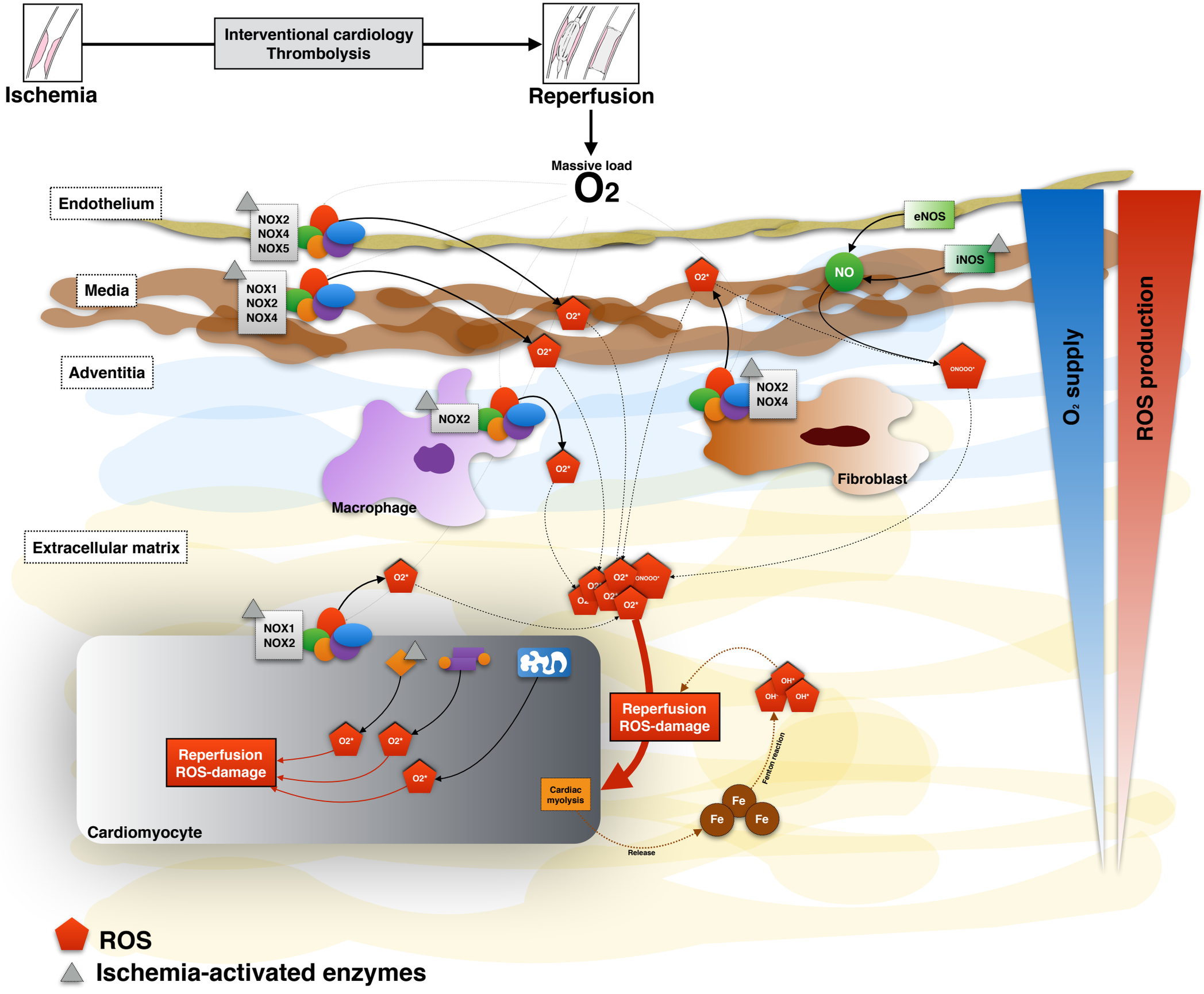
Ischemia
Interventional cardiology
Thrombolysis
Reperfusion
Massive load
O2
Endothelium
Media
Adventitia
Extracellular matrix
NOX2
NOX4
NOX5
NOX1
NOX2
NOX4
eNOS
iNOS
NO
O2*
ONOOO*
NOX2
Macrophage
NOX2
NOX4
Fibroblast
NOX1
NOX2
Reperfusion
ROS-damage
Reperfusion
ROS-damage
Cardiac
myolysis
Cardiomyocyte
OH*
Fenton reaction
Fe
Release
O2 supply
ROS production
ROS
Ischemia-activated enzymes

