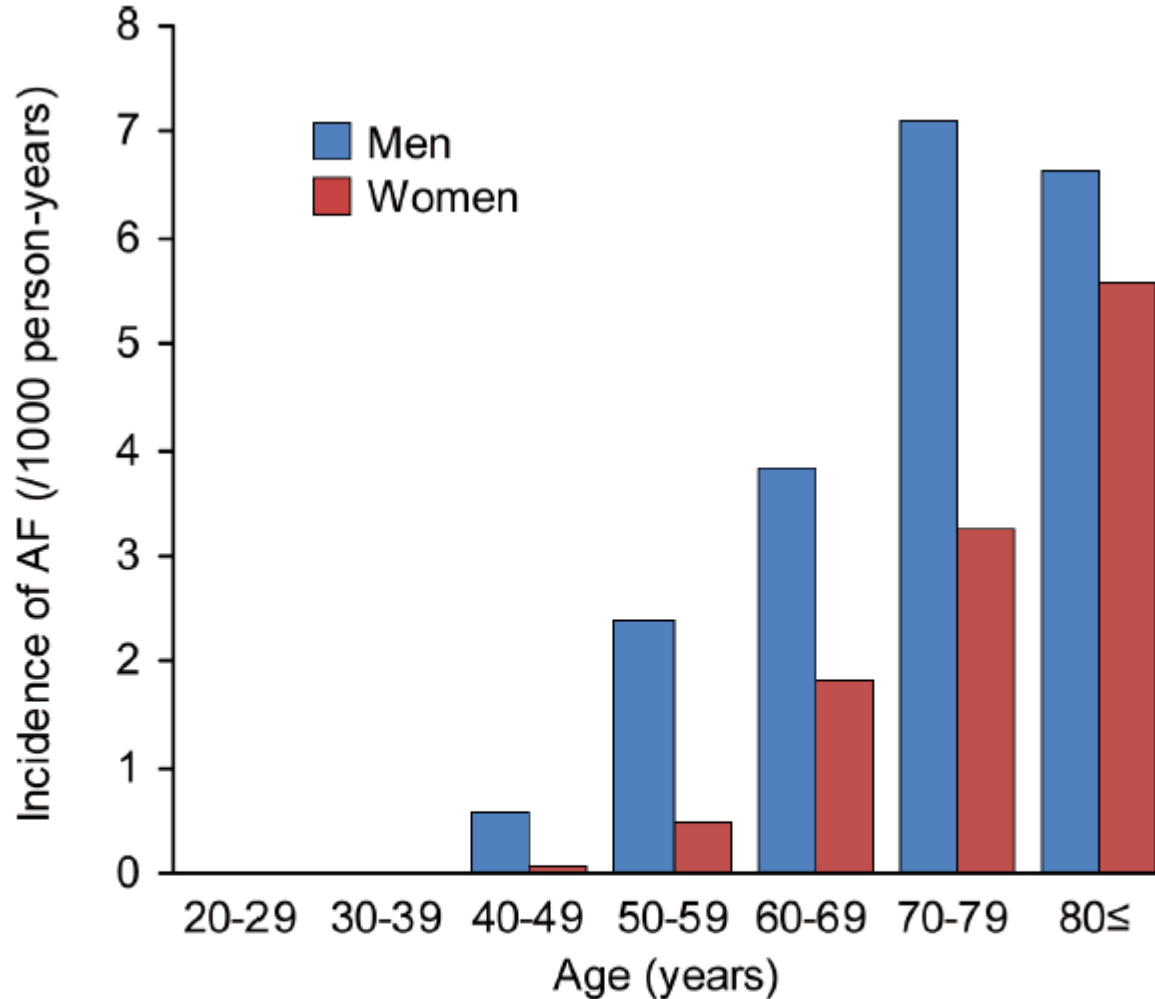
Metabolic Syndrome components vs cumulative probability of AF



Cumulative probability of AF by number of MetSyn components at baseline, ARIC 1987 to 2005. Figure adjusted for the following covariates at baseline: age (45 to b50, 50 to b55, 55 to b60, ≥ 60), sex, race, center, educational attainment, smoking status, and cigarette-years of smoking (quartiles).

Association Between Lipid Profile and Risk of Atrial Fibrillation

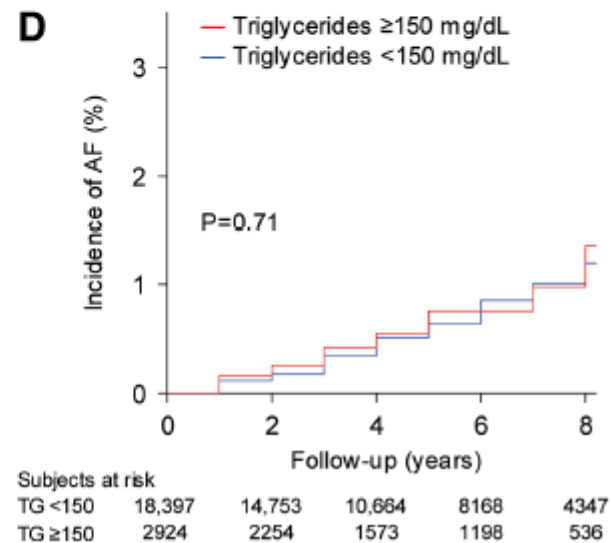
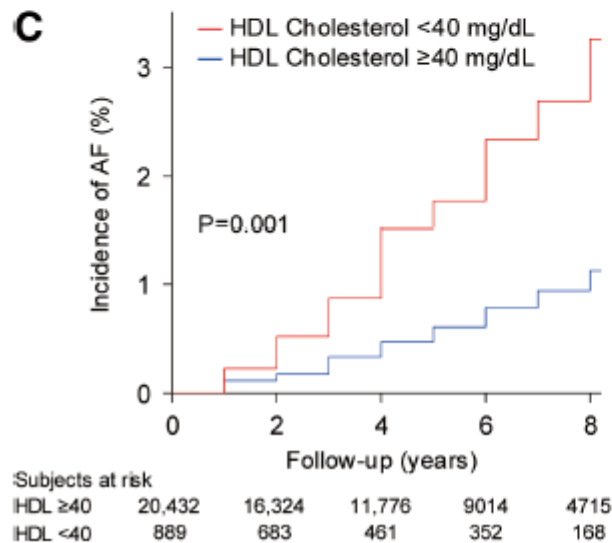
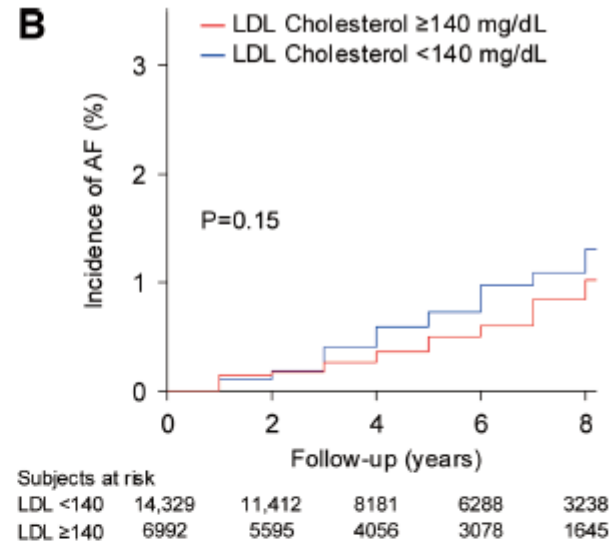
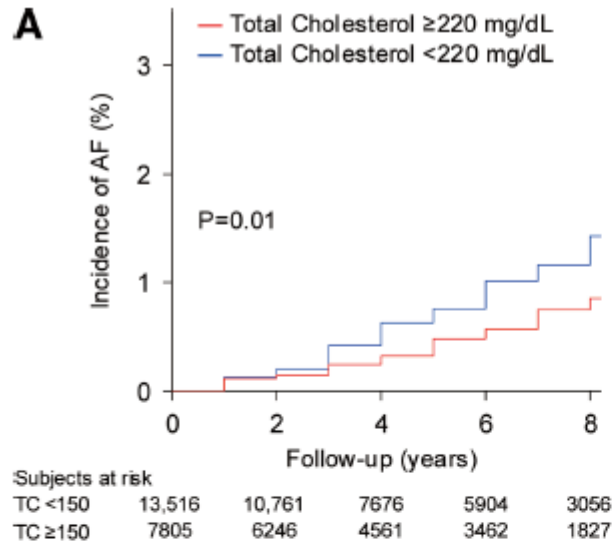
– Niigata Preventive Medicine Study –



Men							
Person-years	240	918	6806	6298	18311	9287	754
AF	0	0	4	15	70	66	5
Women							
Person-years	277	1752	16910	24863	30238	10470	537
AF	0	0	1	12	55	34	3

Association Between Lipid Profile and Risk of Atrial Fibrillation

– Niigata Preventive Medicine Study –



AF vs DM

1. **Conduction and refractory disorders in the diabetic atrium**
Watanabe, *Am J Physiol Heart Circ Physiol* 2012 303: H86–H95,
2. **Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the Atherosclerosis Risk in Communities Study**
Huxley et al *Heart*. 2012 ; 98(2): 133–138.
3. **Meta-Analysis of Cohort and Case–Control Studies of Type 2 Diabetes Mellitus and Risk of Atrial Fibrillation**
Huxley et al *Am J Cardiol* 2011;108:56–62
4. **Prevalence of abnormal glucose metabolism in atrial fibrillation: A case control study in 75-year old subjects**
Johansen et al *Cardiovascular Diabetology* 2008, 7:28

The remodeling of the diabetic atrium was characterized as follows: greater vulnerability to AT, increased conduction slowing and its heterogeneity, the prolongation of APD, the increase in spatial dispersion and frequency dependent shortening of APD, and increased incidence of APD alternans. Interstitial fibrosis was greater and connexin 40 expression was lower in DM than control.

The recurrence of AF after ablation

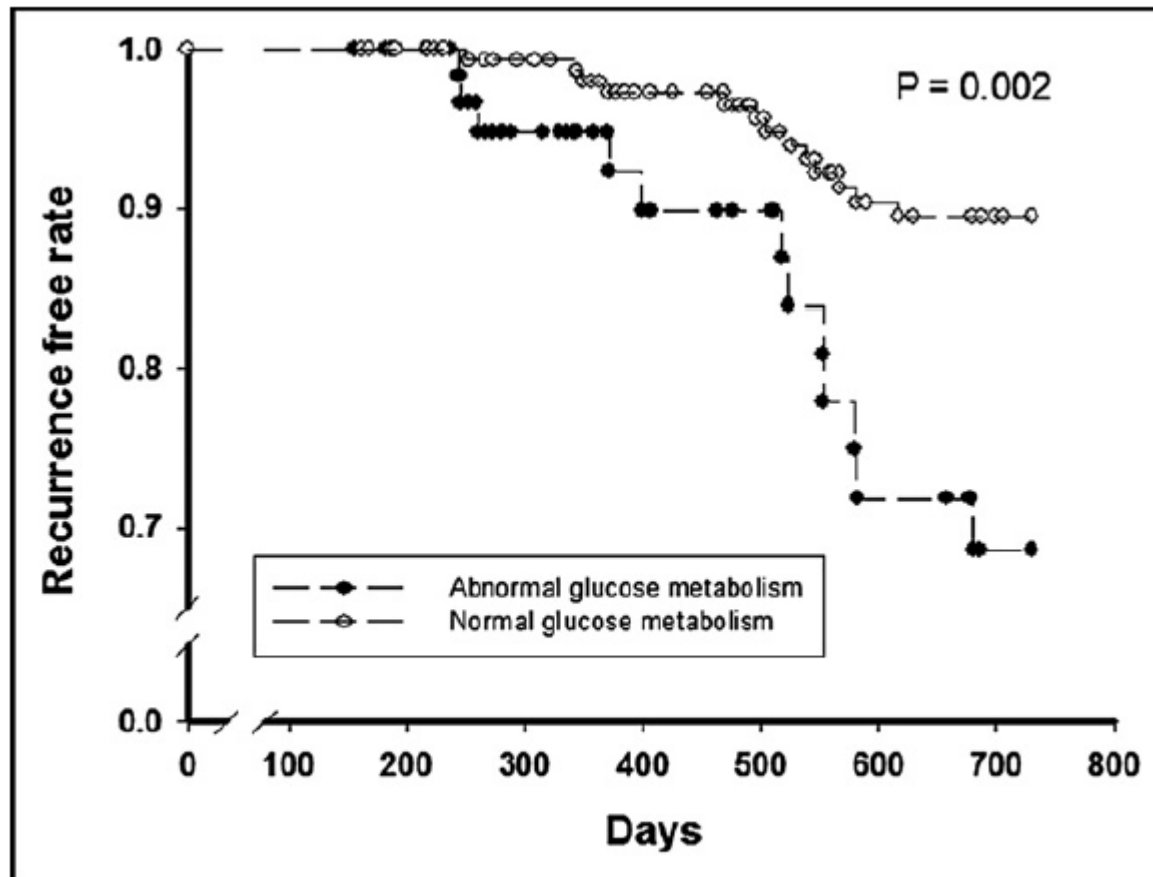


Figure 3. Kaplan-Meier curve demonstrating freedom from AF recurrence during follow-up of patients with normal and abnormal glucose metabolism.

