Probucol attenuates oxidative stress and energy decline in isoproterenol-induced heart failure in rat

HEART FAILURE

"EXHAUSTION OF THE RESERVE FORCE OF THE HEART"

INTRODUCTION

- **Oxidative stress & inflammation:**

  - Vit. E
  - Dimethylthiourea
  - Probucol

PROBUCOL

- Clinically used cholesterol-lowering drug
- Postulated cardioprotective mechanism:
  - -Antioxidant properties
  - - Endogenous antioxidant system

PROBUCOL

- **In heart failure:**
  - Improved survival rate
  - Reduced inflammatory cytokines
  - Reduced cardiac fibrosis

New aspects of probucol cardioprotection against doxorubicin-induced cardiotoxicity.

El-Demerdash et al.,

Cancer Chemotherapy & Pharmacology, 2003; 52: 411-416

Aim of the study

- Examine whether probucol would attenuate the oxidative stress and progression of HF.
- Explore the effect of probucol on myocardial nucleotides and its important role in treatment of HF.

Design of the study

1st week	+ 2nd & 3rd weeks

- Group (1): Saline + Corn oil (Control)
- Group (2): Isoproterenol + Corn oil

  (2.4mg/kg, sc)
- Group (3): Isoproterenol + Probucol

  (2.4mg/kg, sc) (61mg/kg, ip)
- Group (4): Saline + Probucol

  (61mg/kg, ip)

Studied parameters

- HR measurements
- Assessment of oxidative stress
  - Lipid peroxides
  - antioxidant enzymes (GPx & SOD)
- Assessment of myocardial nucleotides
- Assessment of myocardial probucol
- Histopathological examination

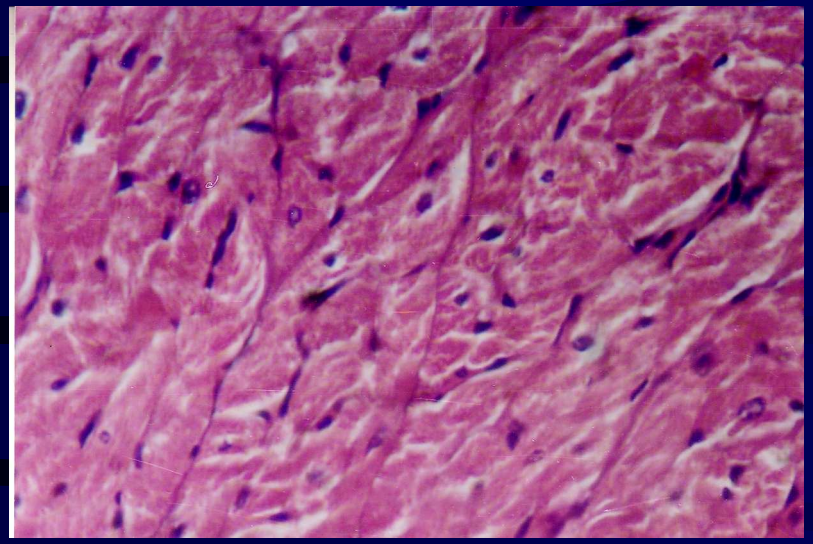
Results

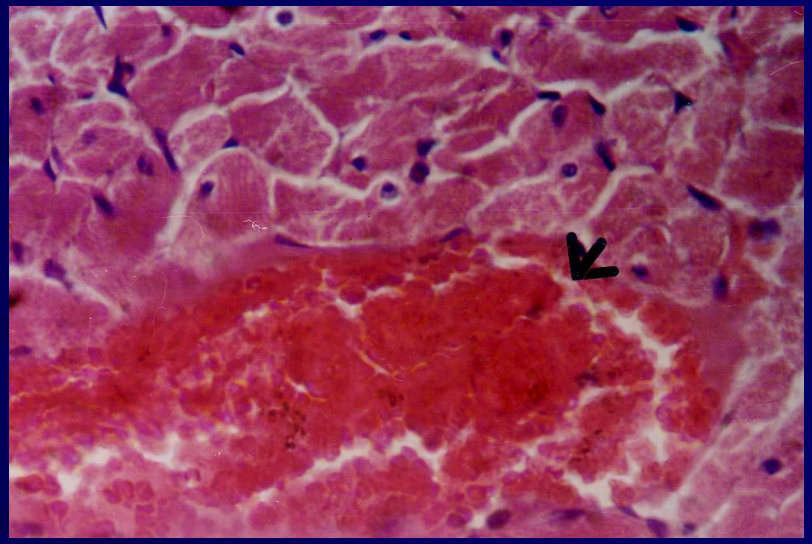
Groups (N = 13-15)	Heart rate (beats/min)		
	Pre value	After one week	After three weeks
Control	383.3 ± 8.03	373.3 ± 9.89	373.3 ± 6.67
Isoproterenol	373.3 ± 8.90	483.3 ± 9.54**	480.0 ± 11.55**
Isoproterenol + Probucol	380.0 ± 8.94	476.7 ± 12.02**	360.0 ± 15.49
Probucol	373.3 ± 7.89	383.3 ± 8.03	376.7 ± 10.85