Figure 1

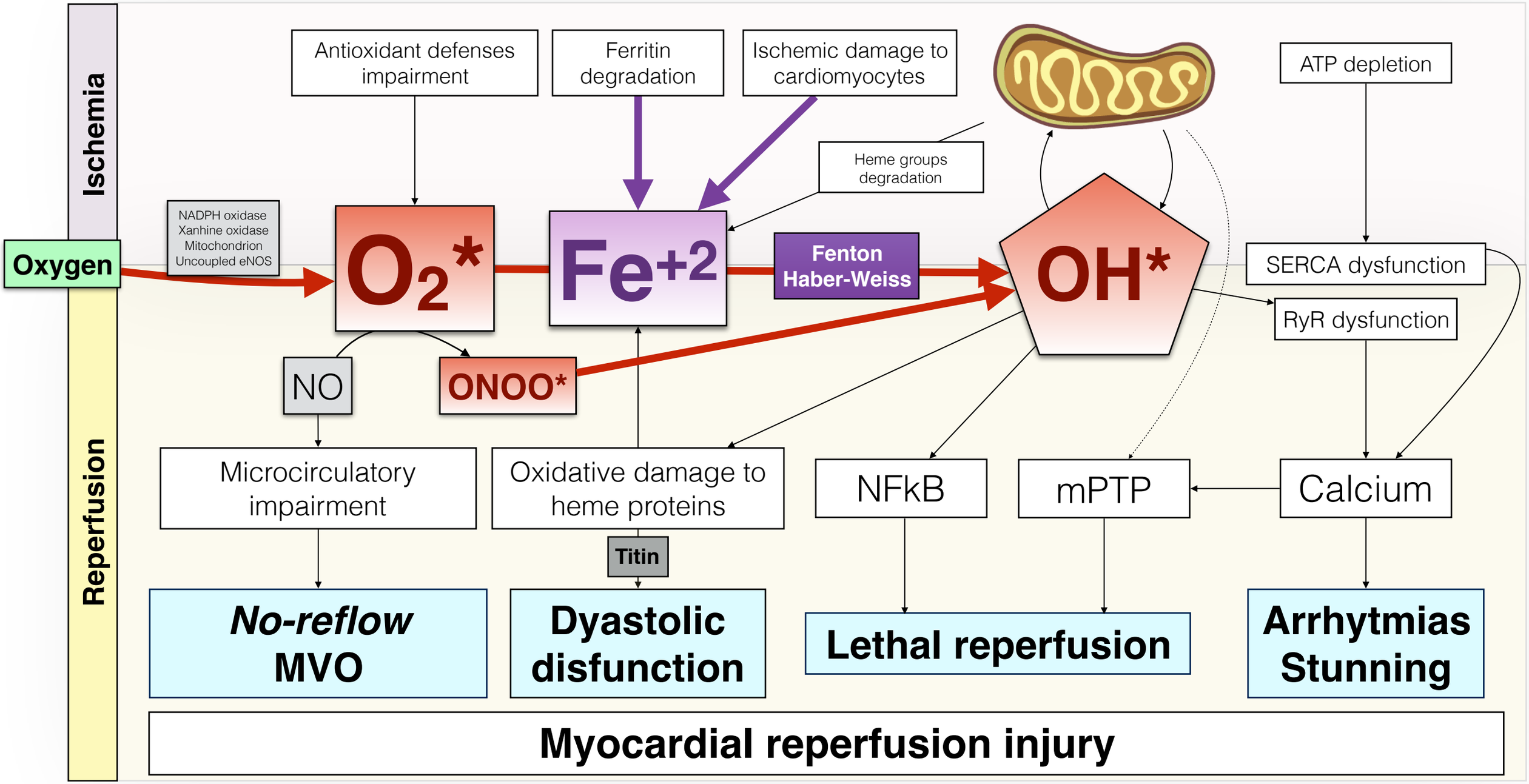
Ischemia
Reperfusion
Oxygen
NADPH oxidase
Xanhine oxidase
Mitochondrion
Uncoupled eNOS
O2*
Antioxidant defenses impairment
Ferritin degradation
Ischemic damage to cardiomyocytes
Heme groups degradation
Fe+2
Fenton Haber-Weiss
OH*
ATP depletion
SERCA dysfunction
RyR dysfunction
NO
ONOO*
Microcirculatory impairment
Oxidative damage to heme proteins
Titin
NFkB
mPTP
Calcium
No-reflow MVO
Dyastolic disfunction
Lethal reperfusion
Arrhytmias Stunning
Myocardial reperfusion injury