High prevalence of abnormal glucose metabolism in atrial fibrillation: A case control study in 75-year old subjects

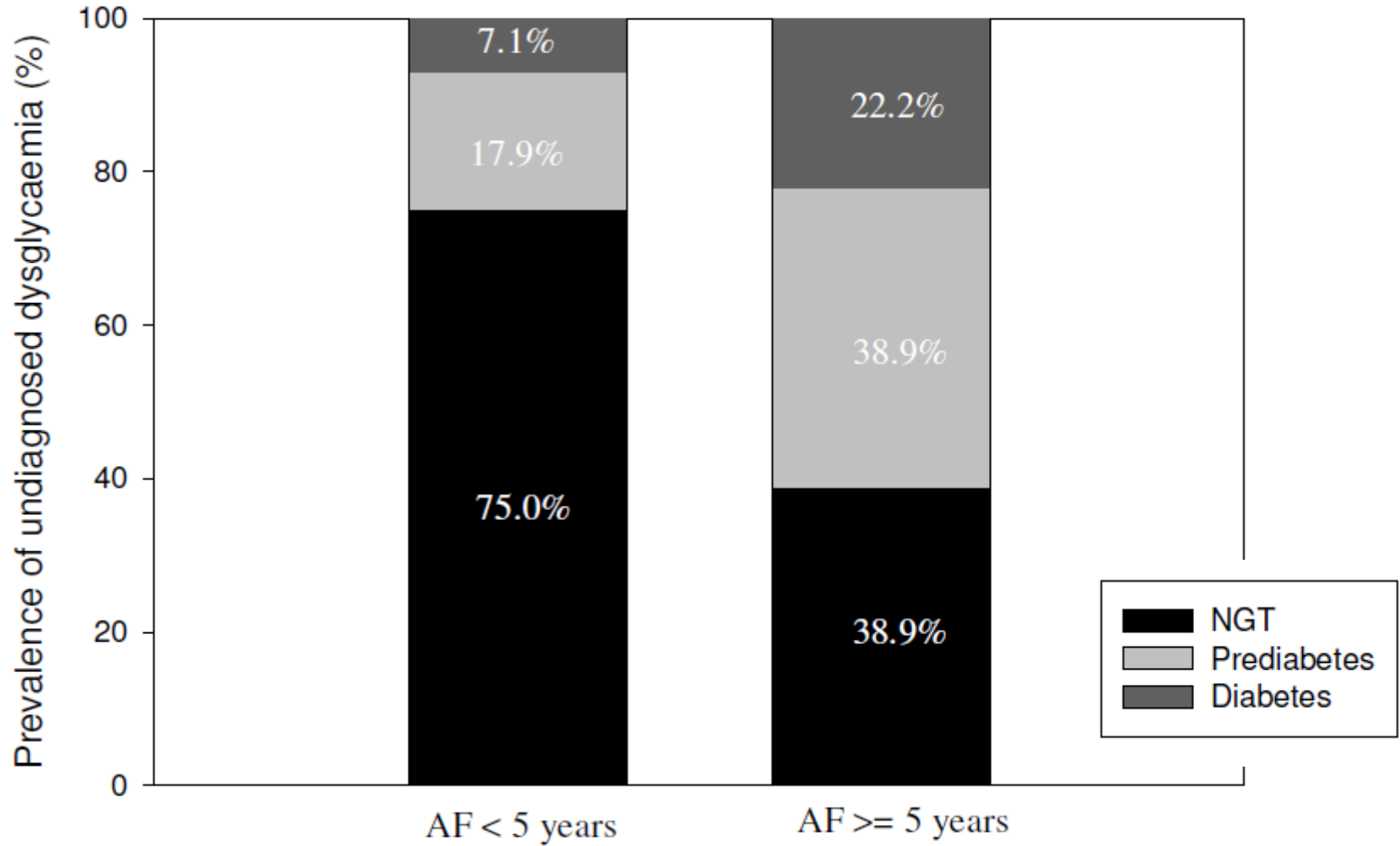
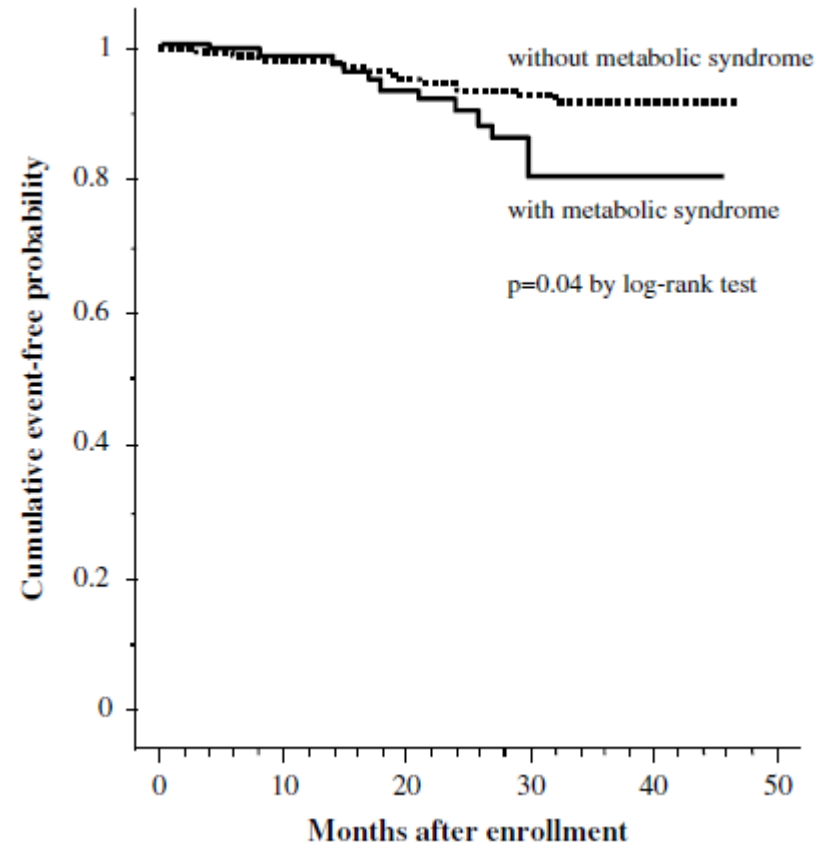
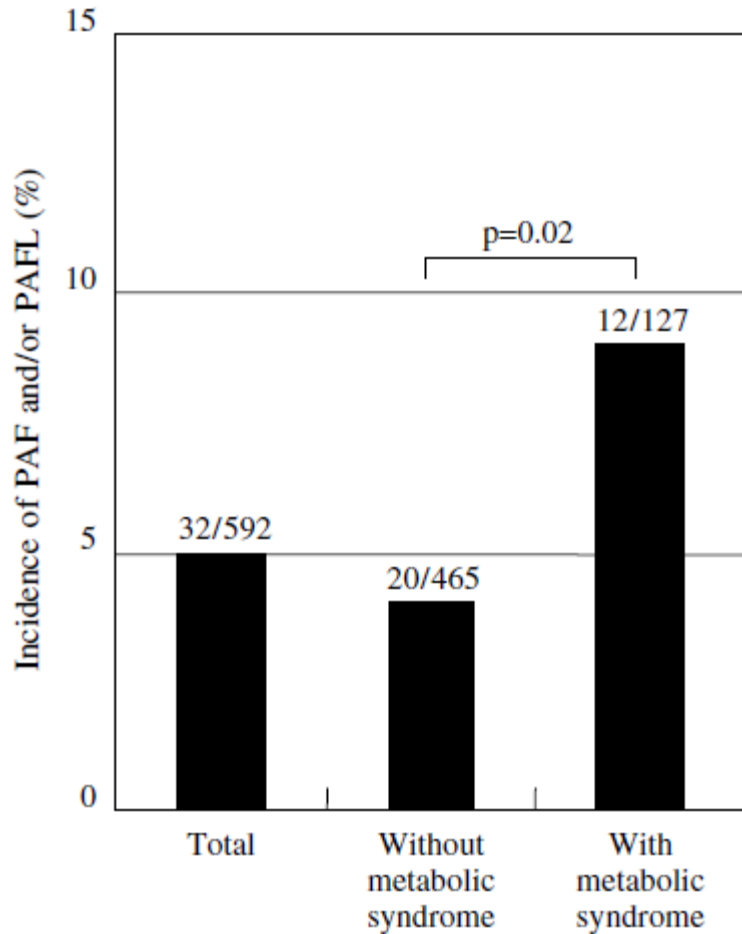


Figure 2. Undiagnosed dysglycaemia according to duration of AF. Prevalence of undiagnosed dysglycaemia in subjects with AF < 5 years and in subjects with AF ≥ 5 years.

High Prevalence of Paroxysmal Atrial Fibrillation and/or Atrial Flutter in Metabolic Syndrome

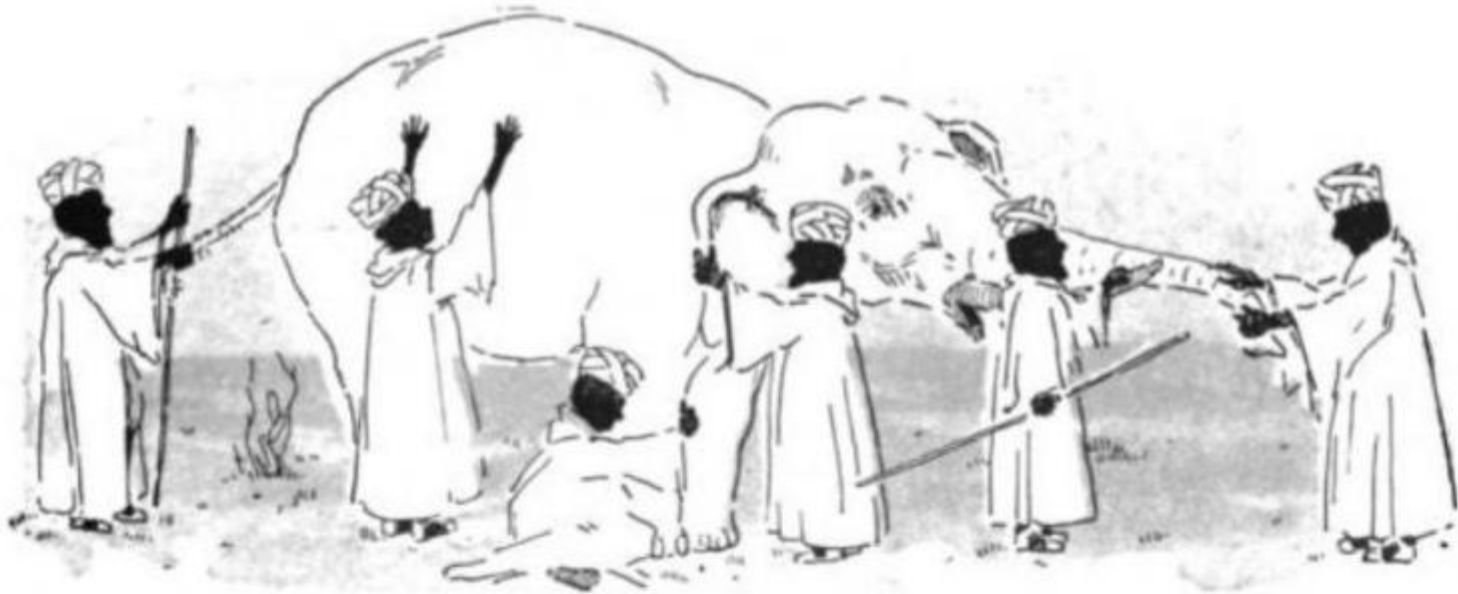


These reports have described significant correlation between metabolic syndrome and AF.

The pathophysiology, however, of developing AF in these conditions has not well elucidated yet.

In the following part of my talk, I will briefly introduce animal experiments to clarify the mechanisms of developing AF in those conditions.

AF looks like elephant!



The underlying diseases and models of AF and their elements

Diseases:

1. Valvular diseases
2. Hypertension
3. Diabetes Mellitus
4. Thyroid diseases
5. Metabolic syndrome
6. Stress
7. Others

Elements:

1. Stretch
2. Pressure-overload
3. Inflammation
4. ROS
5. Other cytokines

Animals

1. Goat
2. Dog
3. Rabbit
4. **Rat**
5. **Mice**
6. Vitro system
7. Others

Interventions

- a. Tachypacing
- b. **Abdominal Aortic Constriction**
- c. Thoracic Aortic Constriction
- d. Atrio-Ventricular block
- e. Chronic Kidney Disease
(**5/6 nephrectomy model**)
- f. Stretch in vitro system
- g. variable drugs (**Ang-II et al**)
- h. **Others (genetic defects et al)**



AF

Clinics:

1. **Increased collagen deposition in patients with AF than in those with control SR.**
2. **Atrial fibrosis with mitral valve diseases.**
3. **LA fibrosis predicts AF recurrence.**
4. **Fibrosis at fractionated potentials.**
5. **Fibrosis at Maze operation.**
6. **Others.**

Animal study

1. Ang-II vs hyperthermia
2. AAC model vs PPAR γ agonist
3. Ob/Ob mouse vs Leptin

Hyperthermia to 42° C for 30 min induce HSP72 expression, peaking at 8 hours after the application of hyperthermia (Fig. 1A).