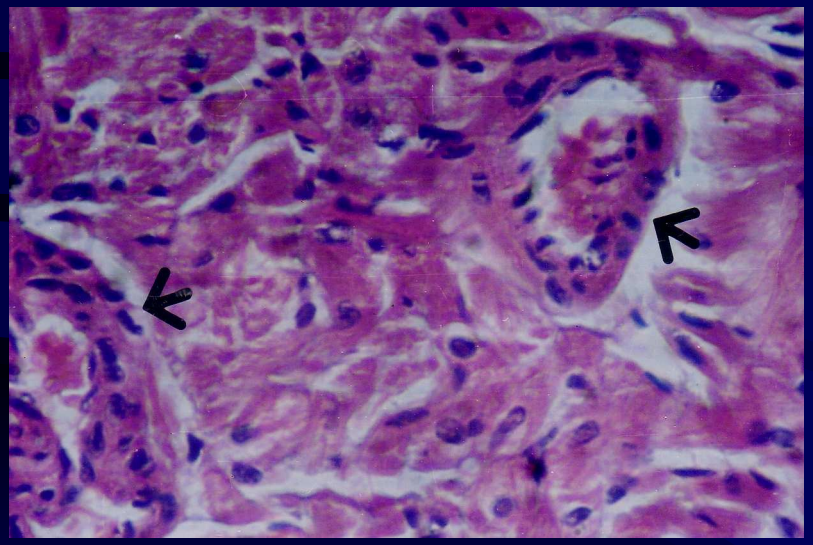
*: Significantly different from pre value

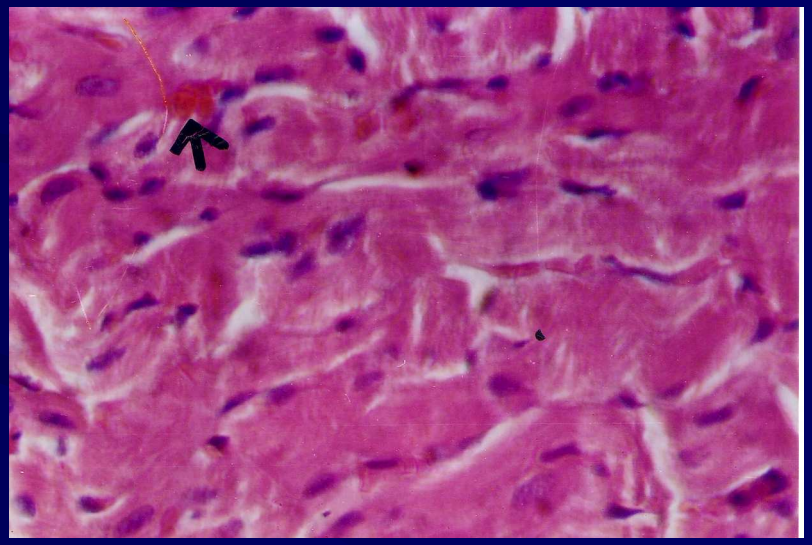
Groups (N = 13-15)	Absolute HW (gm)	Relative HW (%)	Right ventricle (gm)	Left ventricle (gm)
Control	0.64 ± 0.008[b]	0.34 ± 0.007[b]	0.26 ± 0.013[b]	0.35 ± 0.008[b]
Isoproterenol	0.77 ± 0.027[a]	0.41 ± 0.012[a]	0.34 ± 0.031[a]	0.44 ± 0.023[a]
Isoproterenol + Probucol	0.64 ± 0.024[b]	0.35 ± 0.012[b]	0.30 ± 0.02[b]	0.36 ± 0.019[b]
Probucol	0.63 ± 0.022[b]	0.35 ± 0.010[b]	0.27 ± 0.012[b]	0.34 ± 0.013[b]

a: Significantly different from control group
b: Significantly different from isoproterenol group



