

28th Annual Scientific Congress

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Paper ID:25

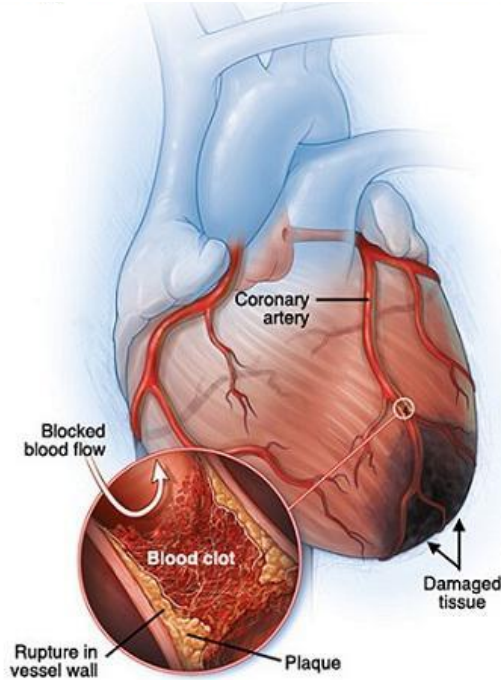
Inhibition of IRE1 branch of ER Stress Ameliorates Myocardial Ischemia/Reperfusion Injury via Inactivation of sEH and JNK/ c-Jun pathway

Hong-Mei Xue, Wen-Tao Sun, Hai-Tao Hou, Huan-Xin Chen, Jun Wang,
Guo-Wei He, Qin Yang



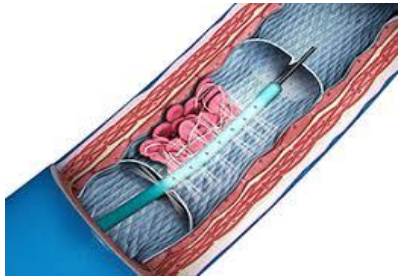
Center for Basic Medical Research & Department of Cardiovascular Surgery, TEDA International Cardiovascular Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

Myocardial Ischemia-Reperfusion Injury (MIRI)



- Ischemia: Occlusion of the coronary artery
- Reperfusion: Re-opening of the coronary artery

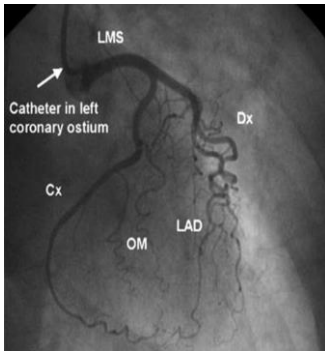
MIRI



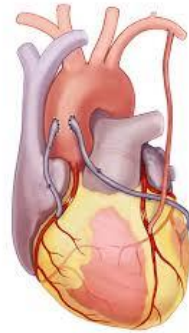
Thrombolytic Therapy



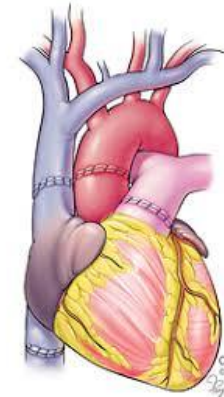
Cardiopulmonary Resuscitation



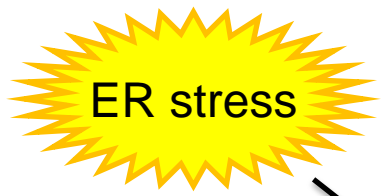
PTCA



CABG



Heart Transplantation



ER stress

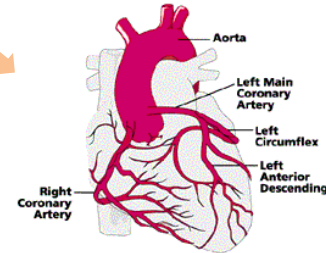
Soluble epoxide
hydrolase
(sEH)

Cardiomyocyte
injury



MIRI

Coronary artery
injury



- Inflammation
- Apoptosis
- Autophagy

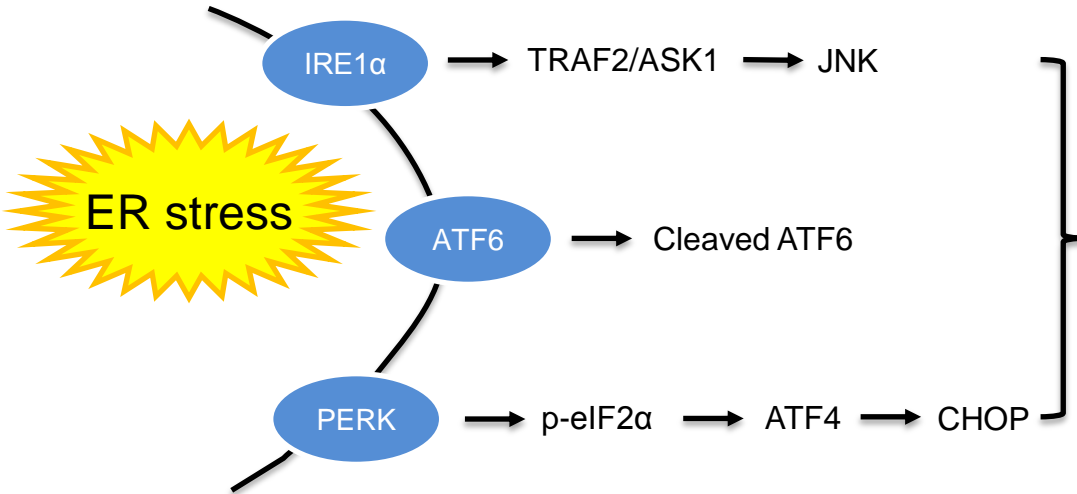
Oxidative stress

- Vasodilator↓: Nitric oxide, Prostacyclin
- Vasoconstrictor↑: Endothelin↑

Endoplasmic Reticulum Stress (ER stress)



- Endoplasmic reticulum (ER) is a multifunctional intracellular organelle.