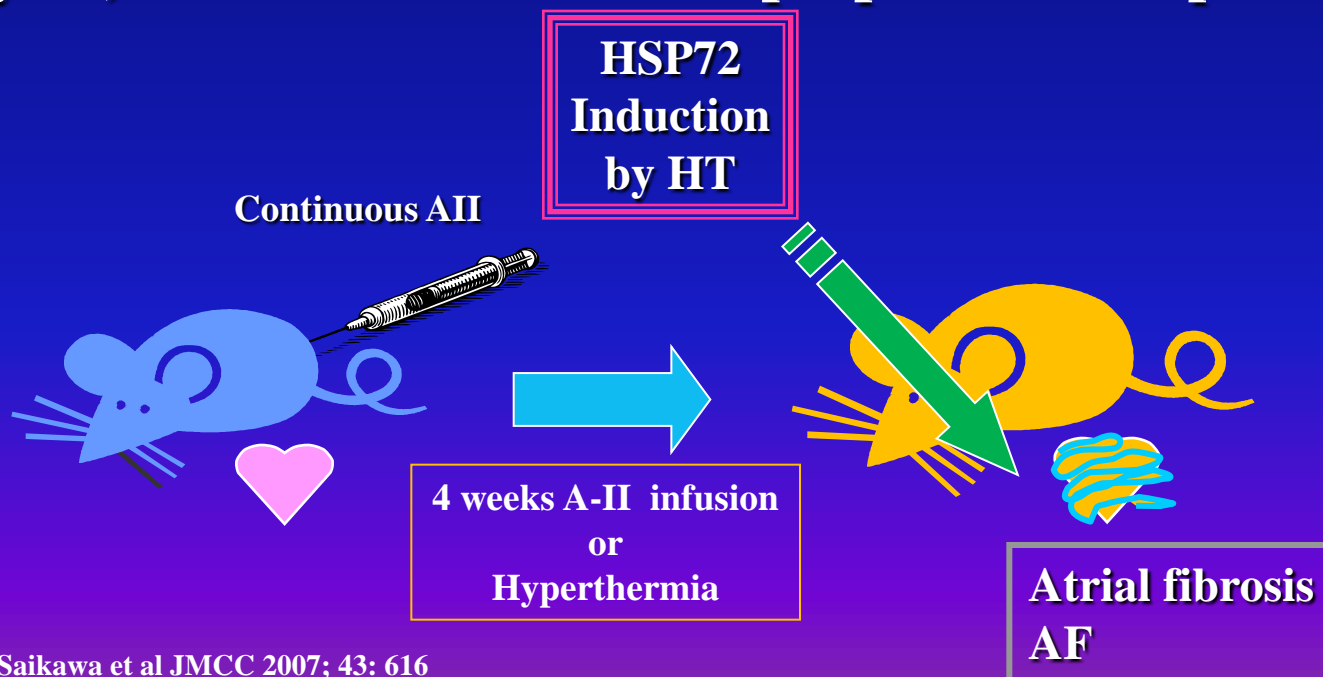
In hyperthermia-treated fibroblasts, AII-induced extracellular signal-regulated kinase (Erk1/Erk2) phosphorylation (Fig. 1B), α -smooth muscle actin (α -SMA) expression (Fig. 2), transforming growth factor- β 1 (TGF- β 1) secretion, collagen synthesis, and expression of collagen type-1 and tissue inhibitor of metalloproteinases-1 were attenuated. Because a small interfering RNA targeting HSP72 abolished these anti-fibrotic effects of hyperthermia (Figs. 1 and 2), we concluded that heat-shock responses, particularly induction of HSP72, have a dominant role in suppression of the AII-induced fibrotic signal.⁷ In addition, in experiments in vivo, repeated hyperthermia (43° C for 20 min) prevented the left atrial interstitial fibrosis induced by continuous infusion of AII (Fig. 3).

Protocol: Whole heart experiments

In male rats, mini-pump was subcutaneously implanted for continuous infusion of AII (400 ng/kg/min).

Whole body hyperthermia (HT; 43°C for 20 min) was applied every 7 days.

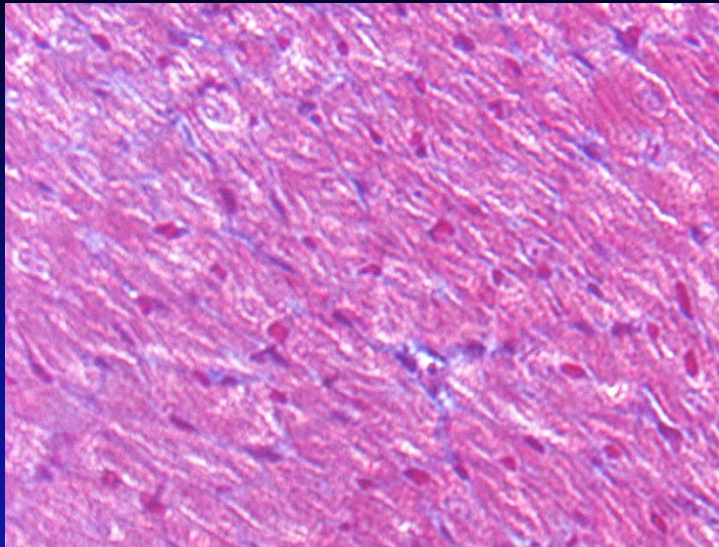
On day 28, heart was isolated and prepared for experiments.





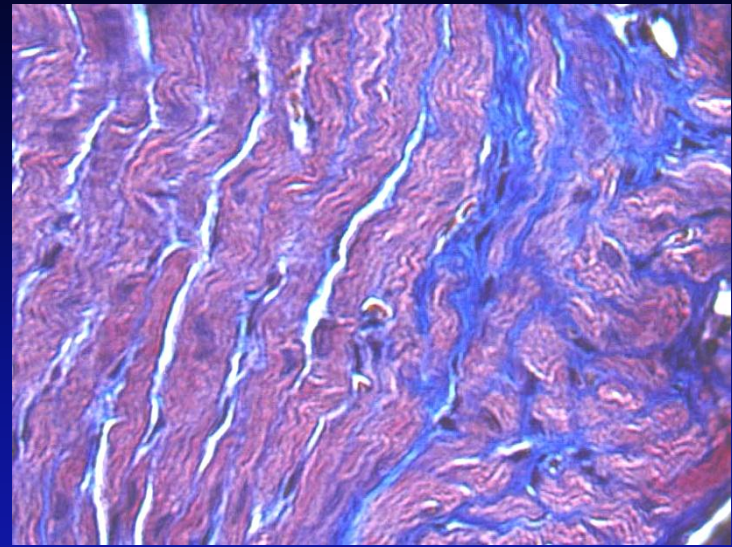
Masson trichrome staining (LA free wall)

Control



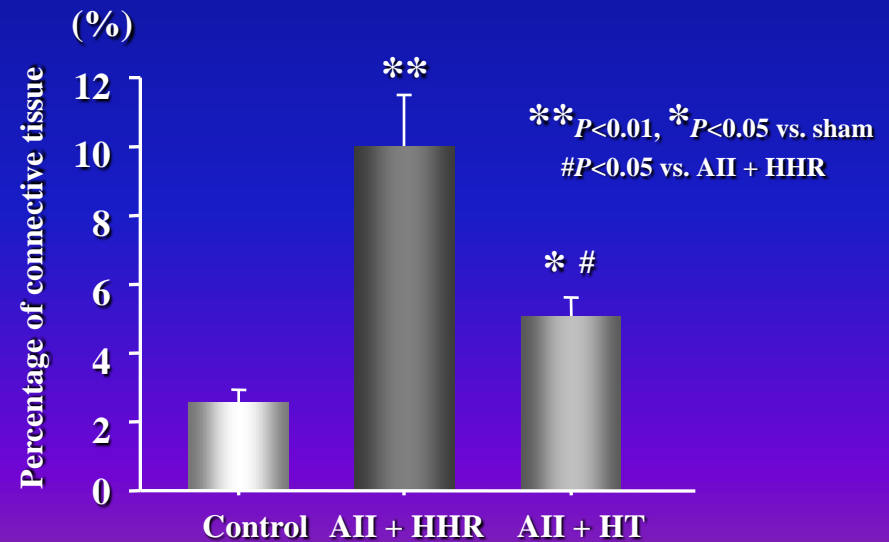
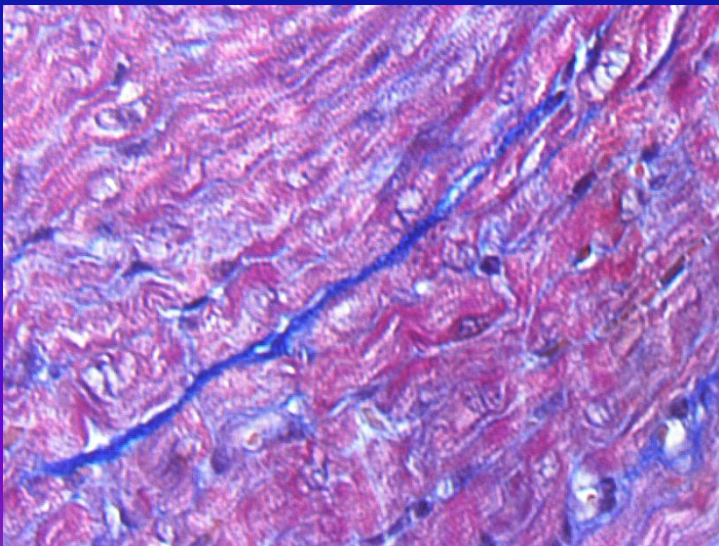
100µm

AII + HHR

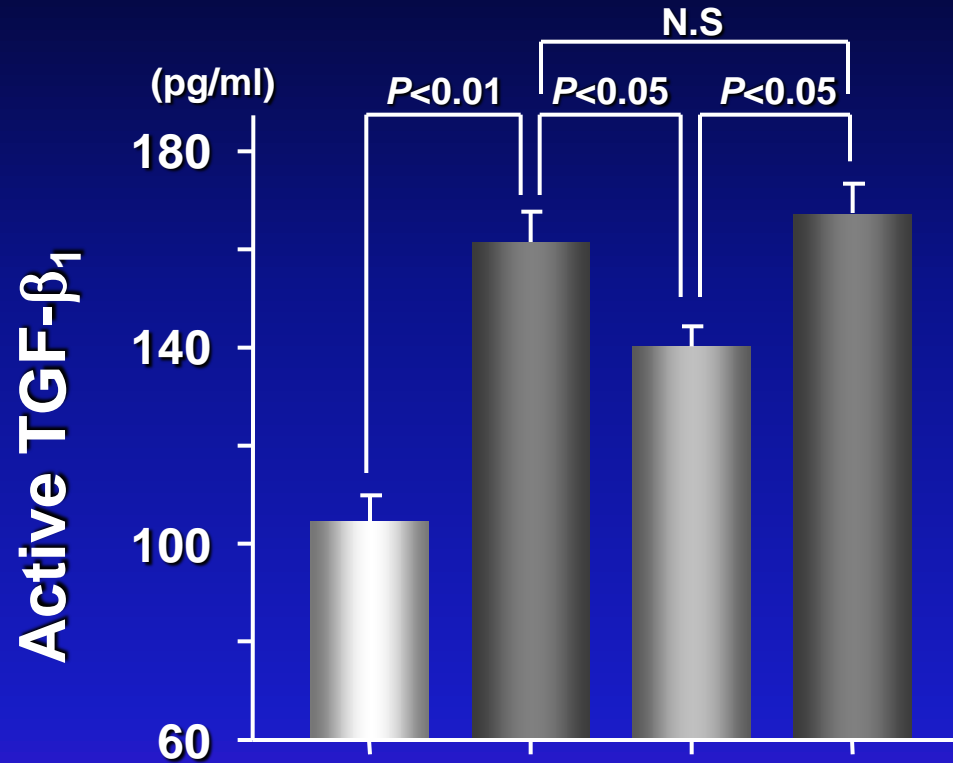


(HHR: Hydraladine, Hydrochrolothiazide, Reserpine)