Figure 2

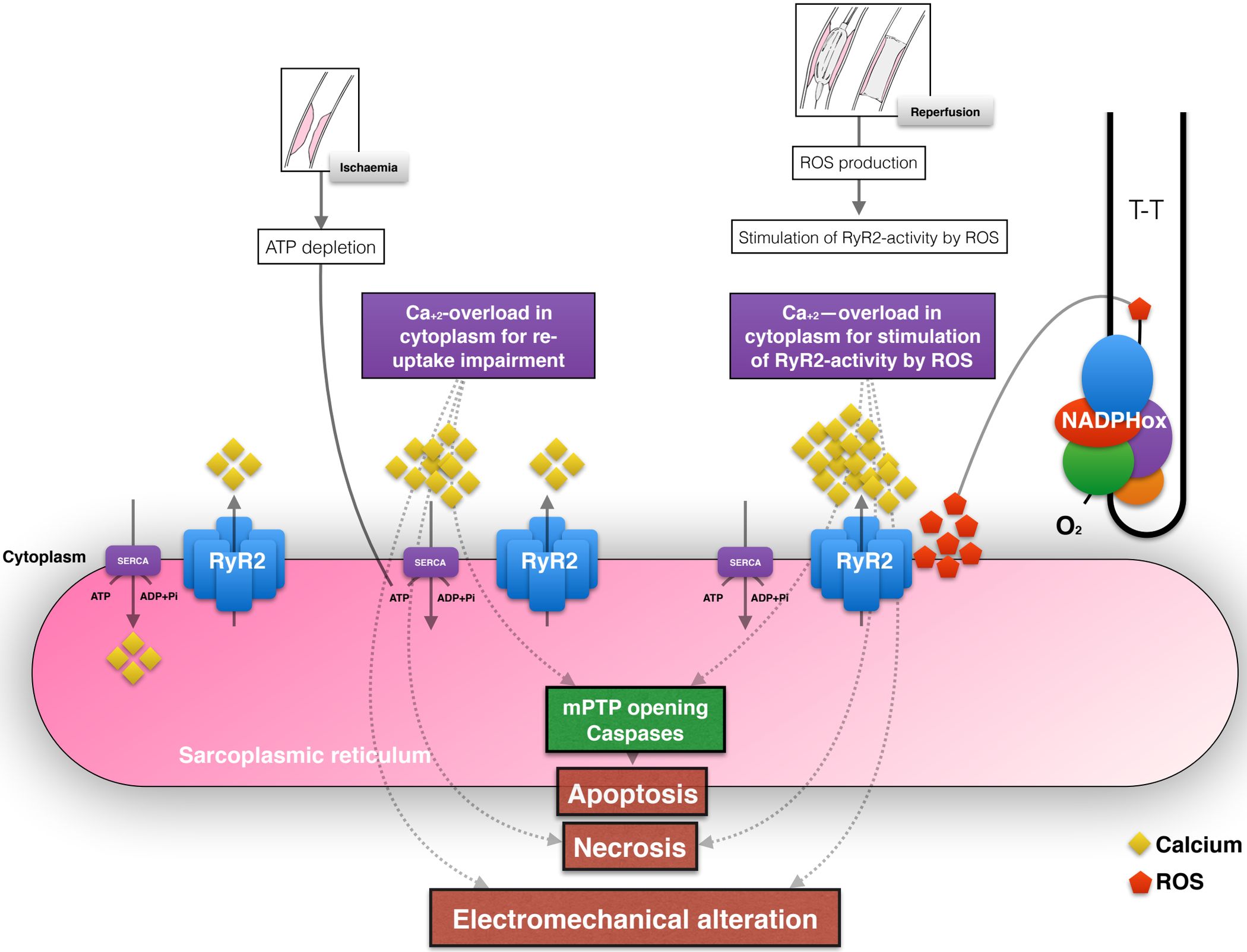
Ischaemia
ATP depletion
Ca+2-overload in cytoplasm for re-uptake impairment
Reperfusion
ROS production
Stimulation of RyR2-activity by ROS
Ca+2—overload in cytoplasm for stimulation of RyR2-activity by ROS
T-T
NADPHox
O2
Cytoplasm
SERCA
ATP
ADP+Pi
RyR2
Sarcoplasmic reticulum
mPTP opening
Caspases
Apoptosis
Necrosis
Electromechanical alteration
Calcium
ROS