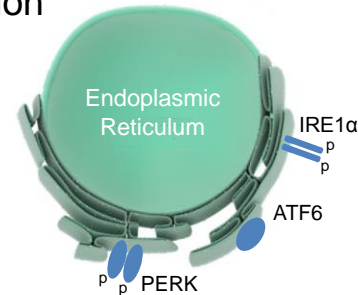


Heart

- Ischemic heart disease
- Cardiomyopathy
- Cardiac hypertrophy & heart failure

Vasculature

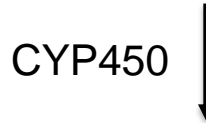
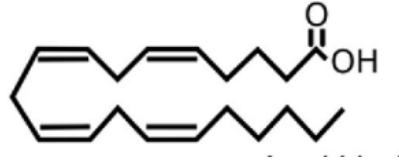
- Endothelial dysfunction
- Atherosclerosis
- Hypertension



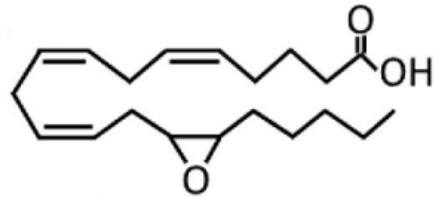


Soluble epoxide hydrolase (sEH)

Arachidonic Acid

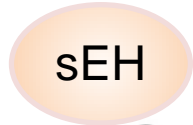


Epoxyeicosatrienoic acids
(EETs)

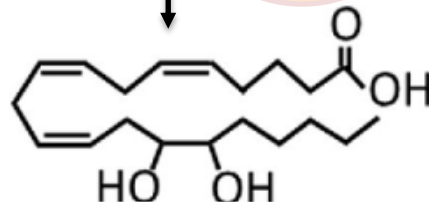


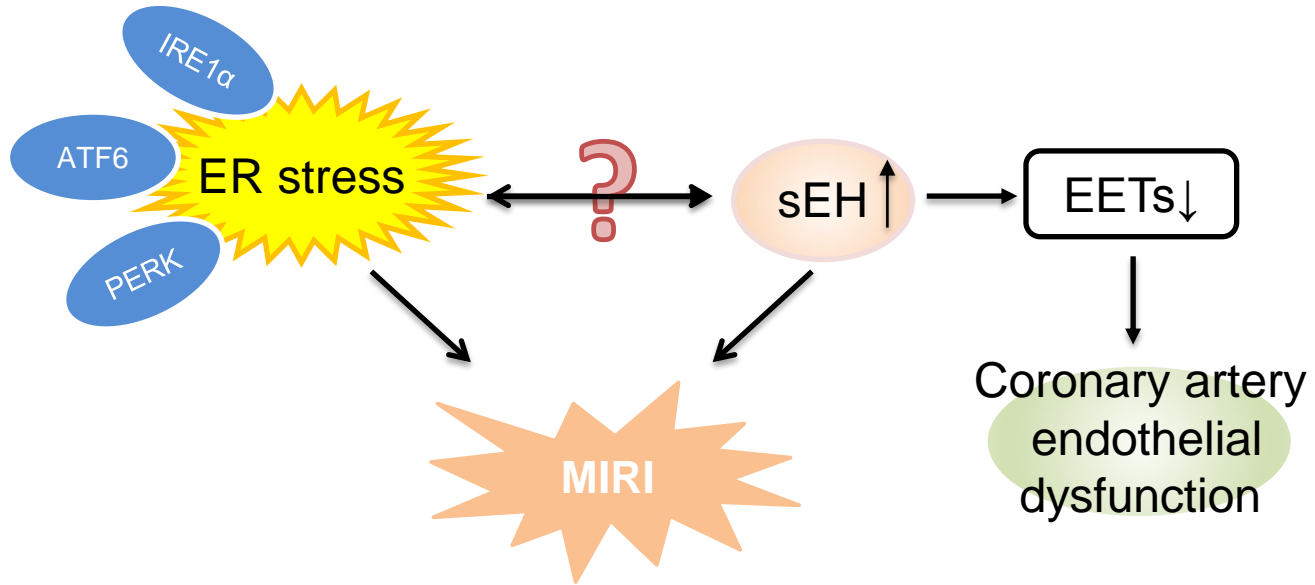
Vasodilator

Cardioprotection



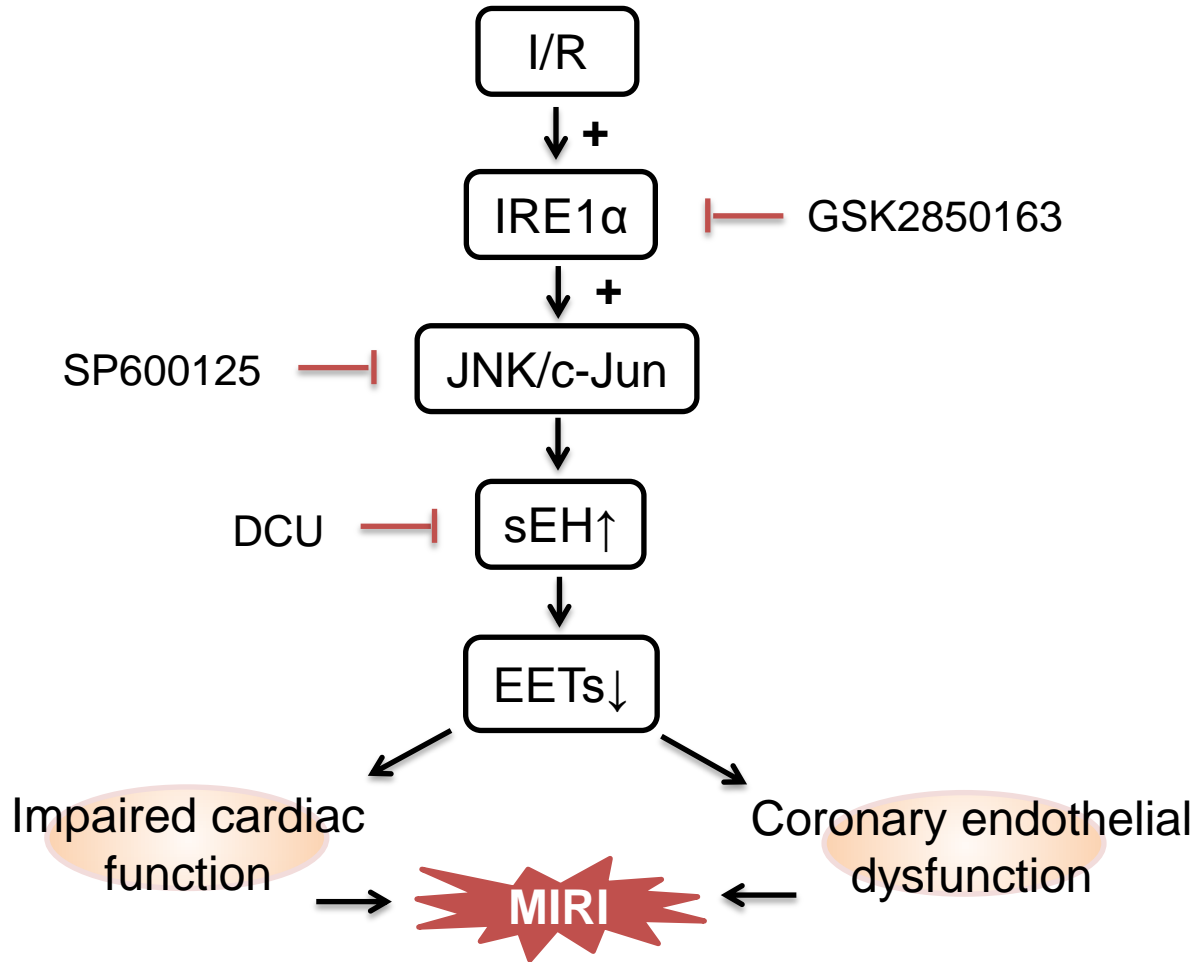
Dihydroxyeicosatrienoic acids
(DHETs)