AII + HT



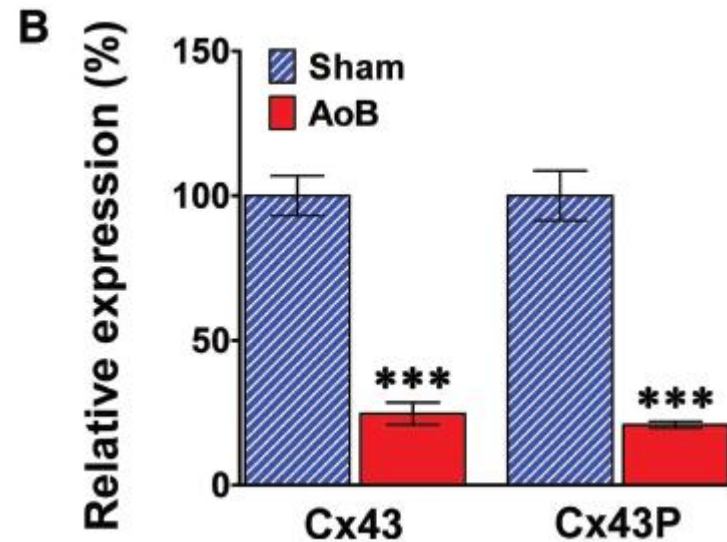
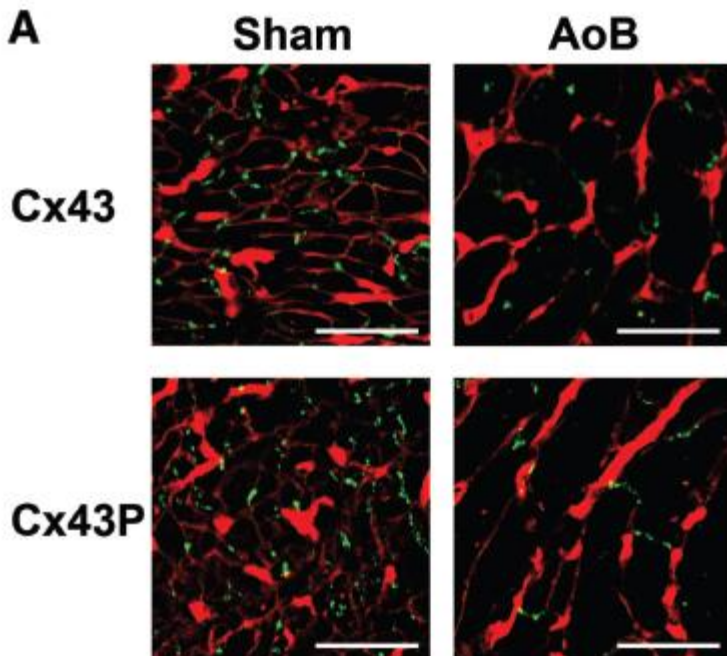
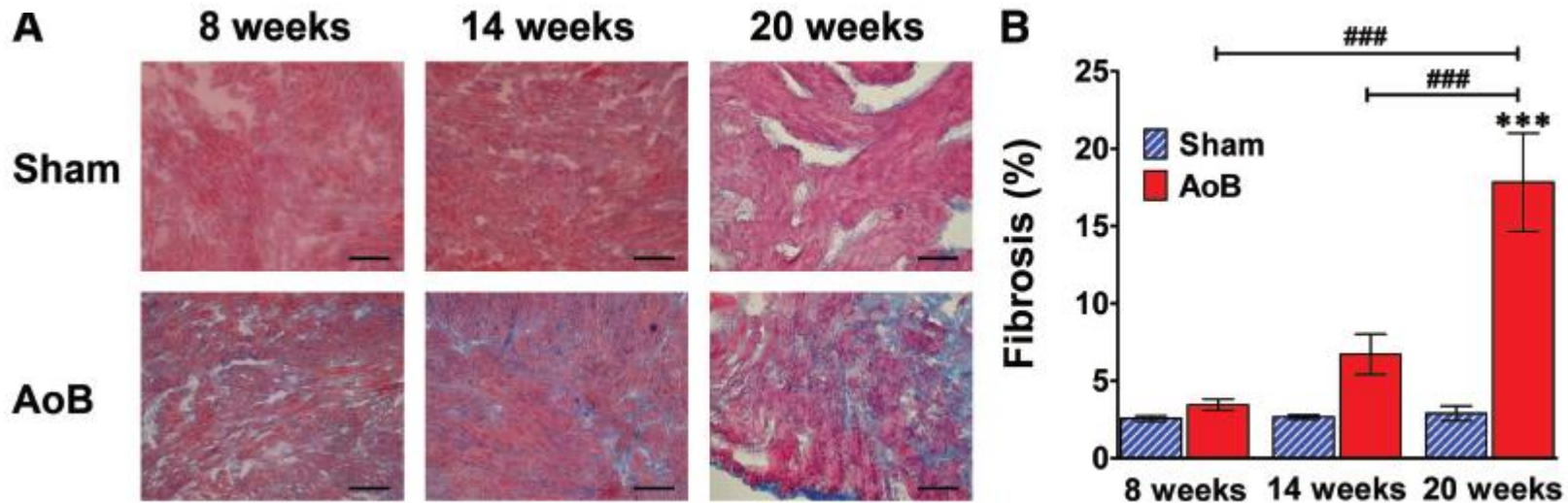
Secretion of TGF- β_1 by atrial fibroblast



All (100nM)	-	+	+	+
HT	-	-	+	+
HSP72 siRNA	-	-	-	+



Left atrial fibrosis and Connexin expression after elevated afterload.



PPAR : Peroxisome proliferator-activated receptor- γ agonist
Anti-inflammatory and anti-fibrotic action
Pioglitazone
Tx for DM

PPAR : Peroxisome proliferator-activated receptor- γ

PGC -1 : peroxisome proliferator-activated receptor- γ coactivator 1,
3 subtypes such as α & β and **PRC** peroxisome proliferator-activated
receptor- γ coactivator 1-related coactivator

PGC-1 Coactivators in Cardiac Development and Disease

Glenn C. Rowe, Aihua Jiang, Zolt Arany *Circ Res.* 2010;107:825-838.

PGC-1 coactivators in the cardiovascular system

Ian S. Patten and Zolt Arany *Trends in Endo Metab* 2012; 23: 90-97

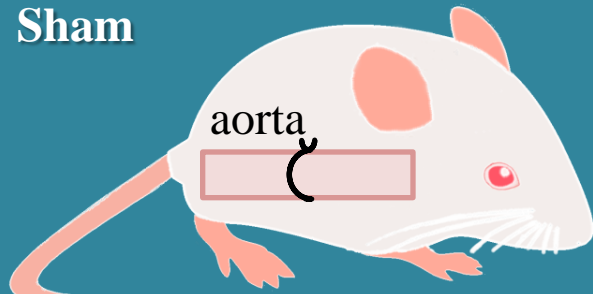
Deletion of the metabolic transcriptional coactivator PGC1b induces cardiac arrhythmia.

Iman S. Gurung^{1,2*†}, *Cardiovascular Research* (2011) 92, 29–38

Protocol

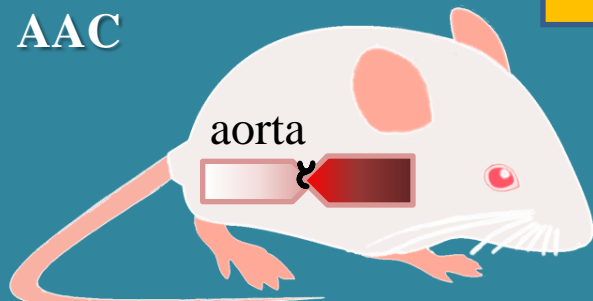
6w male SD rat

Sham



Sham operation

AAC



Suprarenal abdominal aortic constriction (AAC)

Four groups:

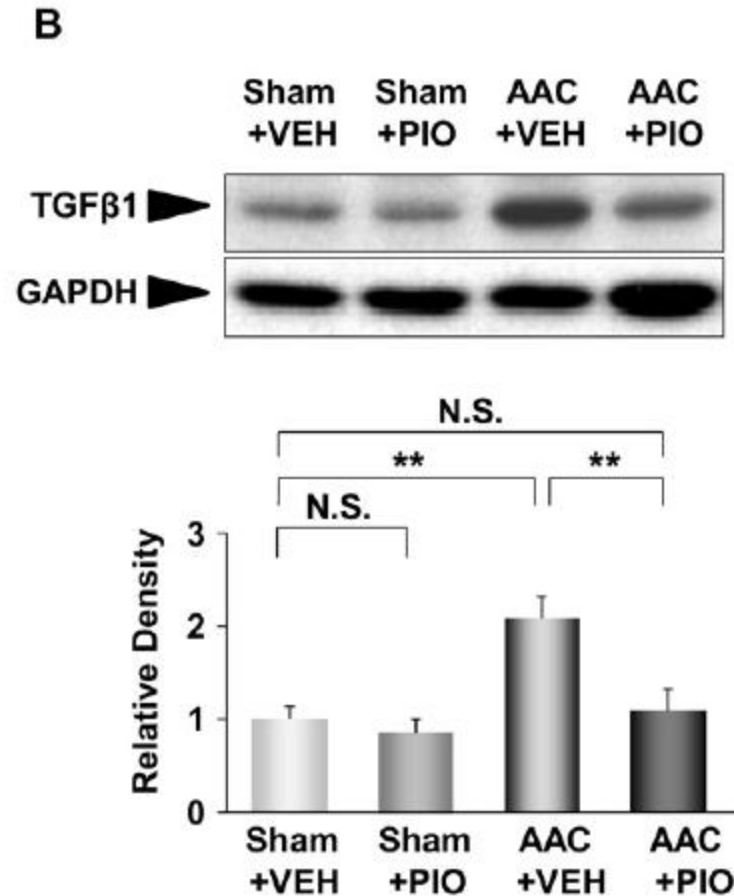
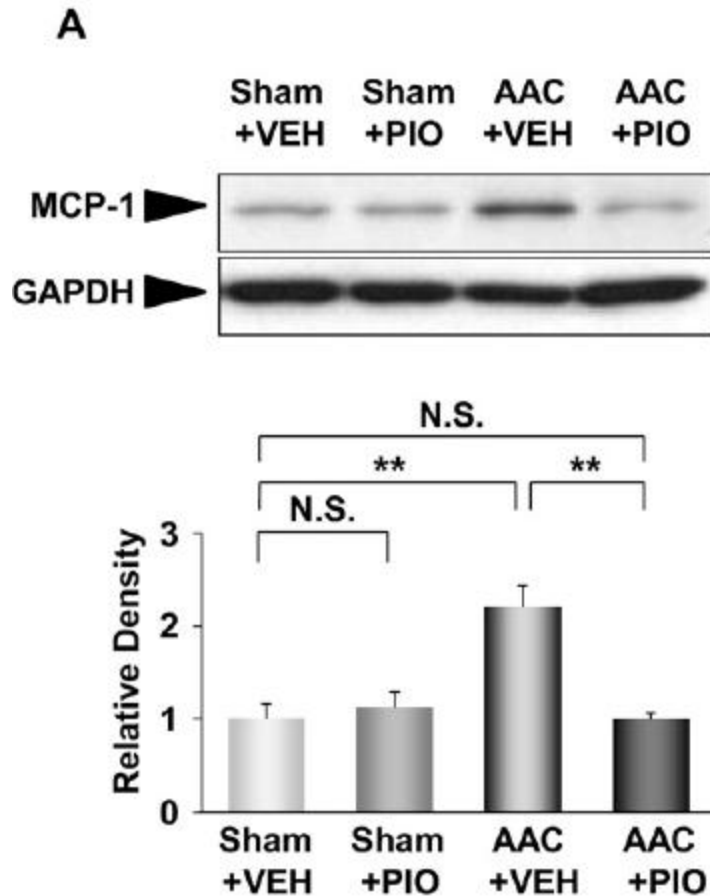
1. Sham-VEH
2. Sham-Pio (3 mg/kg/day, 4 weeks)
3. AAC-VeH
4. AAC-Pio (3 mg/kg/day, 4 weeks)

28 days

Sacrificed to perform experiments

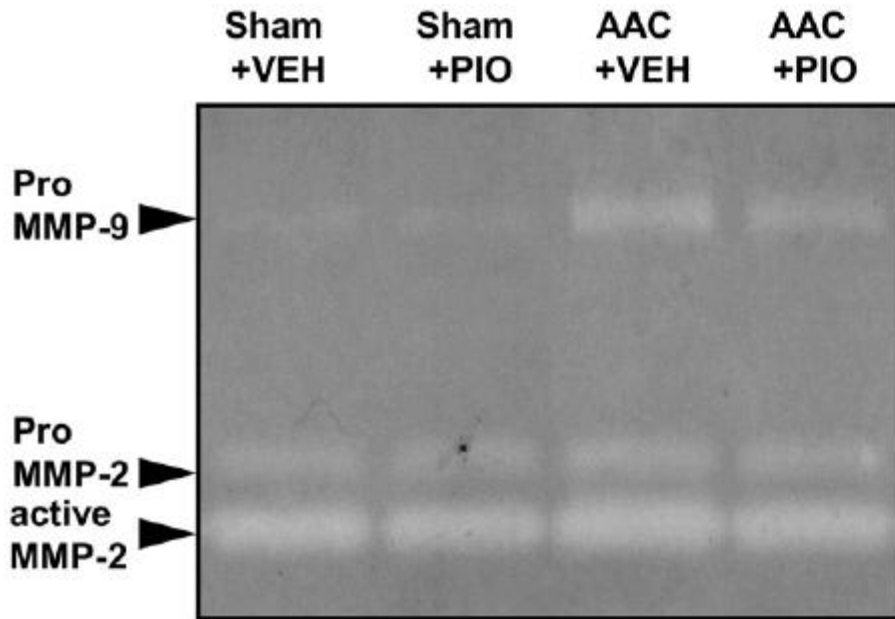
- western blot
- immunohistochemistry
- scanning electron microscopy (SEM)