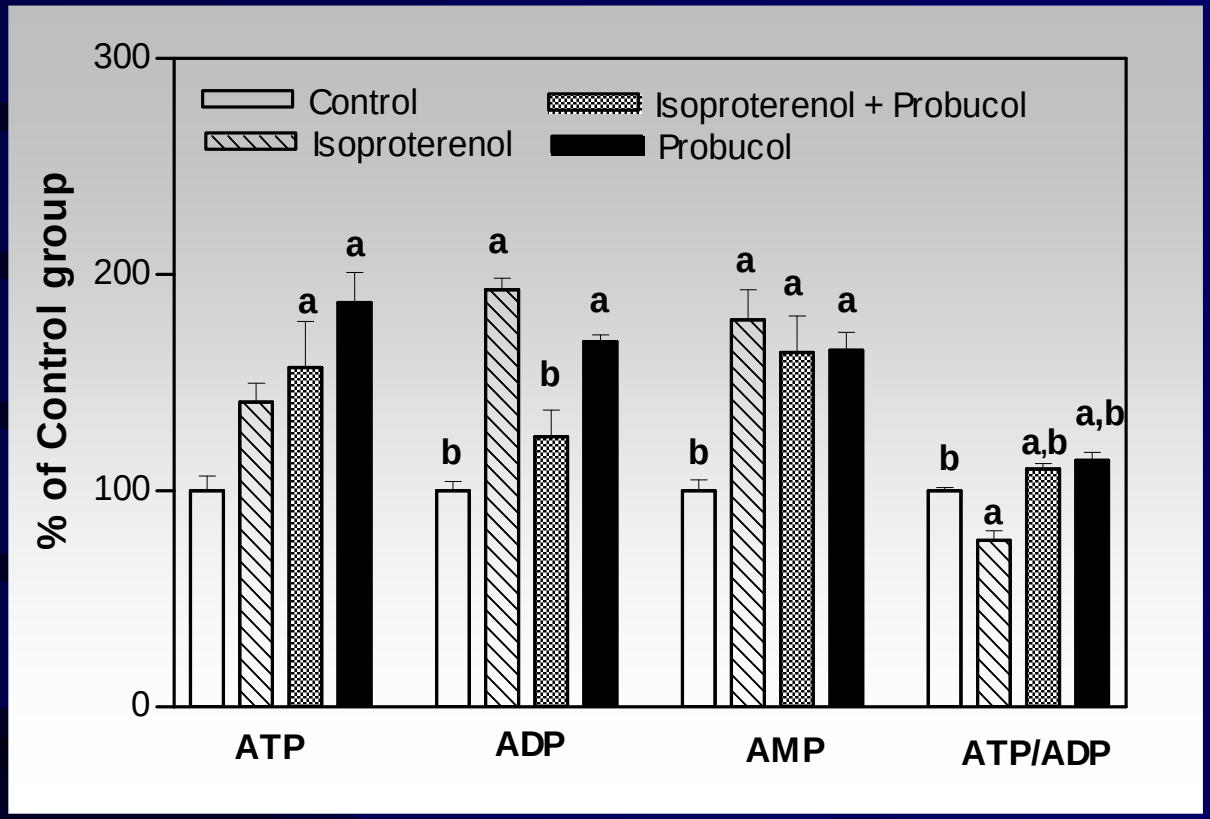






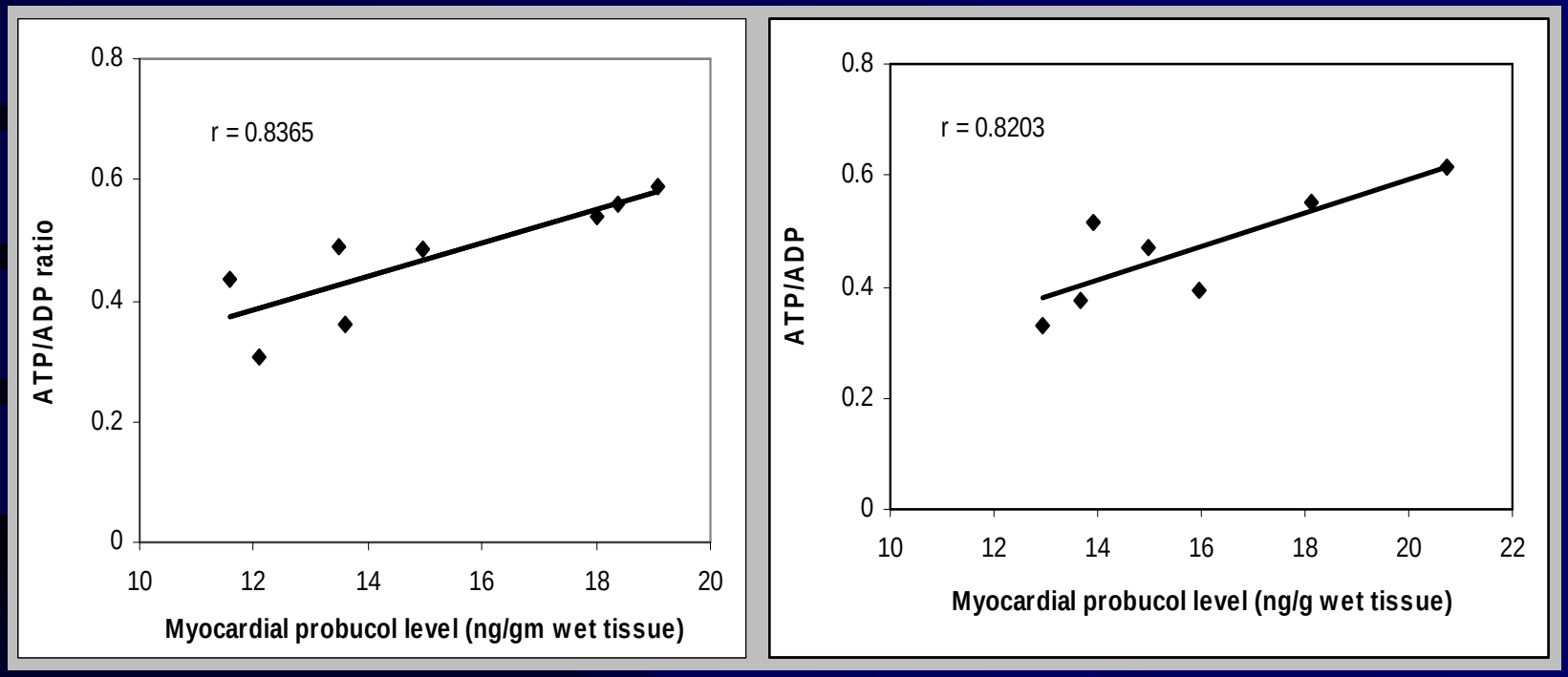
Groups (N = 7)	Lipid peroxides (nmol/gm tissue)	Myocardial antioxidant enzymes	
		GPx (U/mg protein)	SOD (U/mg protein)
Control	43.82[b] ± 3.43	48.55[b] ± 3.93	36.11 ± 2.75
Isoproterenol	71.41[a] ± 6.67	31.45[a] ± 2.52	31.87 ± 2.92
Isoproterenol + Probucol	47.88[b] ± 3.79	73.38[a,b] ± 5.79	43.18 ± 3.71
Probucol	46.13[b] ± 3.84	66.03[a,b] ± 4.13	47.93[b] ± 3.2