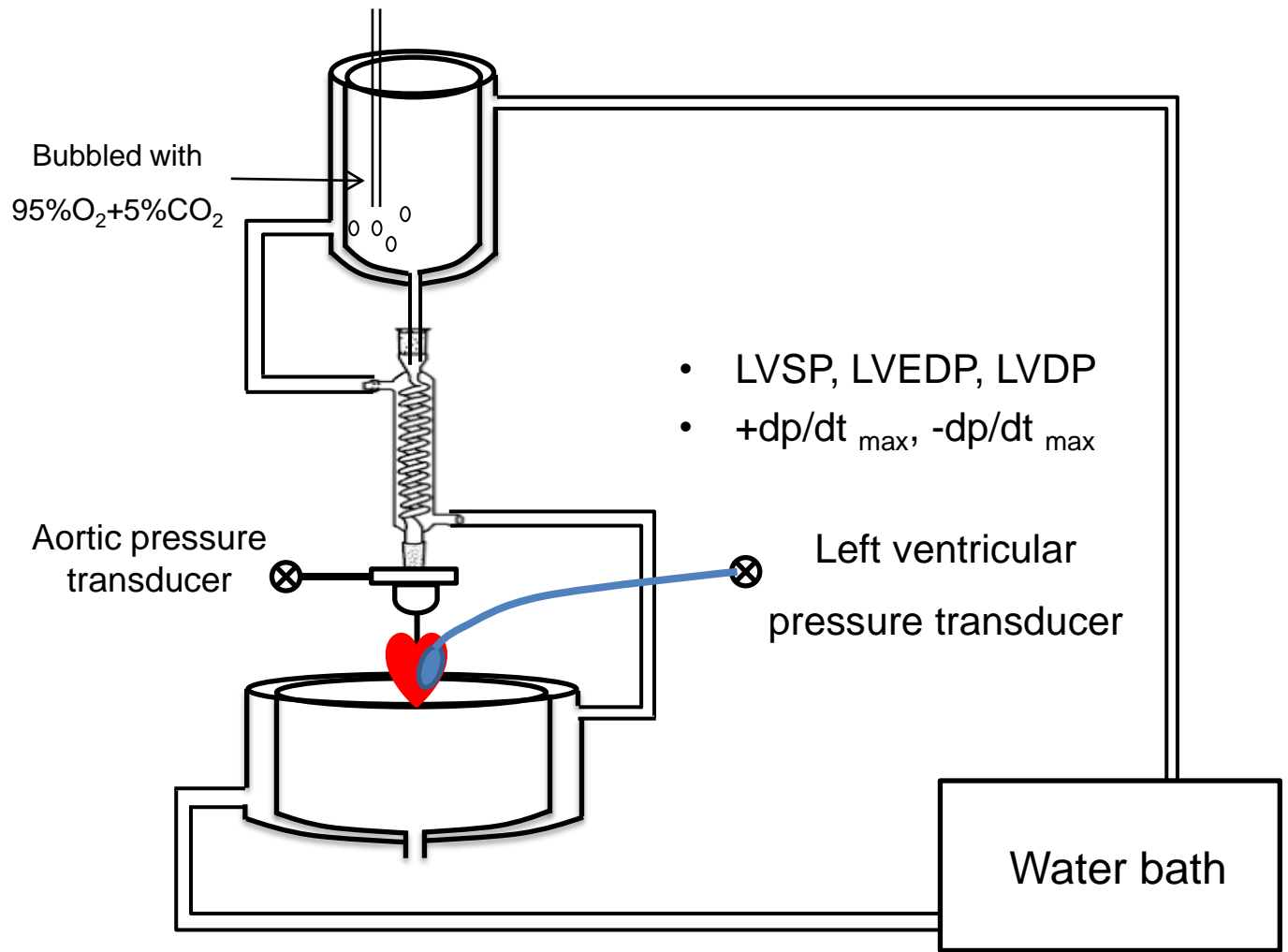




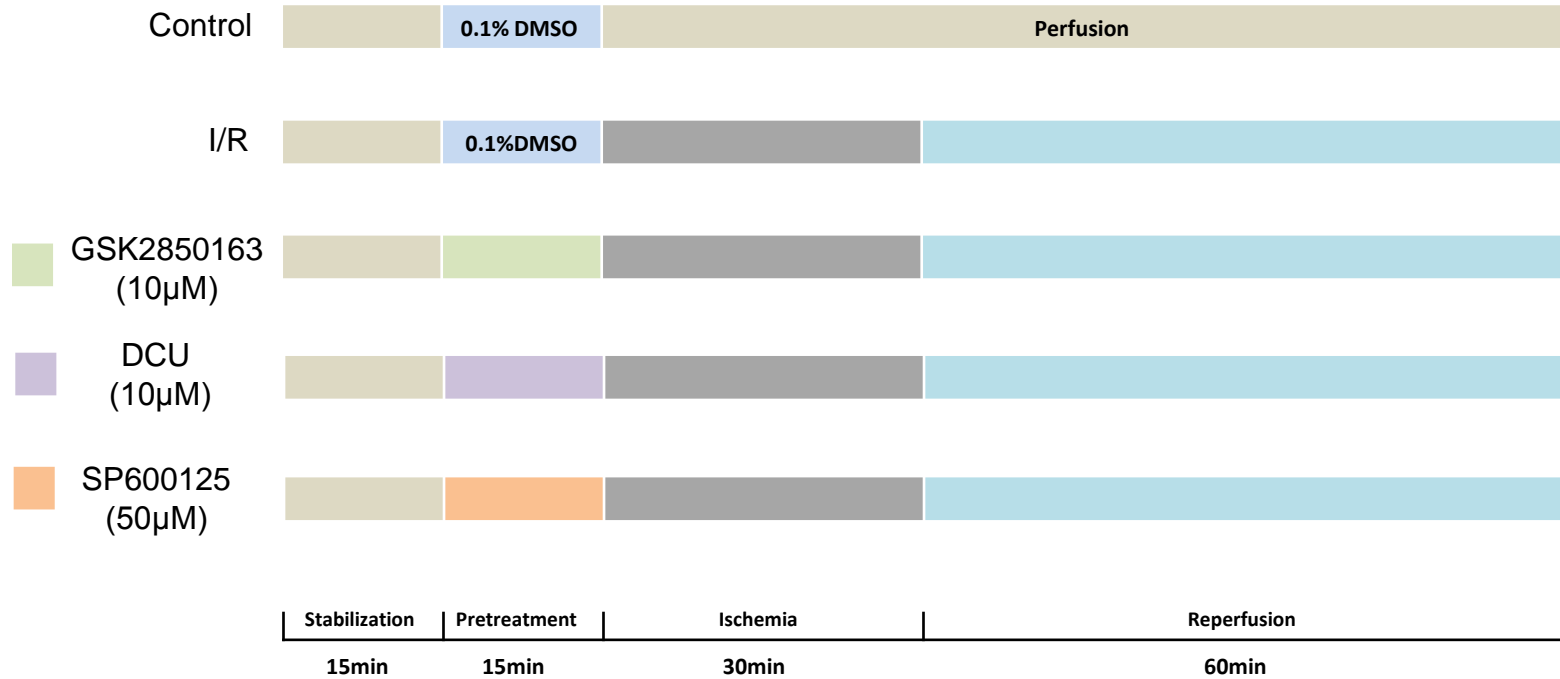
Study from our group: Shiu-Kwong Mak et al., *Toxicology and Applied Pharmacology*, 2017.

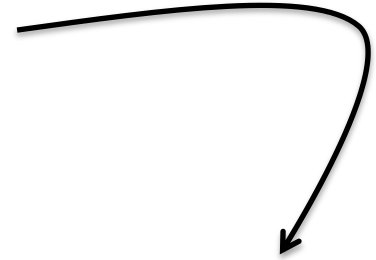
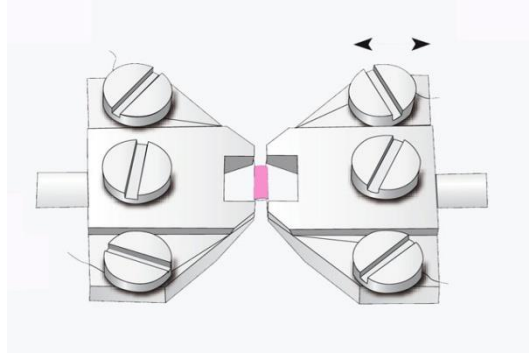
“Tetramethylpyrazine suppresses angiotensin II-induced soluble epoxide hydrolase expression in coronary endothelium via anti-ER stress mechanism”.