The increased expression of MCP-1 & TGF- β_1 in LA

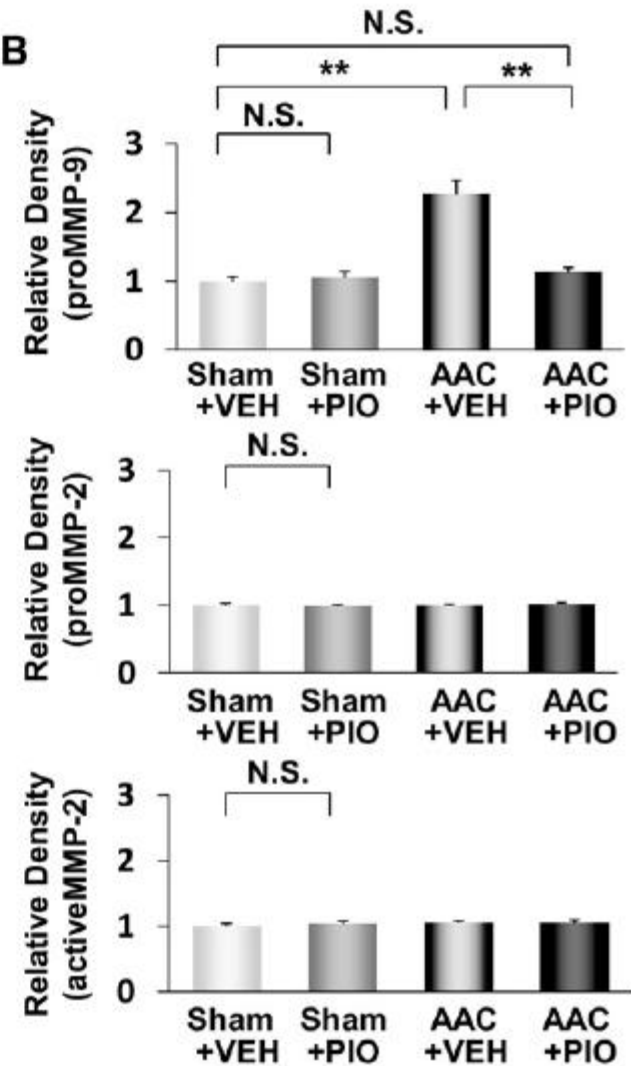


The expression of MMP-2 & MMP-9 in LA

A

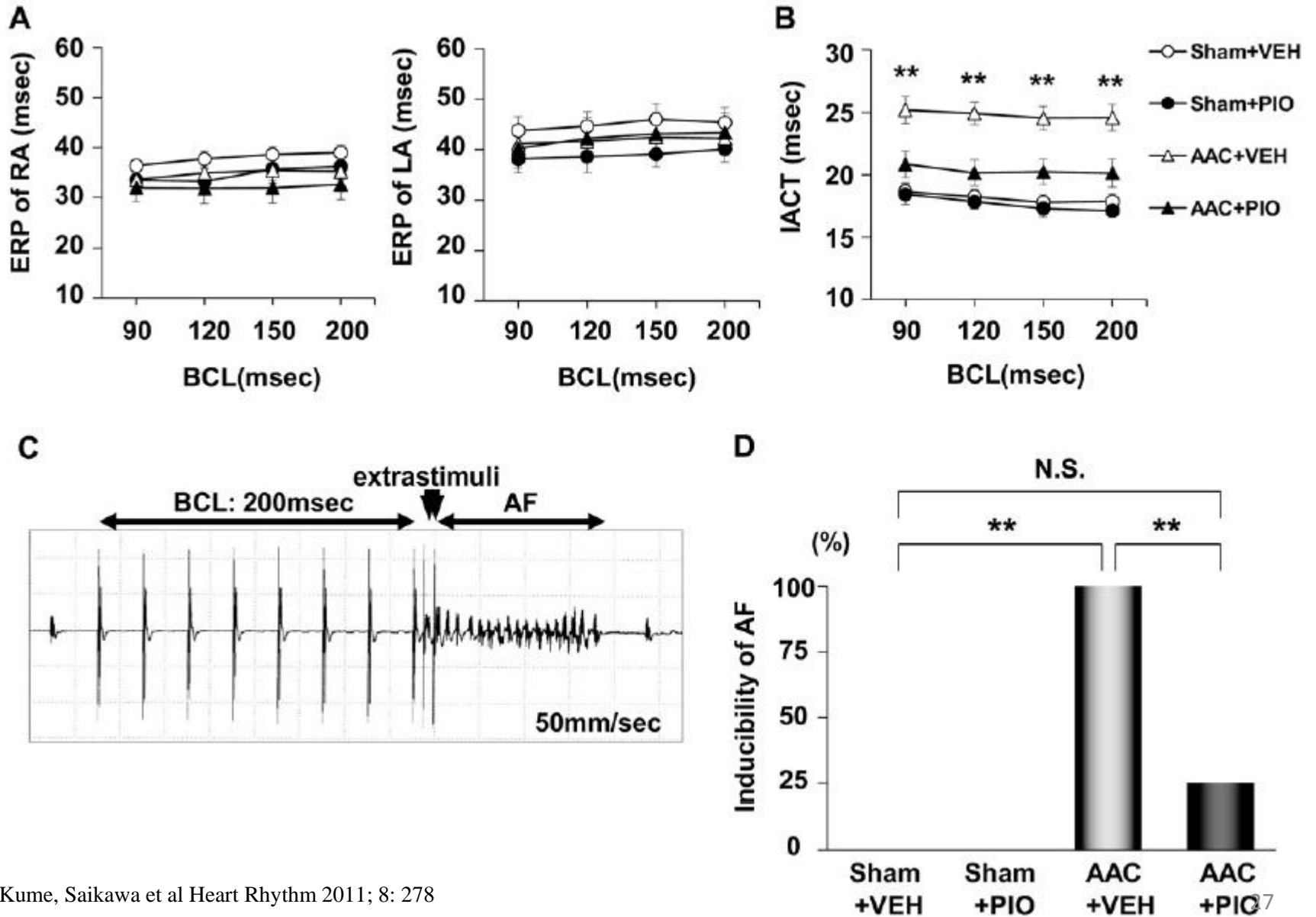


B



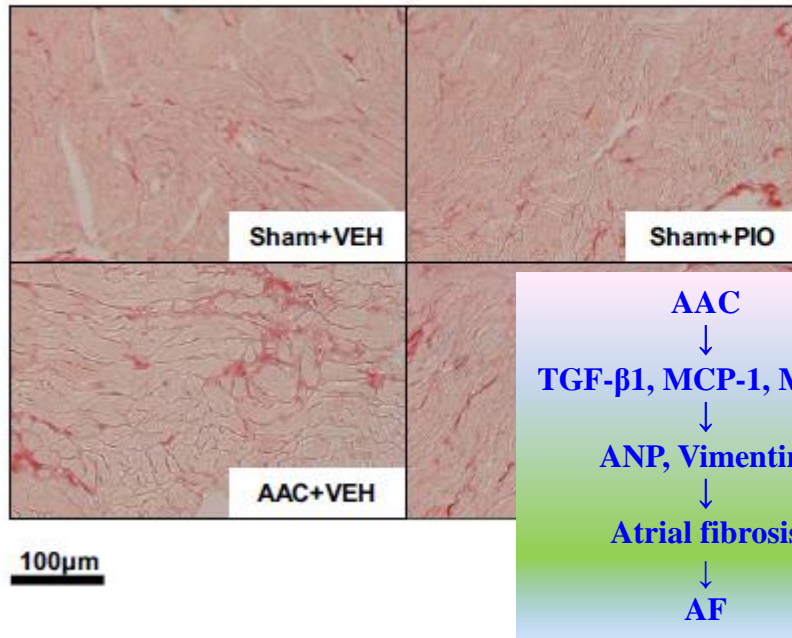
Electrophysiological study: ERP (A), IACT (B), Electrogram (C), and Inducibility (D).

OITA UNIVERSITY



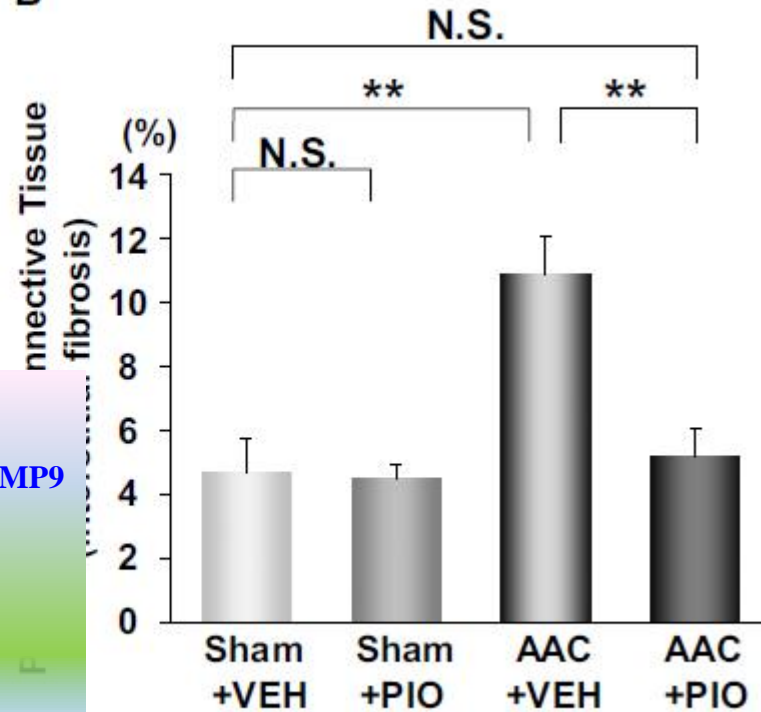
Left Atrial Fibrosis

A



Sirius red staining

B



Mean % of interstitial fibrosis

Thiazolidinediones can prevent new onset atrial fibrillation in patients with non-insulin dependent diabetes.

OADs = oral anti-diabetic agents
 NHIRD = the National Health Insurance Research Database
 TZDs = thiazolidinediones

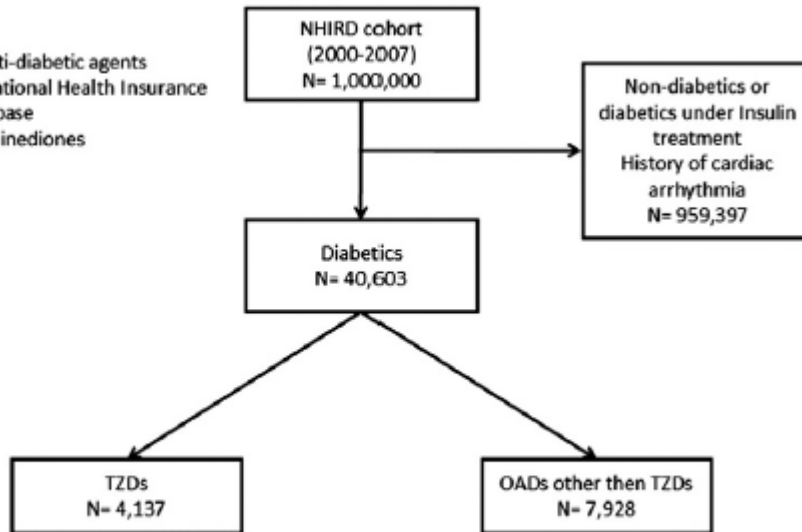


Fig. 1. The flowchart to identify the cohorts with and without TZD use.

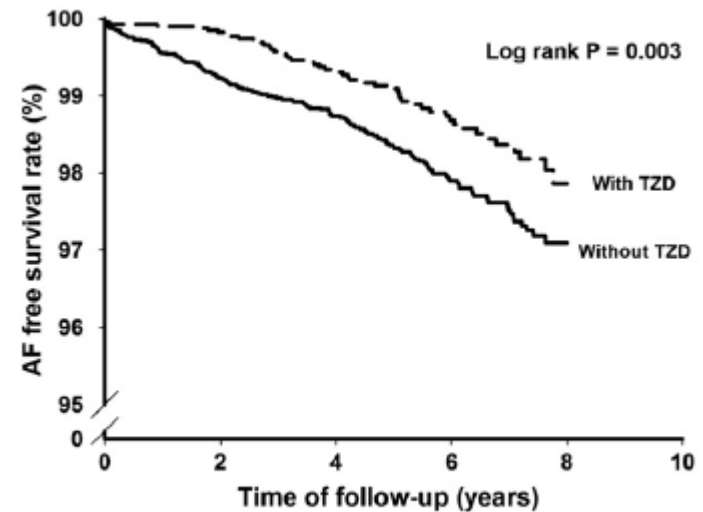
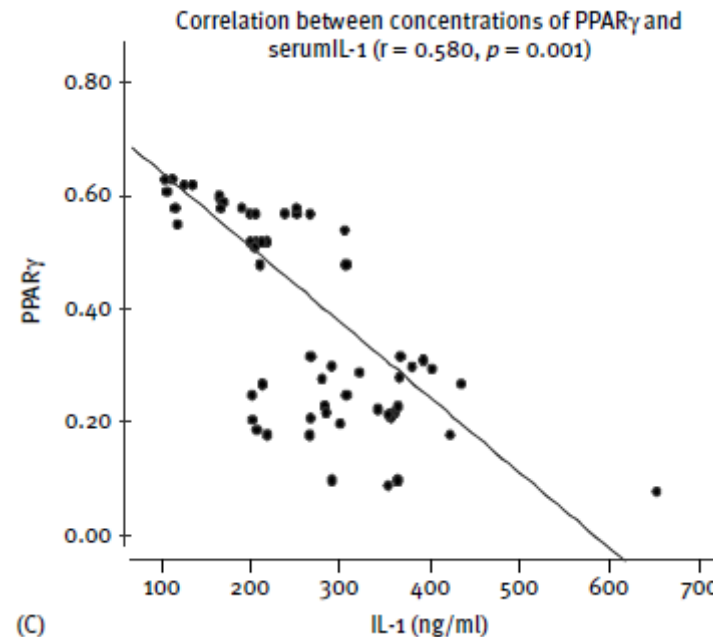
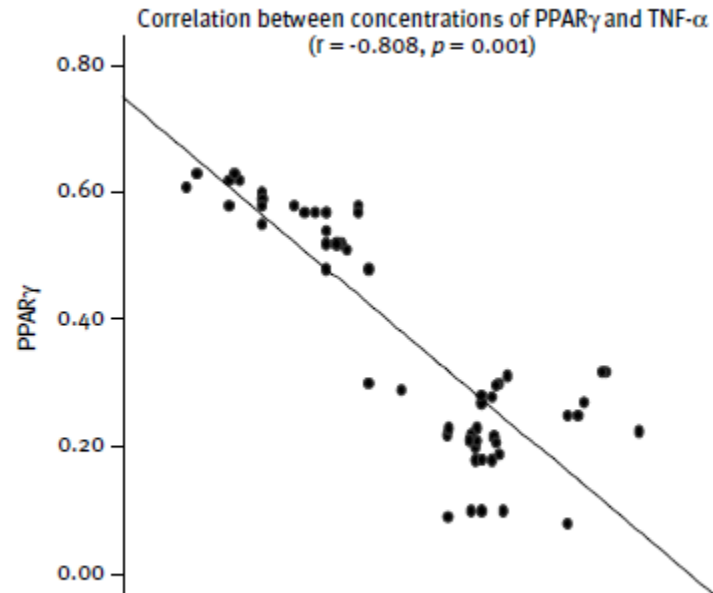
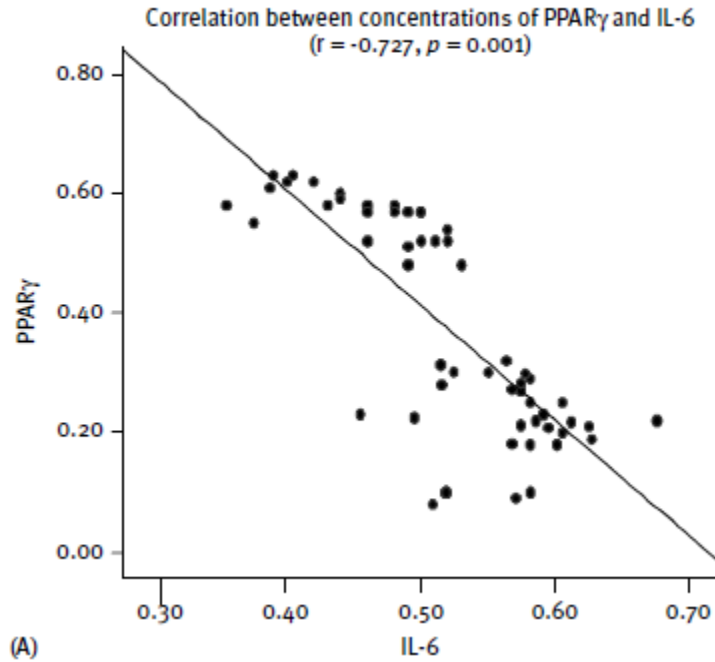


Fig. 2. AF-free survival rate for diabetic patients with and without TZD use. AF = atrial fibrillation.