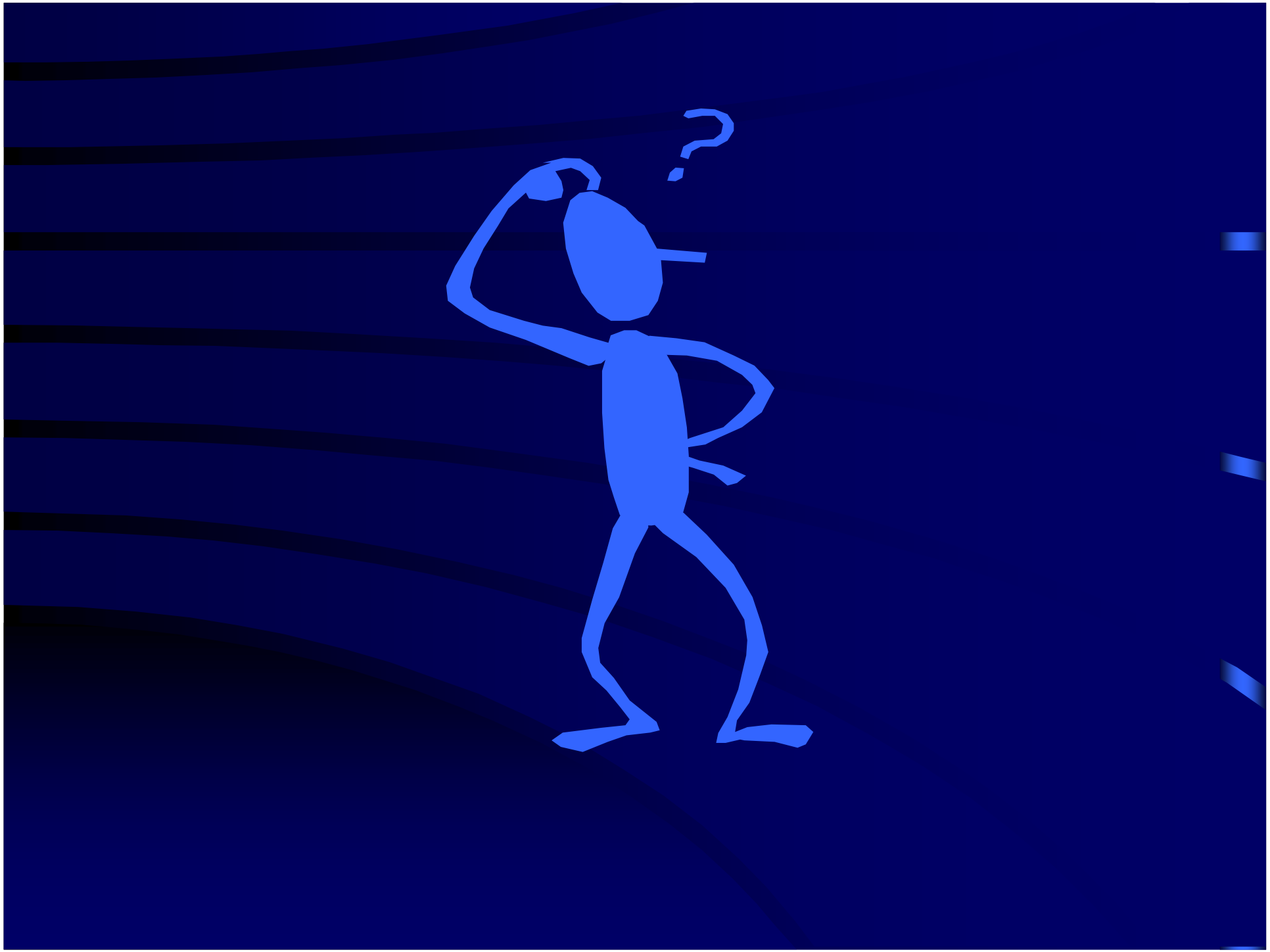
a: Significantly different from control group
b: Significantly different from isoproterenol group



a: Significantly different from control group

b: Significantly different from isoproterenol group


r = 0.8365
ATP/ADP ratio
0.8
0.6
0.4
0.2
0
10
12
14
16
18
20
Myocardial probucol level (ng/gm wet tissue)
r = 0.8203
ATP/ADP
0.8
0.6
0.4
0.2
0
10
12
14
16
18
20
22
Myocardial probucol level (ng/g wet tissue)



Conclusions

- The present study demonstrates that the cardioprotective effect of probucol in treatment of HF is a result of an inhibition of myocardial oxidative stress, an enhancement of endogenous antioxidant reserve (mainly GPx), and an increase of myocardial ATP level.
- The question, which needs to be answered in further studies, is the mechanistic pathway by which probucol stimulates the ATP synthesis.

Thank You