Langendorff Protocols





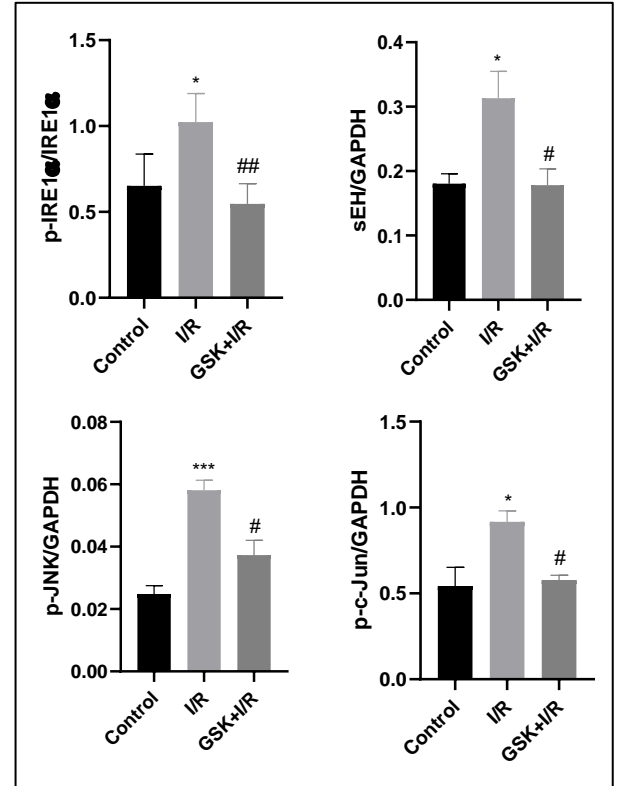
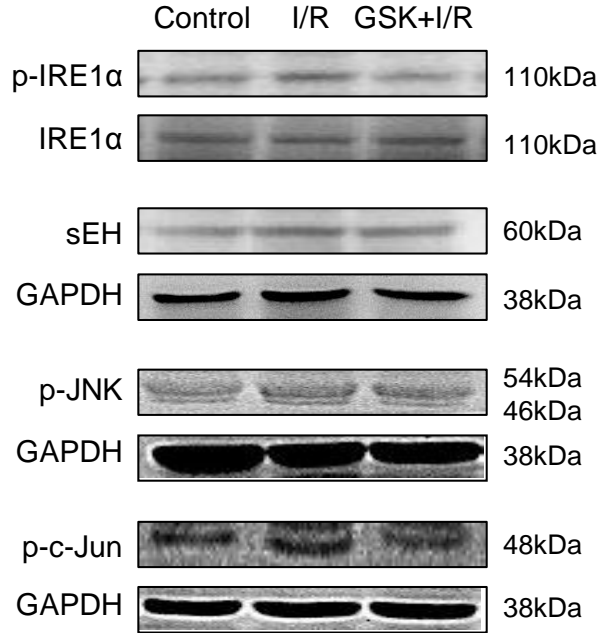
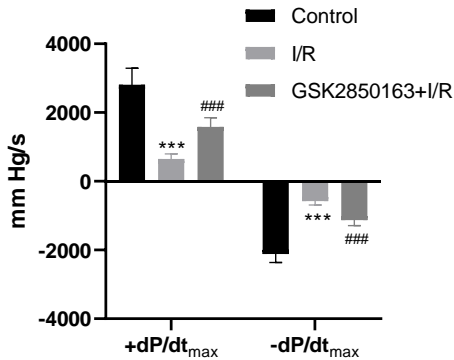
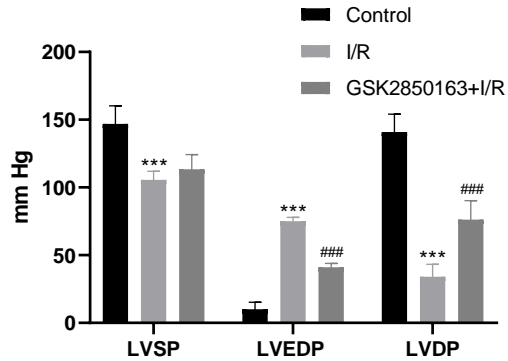
ACh-induced
endothelium-dependent
relaxation

- Western blotting

Inhibition of IRE1 α activation improved cardiac function by downregulating sEH and p-JNK/c-Jun



Myocardium

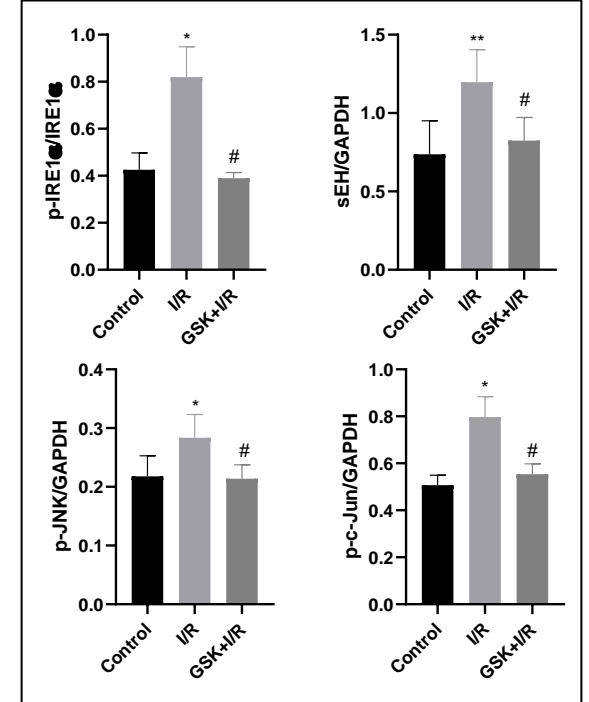
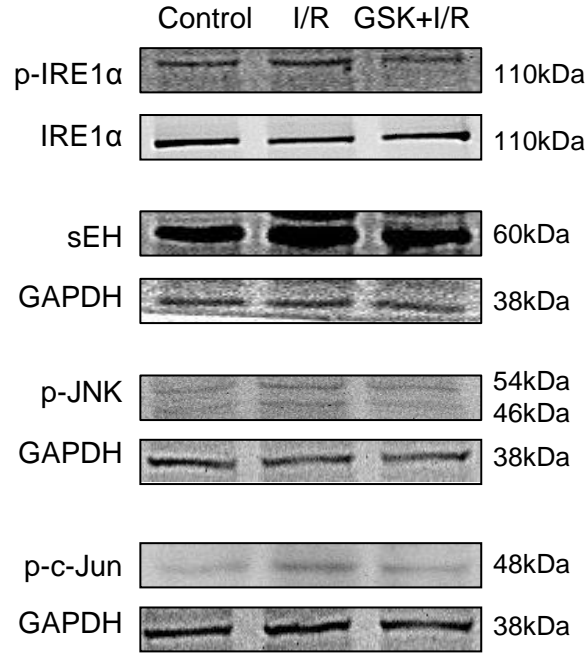
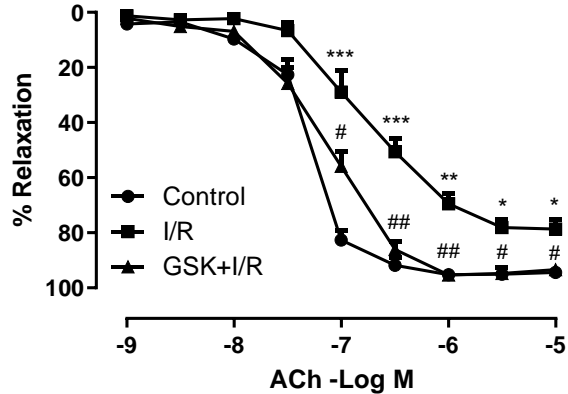