Downregulation of Peroxisome Proliferator-activated Receptor- γ Expression in Hypertensive Atrial Fibrillation



A pilot study of circulating PPAR- γ receptor protein in elderly patients with atrial fibrillation

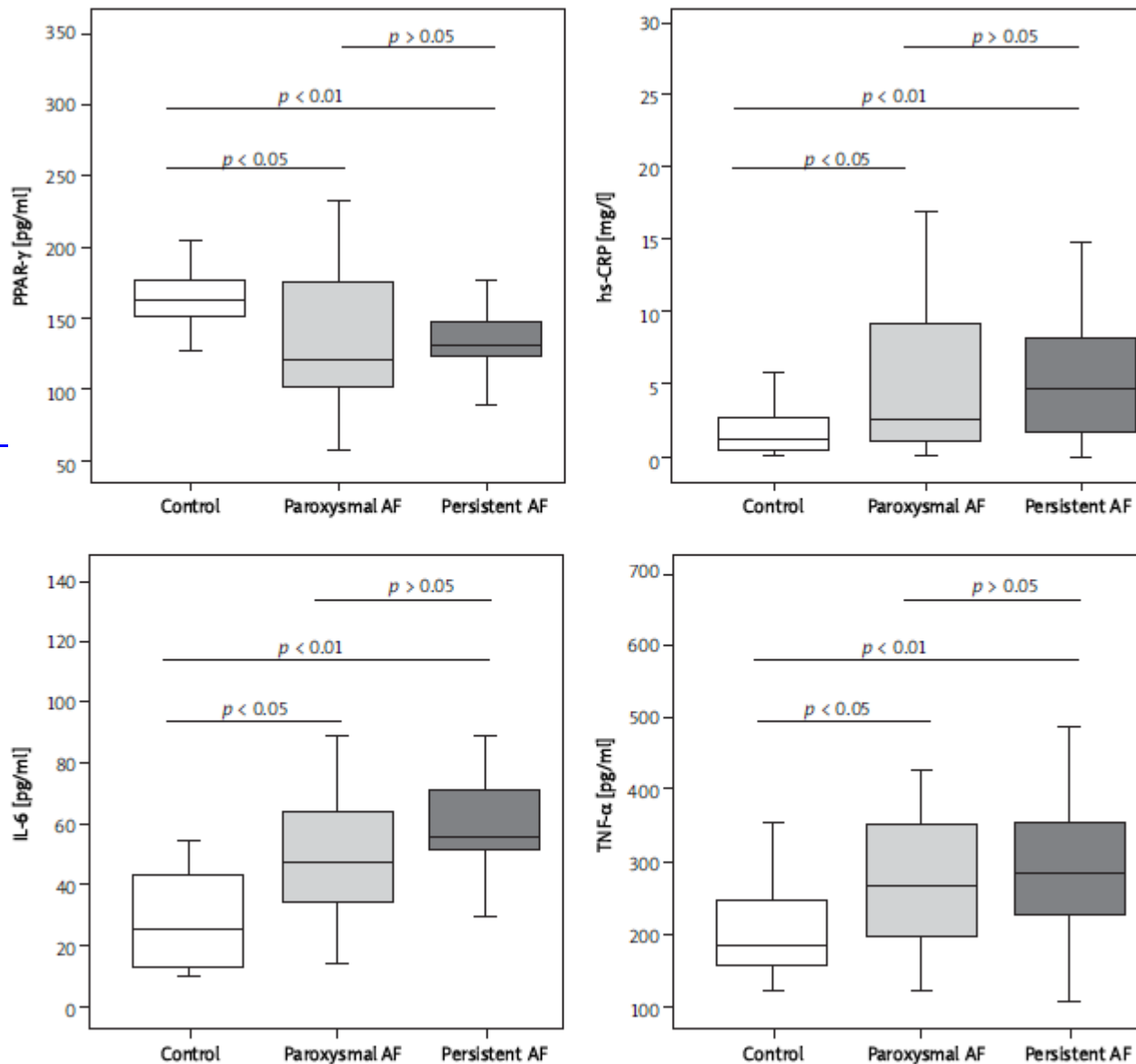


Figure 1. Serum levels of PPAR- γ and inflammatory factors in controls and patients with paroxysmal and persistent AF. Box plots demonstrate median, and 25th and 75th percentile values

In the metabolic syndrome, especially in case of Obesity, leptin has been known to play an important role by modulating food intake.

AF has reportedly shown to prevail in Obese patients, however, little has been known about the role of leptin in the development of AF.

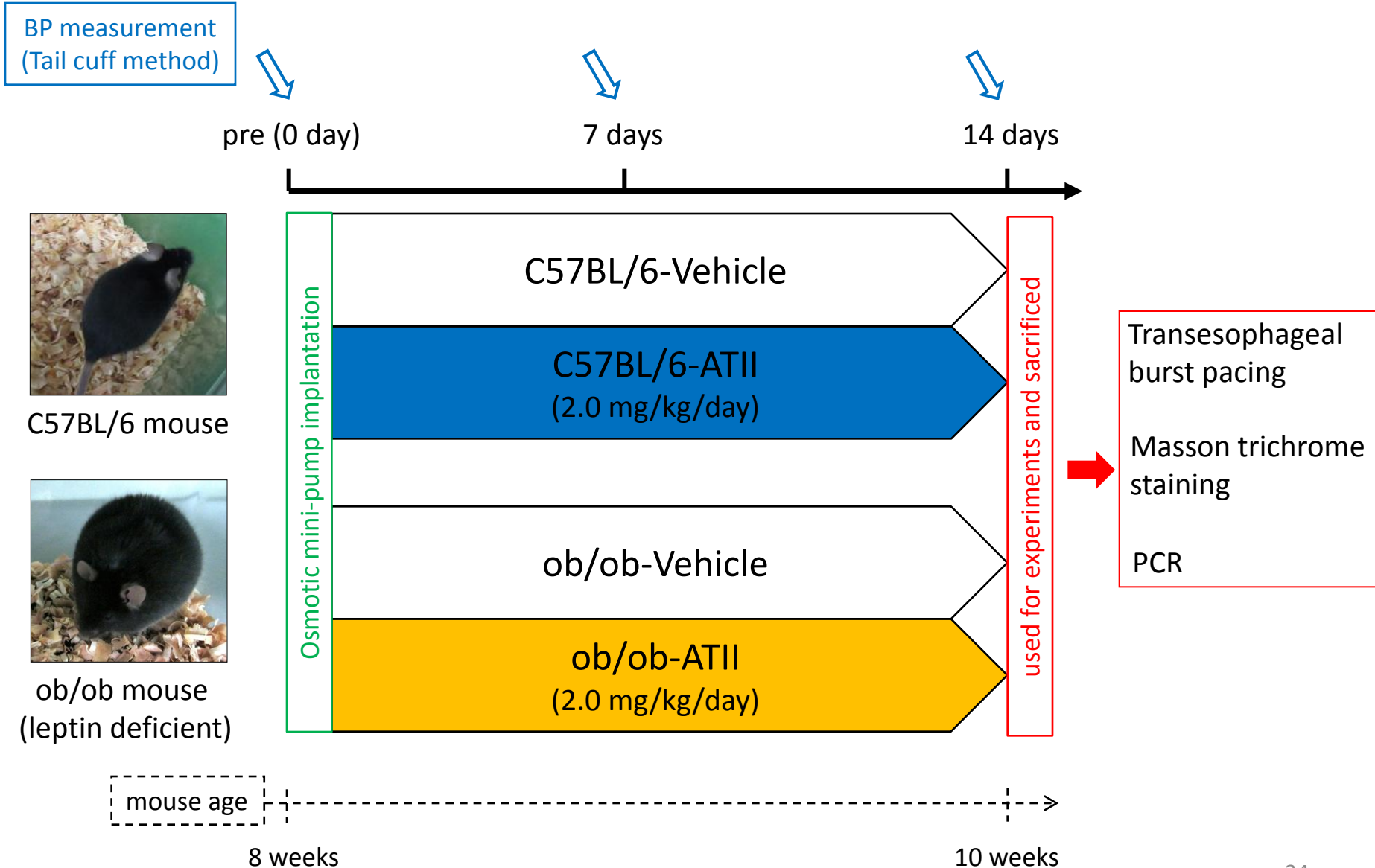
Role of Leptin Signaling in Pathogenesis of Atrial Fibrosis and Fibrillation

- ✓ *Leptin was discovered by Friedman and his colleagues in 1994. (Zhang Y et al. Nature. 1994;372:425-32)*
- ✓ *In addition to the regulation of energy balance, leptin has diverse effects, including pro-fibrotic effects.*
 - *Ikejima K et al. Hepatology. 2001;34:288-297*
 - *Tanaka M et al. Endocr J. 2010;57;61-72*
- ✓ *However, its role in atrial fibrosis and atrial fibrillation (AF) has not yet been investigated.*

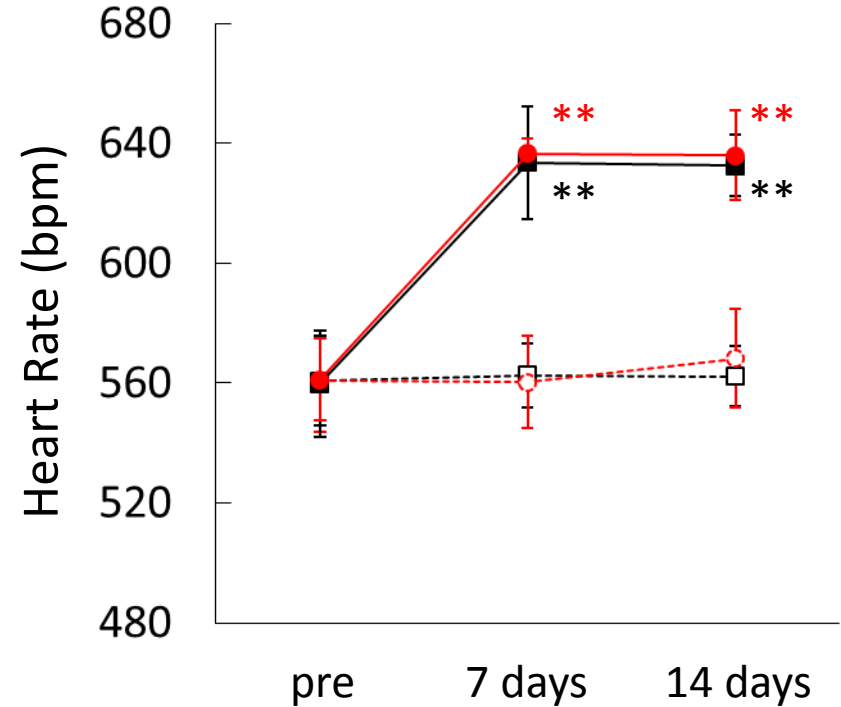
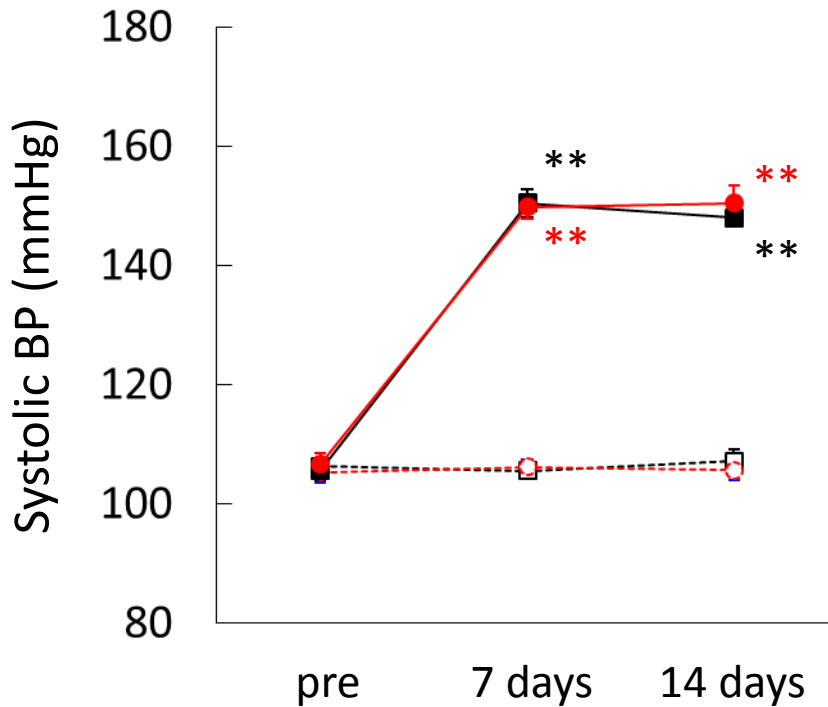
Aim:

To test the hypothesis whether leptin signaling would contribute to atrial fibrosis and enhanced AF vulnerability evoked by angiotensin II (ATII).