Figure 3

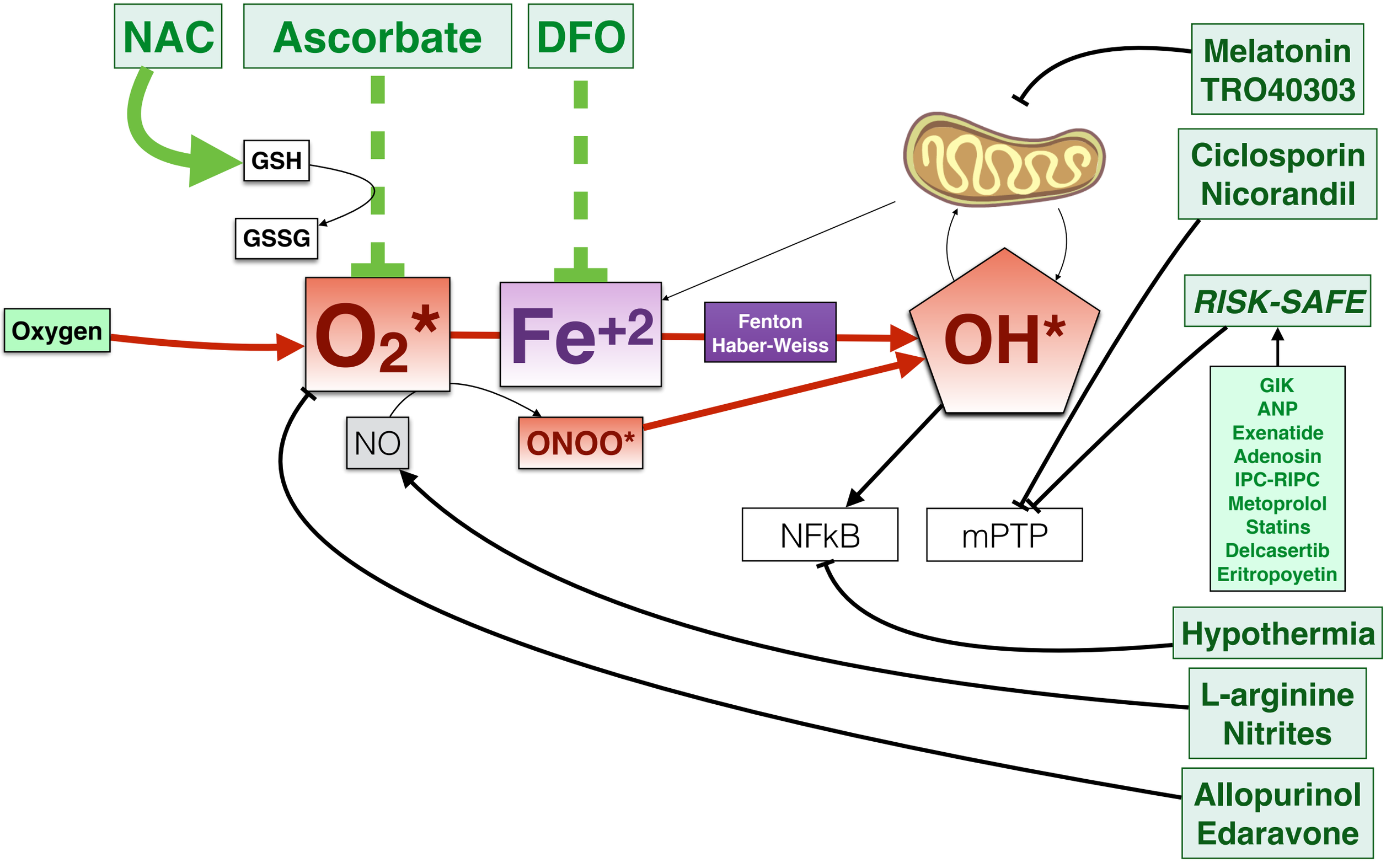
NAC
Ascorbate
DFO
GSH
GSSG
Oxygen
O2*
Fe+2
Fenton
Haber-Weiss
OH*
NO
ONOO*
NFkB
mPTP
Melatonin
TRO40303
Ciclosporin
Nicorandil
RISK-SAFE
GIK
ANP
Exenatide
Adenosin
IPC-RIPC
Metoprolol
Statins
Delcasertib
Eritropoyetin
Hypothermia
L-arginine
Nitrites
Allopurinol
Edaravone