GSK2850163 (GSK) : IRE1 α inhibitor



Inhibition of IRE1 α activation improved coronary endothelial function by downregulating sEH and p-JNK/c-Jun

Coronary artery

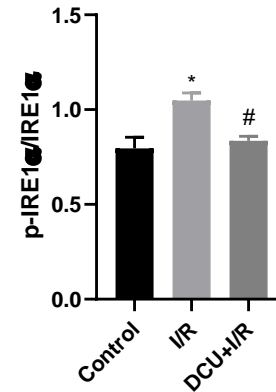
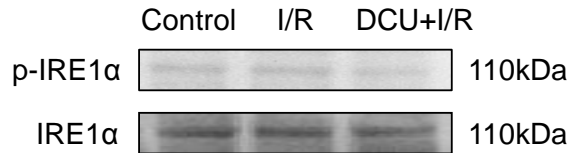
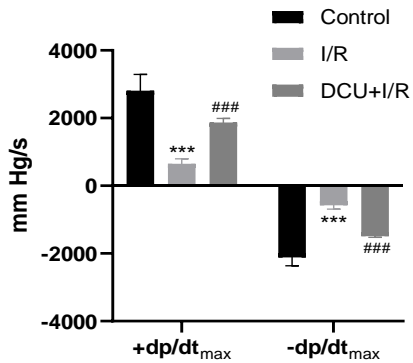
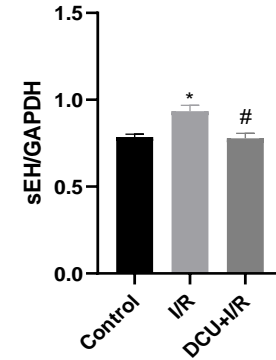
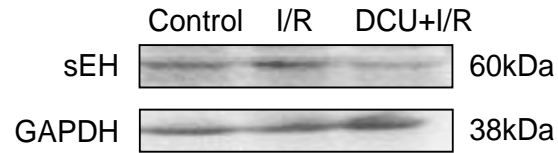
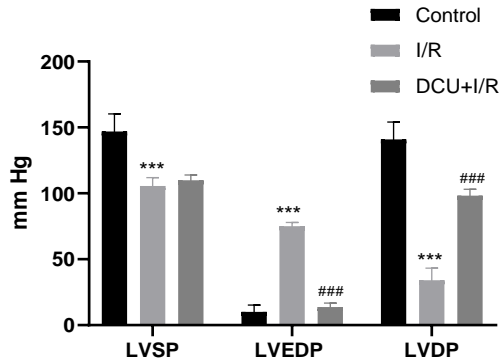


GSK2850163 (GSK) : IRE1 α inhibitor



Inhibition of sEH improved cardiac function and suppressed IRE1 α activation

Myocardium

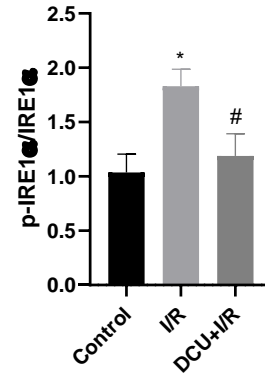
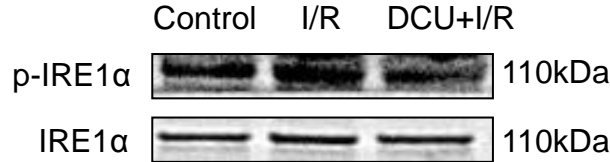
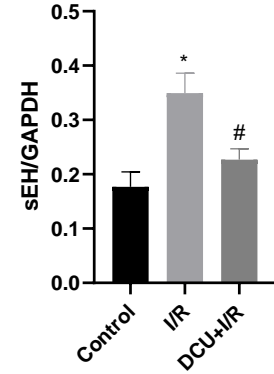
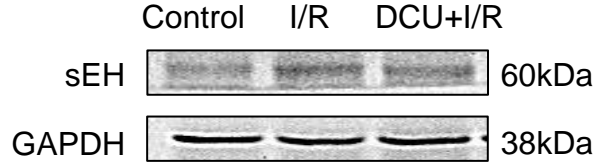
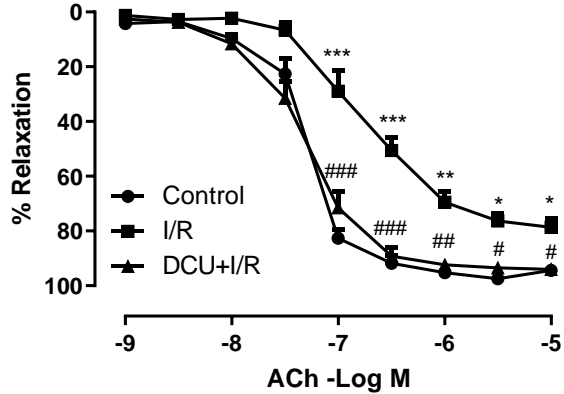


DCU: sEH inhibitor



Inhibition of sEH improved coronary endothelial function and suppressed IRE1 α activation