Method (in vivo)



Hemodynamic change by ATII infusion



- C57BL/6 Vehicle
- ob/ob Vehicle
- C57BL/6 ATII
- ob/ob ATII

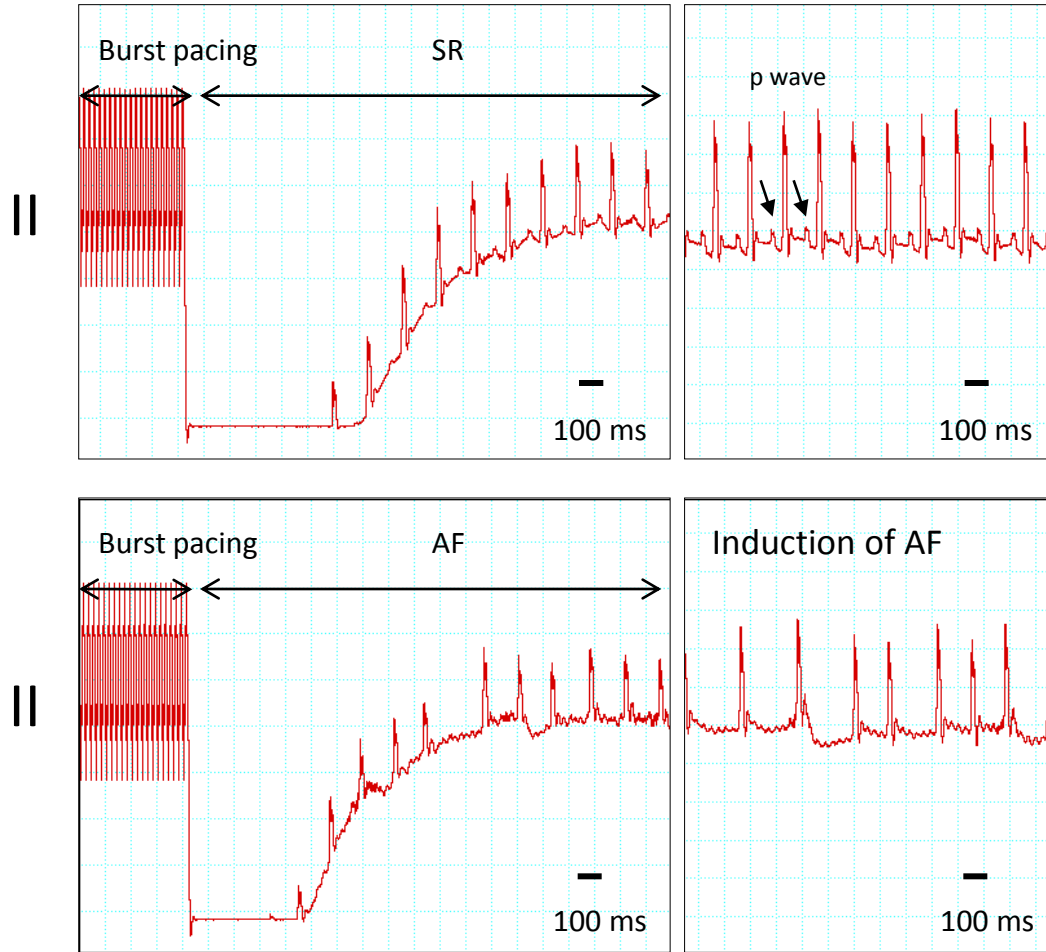
n=8 for each group, Data are mean ± SED.

BP: blood pressure, ATII: angiotensin II.

** p < 0.01 vs corresponding VEH.

Induction of AF by Transesophageal burst pacing

A. Representative AF induction in C57BL/6-All group

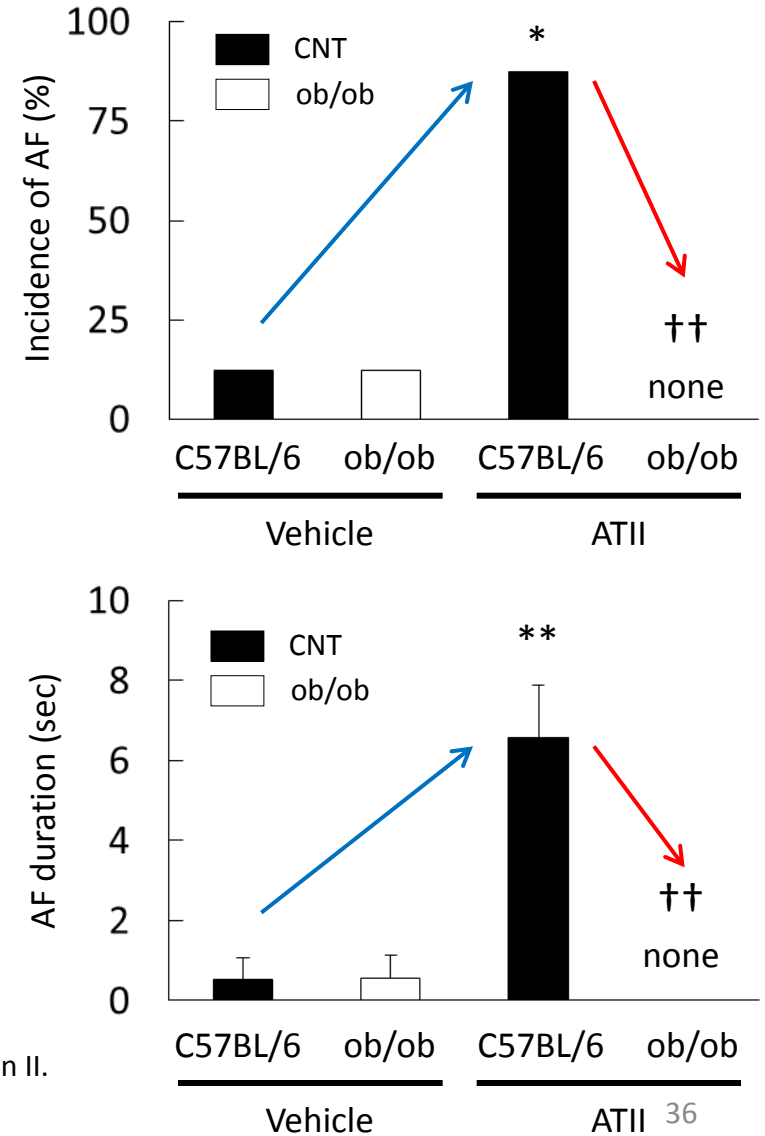


n=8 for each group, Data are mean \pm SEM.

AF: atrial fibrillation, SR: sinus rhythm, CNT: control, VEH: vehicle, ATII :angiotensin II.

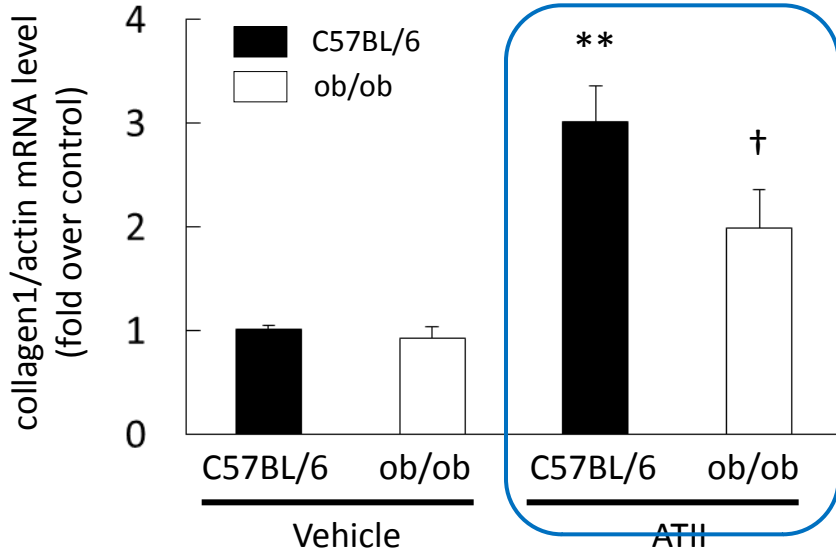
* $p < 0.05$ vs CNT+VEH, ** $p < 0.01$ vs CNT+VEH, †† $p < 0.01$ vs CNT+ATII.