Figure 4

	Study details	Country	n		Main findings	Reference
			Placebo	Intervention		
AA	Ascorbate previous to elective coronary angioplasty	Italy	28	28	Decrease in oxidative stress and improves reperfusion parameters	**Basili** et al. JACC Cardiovasc Interv 2010, 3:221-9.
	Ascorbate previous to primary coronary angioplasty in patients with AMI	Chile	53	46	Improve ventricular function and reperfusion No differences in infarct size	**Ramos** et al. Arch Med Sci 2017, 3:558–67
NAC	N-acetylcysteine previous and after primary coronary angioplasty in patients with AMI	Germany	126	126	Decrease in oxidative stress No differences in infarct size	**Thiele** et al. J Am Coll Cardiol. 2010, 55:2201-9
	N-acetylcysteine and nitroglycerine previous to primary coronary angioplasty in patients with AMI	Australia	67	65	Decrease in infarct size and cardiac damage biomarkers	**Pasupathy** et al. Circulation. 2017, 136:894-903
DFO	Deferoxamine previous and after coronary angioplasty in patients with AMI	Australia	28	32	Decrease in oxidative stress No differences in infarct size	**Chan** et al. 2012 Circ Cardiovasc Interv 2012, 5:270-8.

Table 1

Table 1. Clinical highlights. Main clinical studies that have used ascorbate, N-acetylcysteine or deferoxamine to prevent reperfusion injury in patients affected by acute myocardial infarction and treated with coronary angioplasty . AA: Ascorbate. NAC: N-acetylcysteine. DFO: Deferoxamine. IR: Ischemia reperfusion. AMI: Acute myocardial infarction.

Figure 1. Generation of reactive oxygen species and mobilization of iron after myocardial reperfusion. There is a massive production of reactive oxygen species and iron mobilization by the different cellular types of the myocardial tissue. The iron reacts with superoxide anion to produce hydroxyl radical by the Fenton reaction. Inside cardiomyocyte, there is intracellular production of reactive oxygen species through NADPH oxidase, eNOS uncoupled, xanthine oxidase and mitochondrion. NOX: NADPH oxidase. ROS: reactive oxygen species. Fe: Iron.

Figure 2. Role of reactive oxygen species and iron mobilization in myocardial reperfusion injury and its clinical implications. MVO: Microvascular obstruction. ONOO: Peroxynitrite. NO: Nitric oxide. OH *: Radical hydroxyl. Fe: Iron. Ryr: Ryanodine receptor channel. SERCA: Sarco/endoplasmic reticulum Ca^{2+}-ATPase

Figure 3. Central role of calcium in the electro-mechanical dissociation of cardiomyocyte after myocardial reperfusion. Ryr: Ryanodine receptor channel. SERCA: Sarco/endoplasmic reticulum Ca^{2+}-ATPase. mPTP: Mitochondrial permeability transition pore. Ca: Calcium. ROS: Reactive oxygen species.

Figure 4. Experimental, pharmacological and clinical approaches to prevent myocardial reperfusion injury at cellular level. RISK: Reperfusion injury salvage kinase pathway. SAFE: Survivor activating factor enhancement pathway. GSH: Reduced glutathione. GSSG: Oxidized glutathione.