Coronary artery

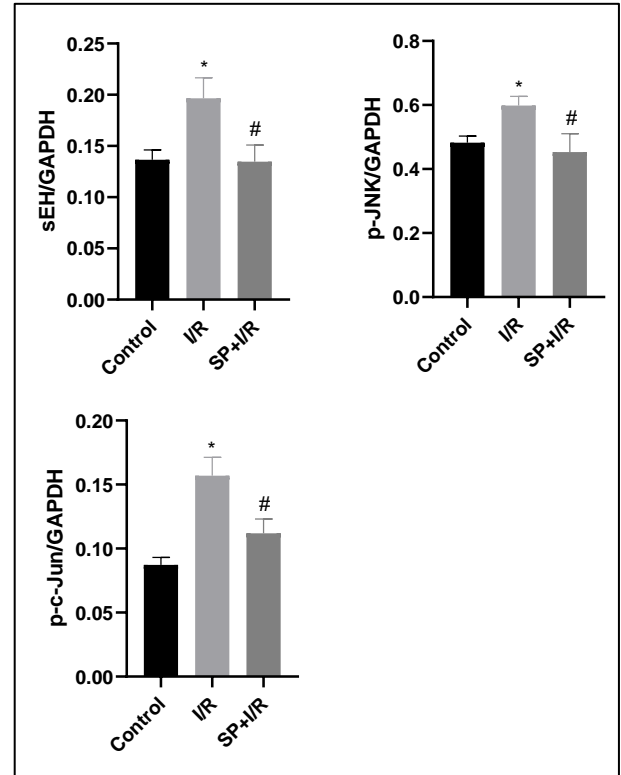
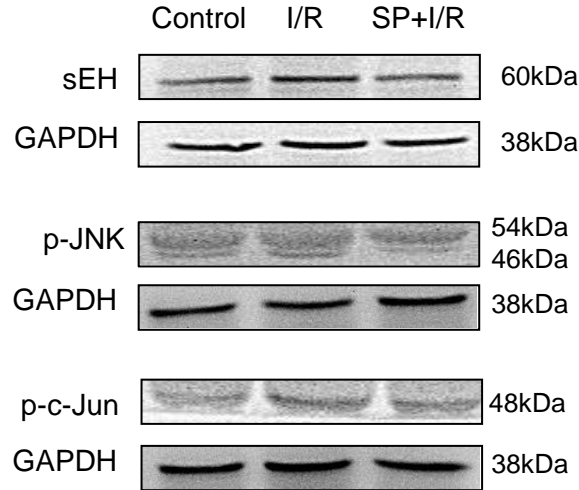
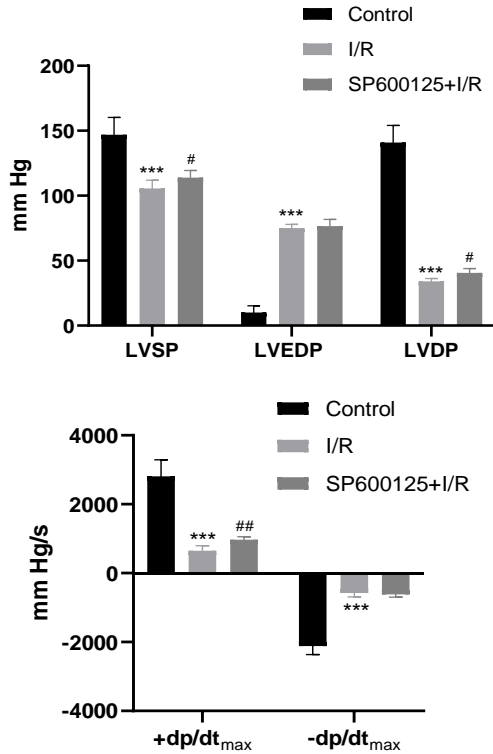


DCU: sEH inhibitor



Inhibition of JNK/c-Jun improved cardiac function by downregulating sEH

Myocardium

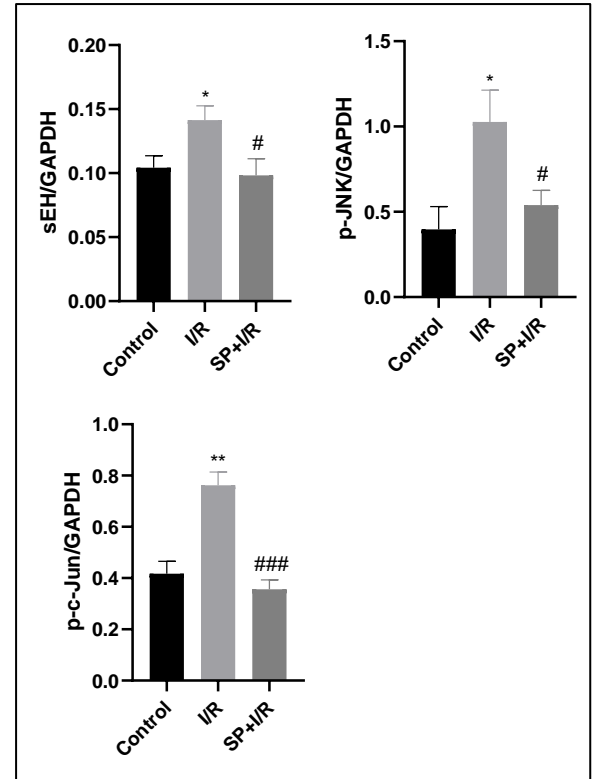
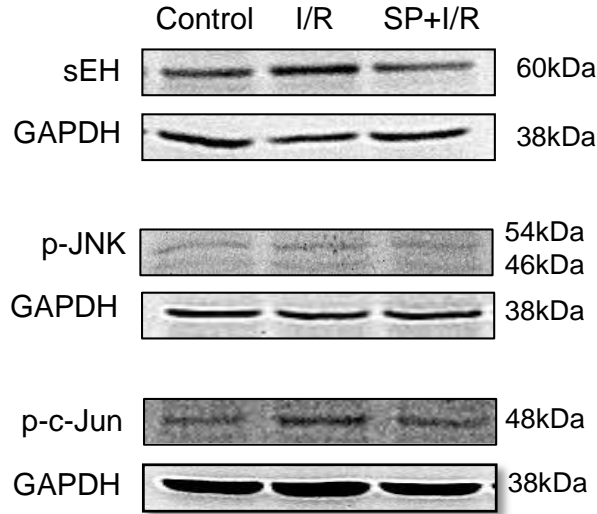
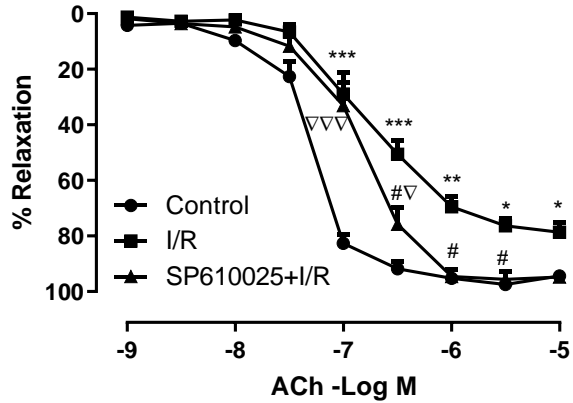


SP600125 (SP): JNK/c-Jun inhibitor



Inhibition of JNK/c-Jun improved coronary endothelial function by downregulating sEH

Coronary artery



SP600125 (SP): JNK/c-Jun inhibitor

Conclusions



- The IRE1 branch of ER stress mediates cardiac and coronary dysfunction in myocardial I/R through activation of sEH and the JNK/c-Jun pathway.
- ER stress and sEH activation interplay to mediate I/R-induced myocardial and coronary endothelial injury.