B. Incidence and duration of AF

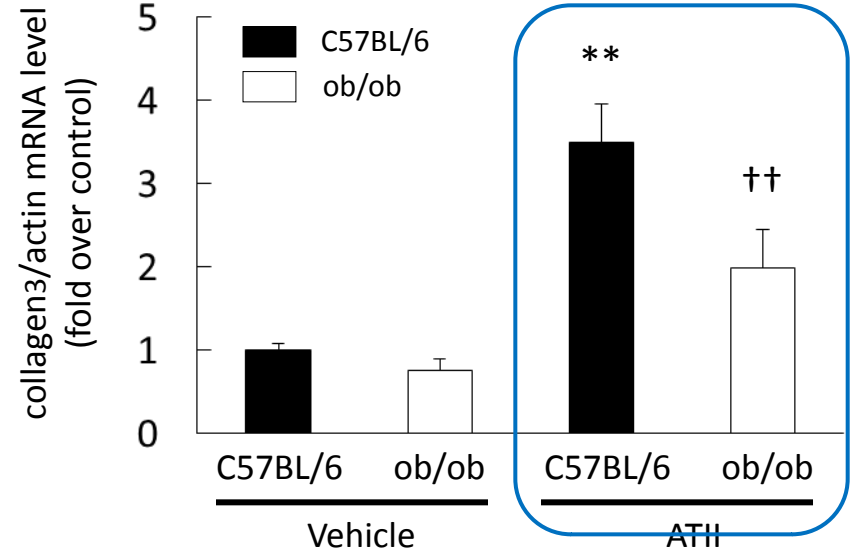


mRNA expression in left atrium

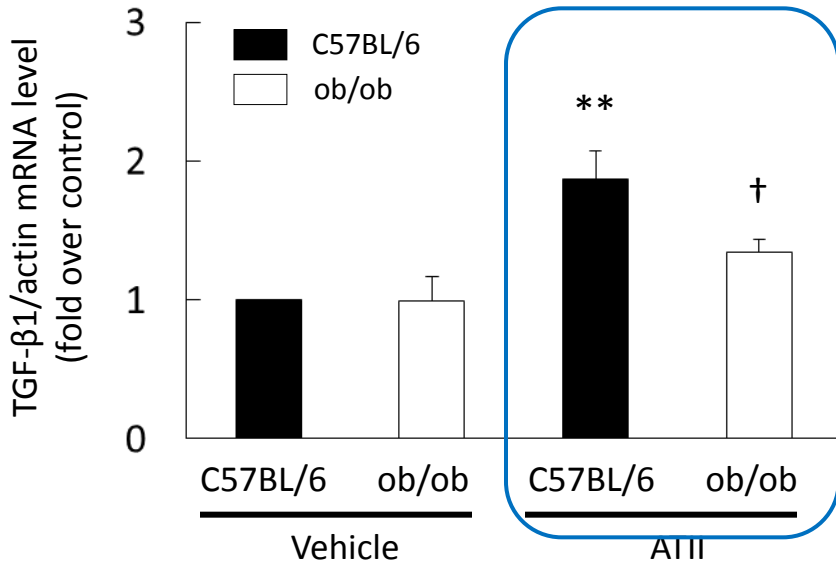
collagen 1 mRNA



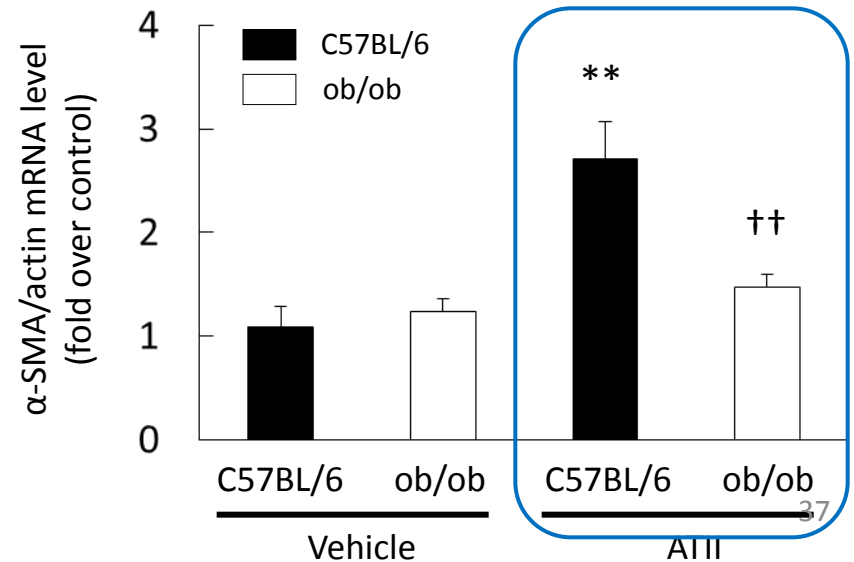
collagen 3 mRNA



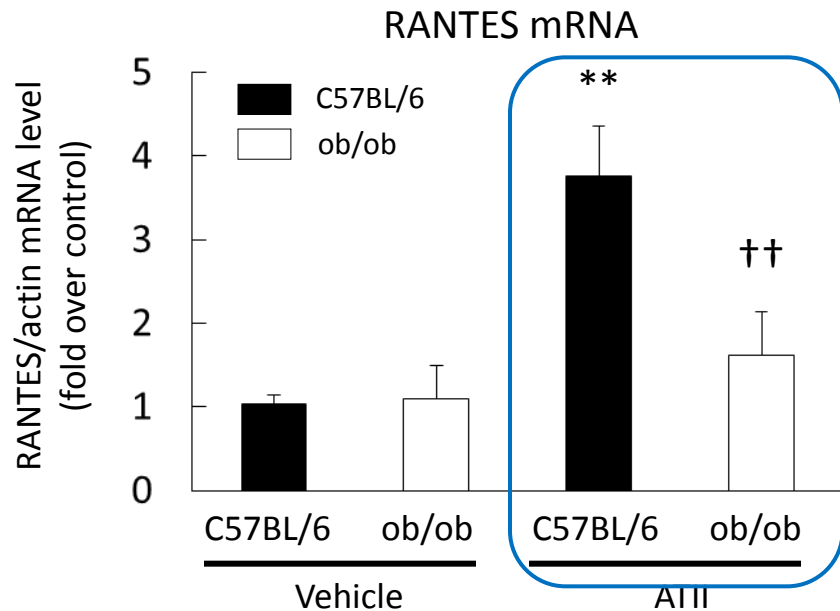
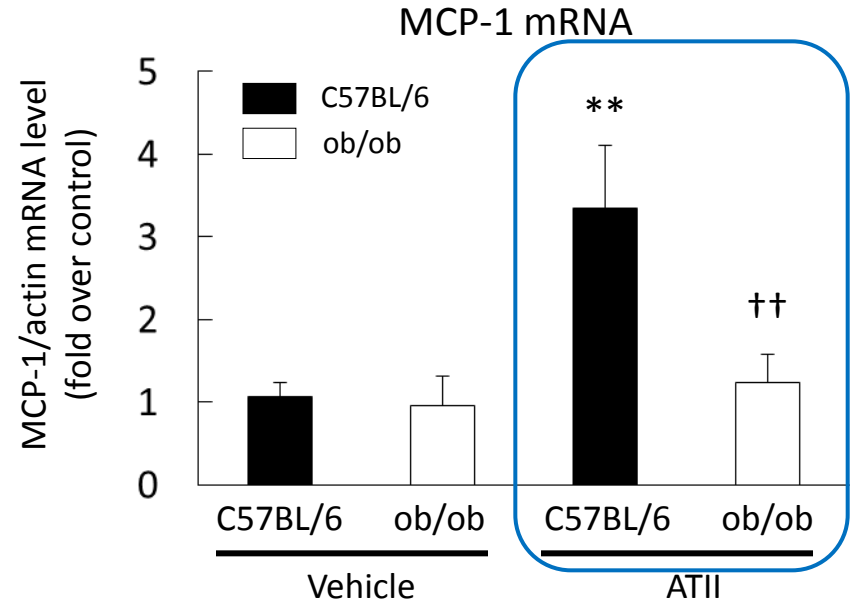
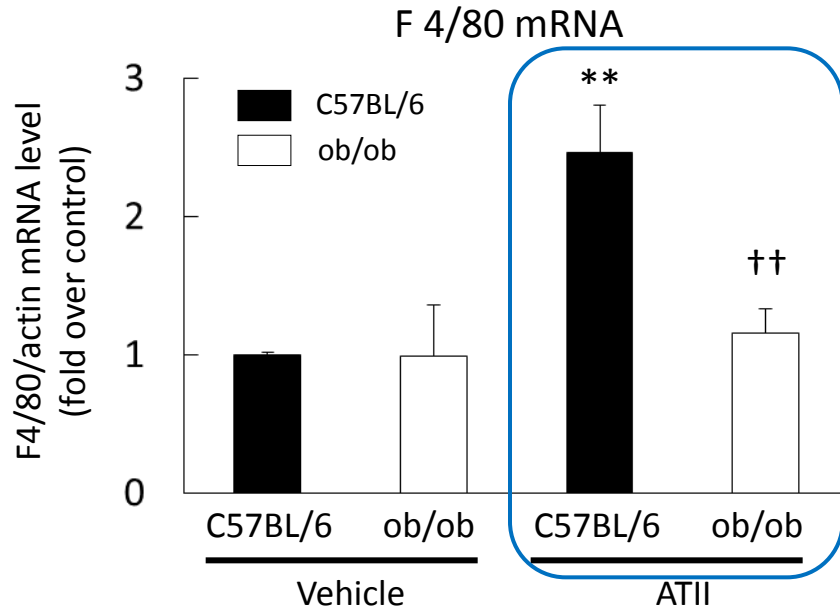
TGF-β1 mRNA



α-SMA mRNA



mRNA expression in left atrium



n=6 for each group, Data are mean ± SEM.

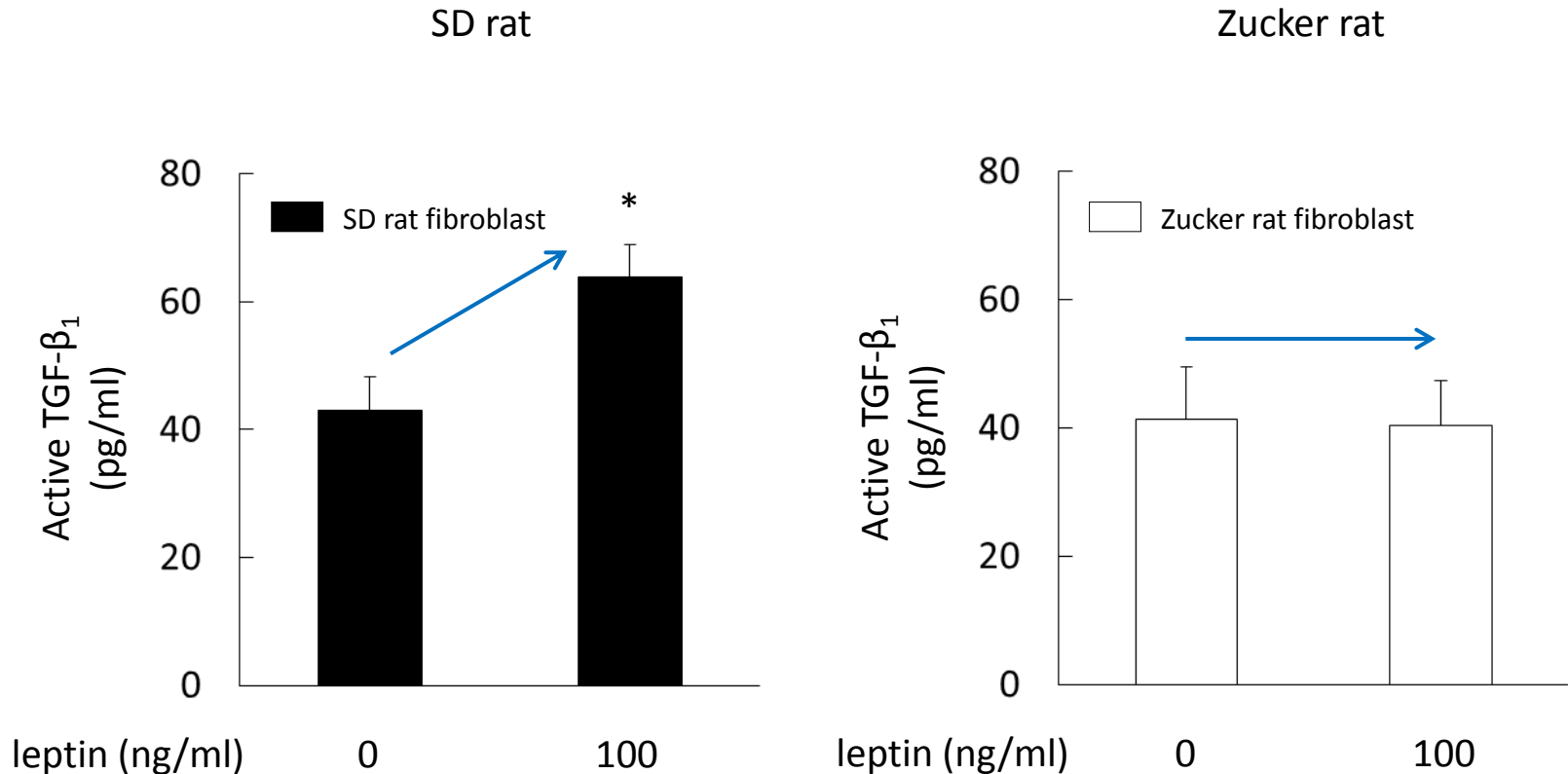
ATII: Angiotensin II, TGF-β1 : transforming growth factor-β1, α-SMA: α-Smooth Muscle Actin, MCP-1: Monocyte Chemoattractant Protein-1, RANTES: Regulated upon Activation, Normal T-cell Expressed, and Secreted (CCL5).

* p<0.05 vs CNT+VEH, ** p<0.01 vs CNT+VEH,

† p<0.05 vs CNT+ATII, †† p<0.01 vs CNT+ATII.

TGF- β_1 in atrial fibroblast culture medium

B. Expression of TGF- β_1 in leptin stimulated atrial fibroblast medium

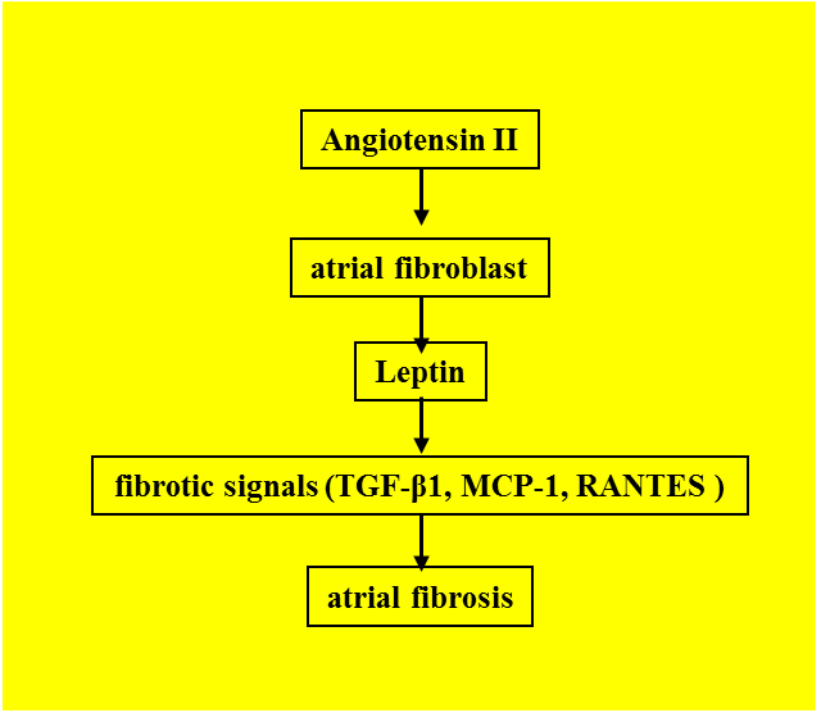


n=6 for each group, Data are mean \pm SEM, TGF- β_1 : transforming growth factor- β_1 .

* $p < 0.05$ vs control.

Summary (in vivo & vitro)

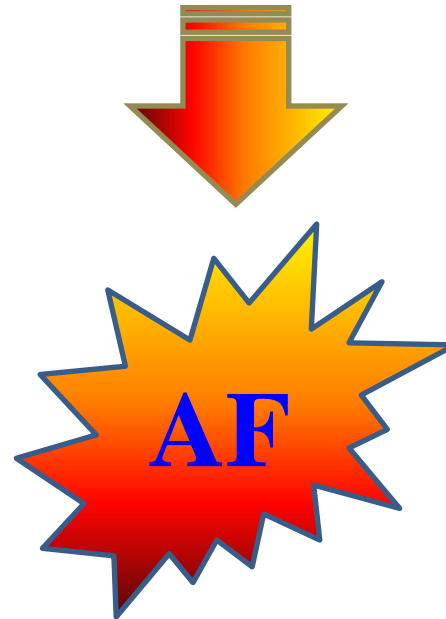
- ✓ Although serum leptin levels decreased, immunohistochemistry and RT-PCR revealed abundant expression of leptin in response to ATII infusion in co
- ✓ Continuous ATII in and AF inducibility infusion was not c
- ✓ Expressions of mR regulated by ATII i responses to ATII i mice.
- ✓ The experiments w The latter rats hav Addition of leptin increased TGF- β 1, α -SMA, MCP-1 and RANTES expressions in SD rat atrial fibroblasts but not in Zucker rat atrial fibroblasts.



What are the final common pathways in these syndrome?

1. Hypertension
2. Obesity
3. Diabetes Mellitus
4. Dyslipidemia, Hyperlipidemia
5. Atherosclerosis

Inflammation!
Fibrosis



Natural Hx of Af

**AF; Progressively worsen like malignant tumor!
A Vicious Cycle**

The final common pathway seems to be

“Inflammation” and “Fibrosis”

Summary

- Atrial fibrillation is prevalent in patients with metabolic syndrome in patients, possible underlying mechanism may be atrial fibrosis.
- Renin-Angiotensin System, TGF- β and Reactive Oxidative Stress pathways are critically involved in the development of atrial fibrosis.
- Further, these 3 pathways often work together, interacting each other, depending on the models such as pressure overload and leptin.
- These situations make the investigation of the development of atrial fibrosis tough and complex.
- When these investigations achieve full blossom,

We may be able to see an “Elephant”

in the real world.

Co-workers & Collaborators

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