Acknowledgements



- Prof. Qin Yang
- Prof. Guo-Wei He
- MS. Jun Wang
- Dr. Wen-Tao Sun
- Dr. Hai-Tao Hou
- Dr. Huan-Xin Chen
- Dr. Xiang-Chong Wang



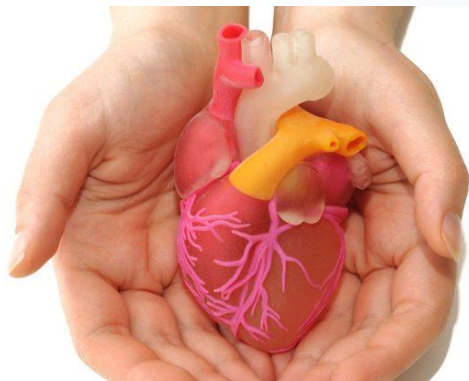
Supported by NSFC 81870227 & 81870288, Tianjin Science and Technology Commission (18PTZWHZ00060), and Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences 2018TX31002 & 2019XK310001.

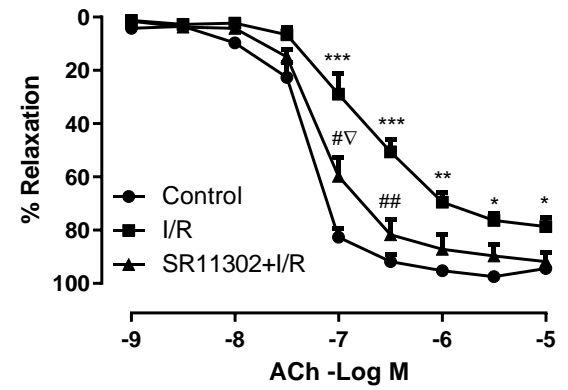
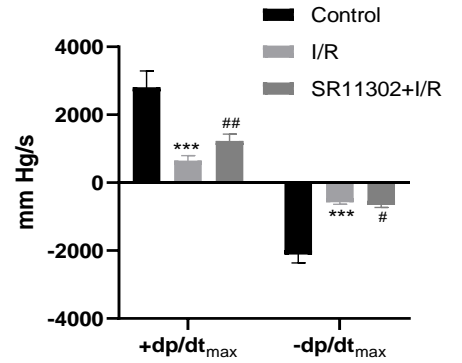
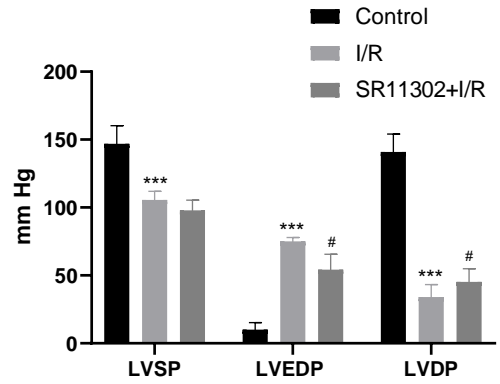
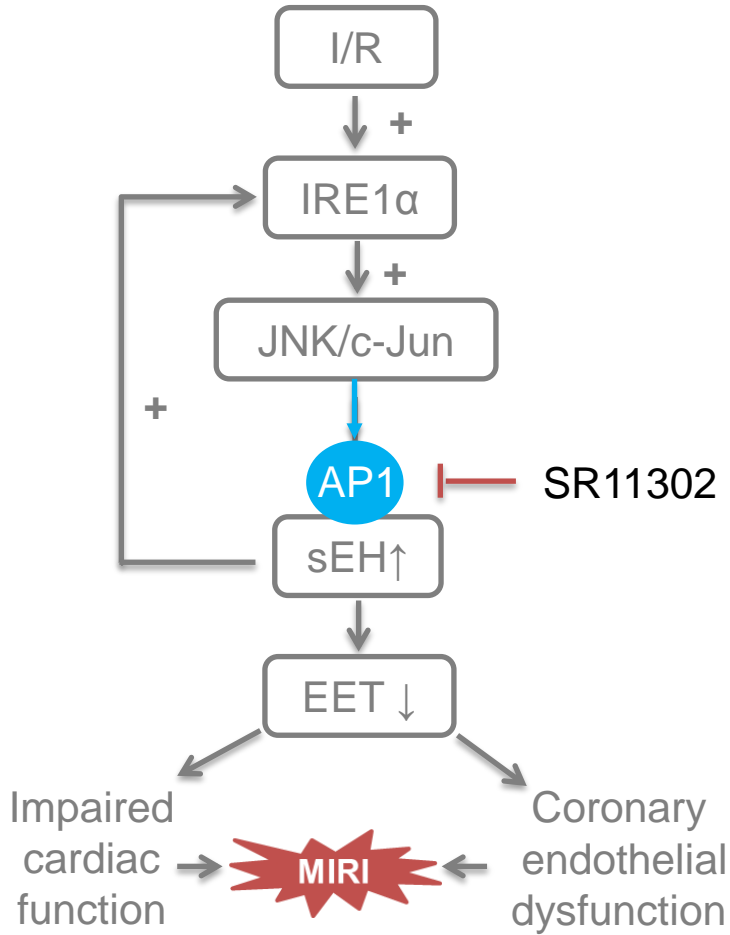


泰达国际心血管病医院
TEDA INTERNATIONAL CARDIOVASCULAR HOSPITAL

LOVE & HELP

Thanks for your attention!





SR11302 (SR): AP-1 inhibitor