Cardiotropic effects of insulin

P Hantson

Department of Intensive Care, Cliniques St-Luc
Université catholique de Louvain, Brussels, Belgium

Background

- Insulin is currently proposed as adjunctive therapy in case of severe cardiocirculatory failure following some drug overdoses (calcium channel blockers, e.g.)
- What is the rationale for the use of insulin in this setting?
- Can we translate in poisoned patients some evidence obtained from ischemia-reperfusion models?
- When to start? When to stop?
- Can we combine a metabolic and a pharmacologic approach?

Points to be discussed

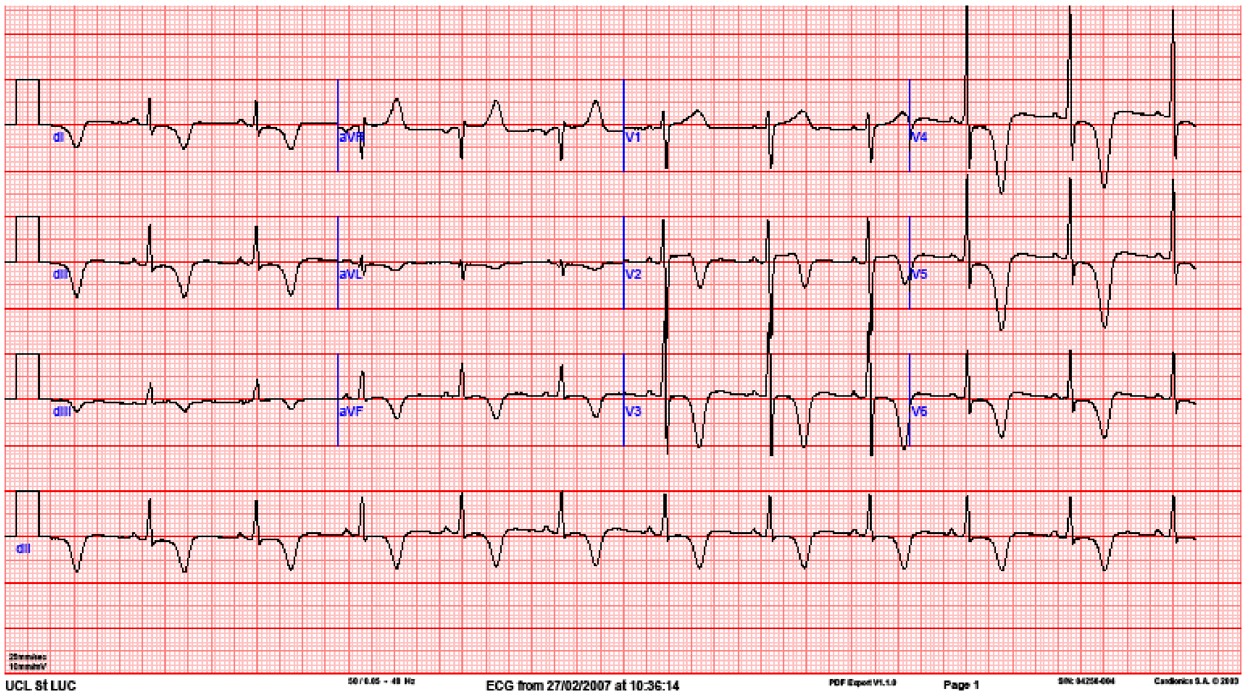
- Insulin signaling
- Regulation of myocardial substrate metabolism by insulin
- Regulation of contractile force development and calcium metabolism by insulin
- Effects of insulin on myocardial blood flow
- Chronotropic effects of insulin?

Clinical case (1)

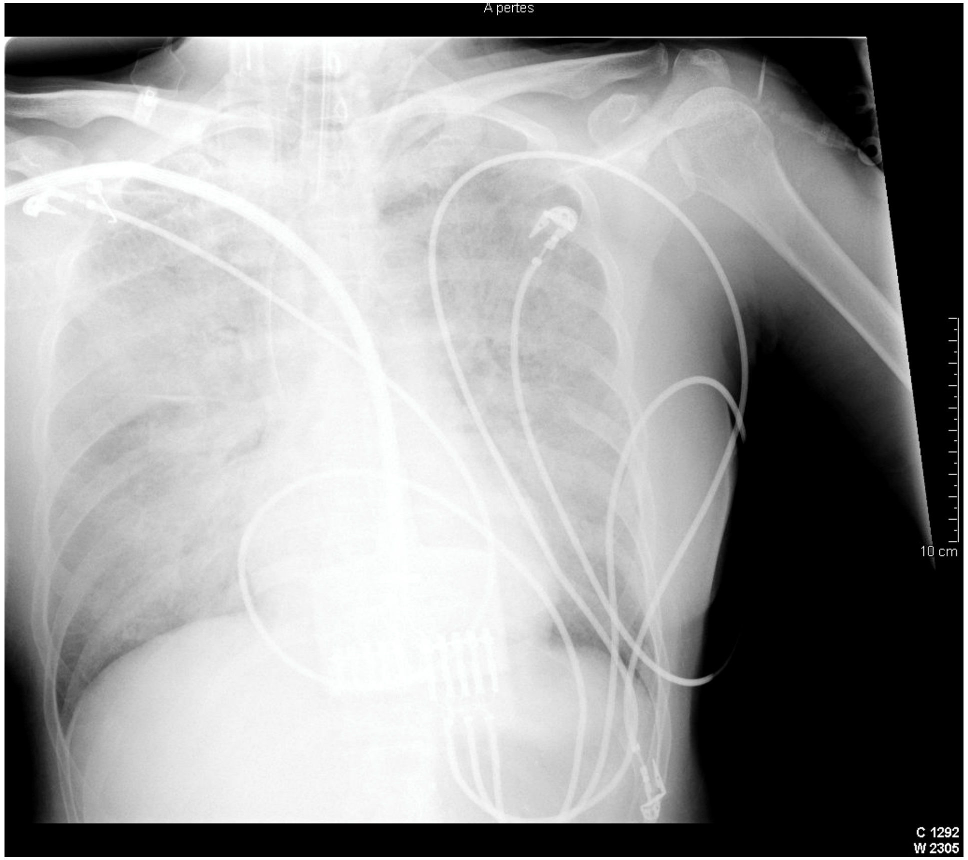
- 50-yr-old woman, no previous medical history
- Admitted to the ED with GCS 4
- Diagnosis: SAH due to a ruptured aneurysm of the left ACA
- Immediate complications:
  - cardiogenic shock
  - ARDS

Clinical case (1)

- Admission EKG
- CK-MB 3.7 µg/ml (<3.5), troponin-I 0.19 ng/ml (<0.06)

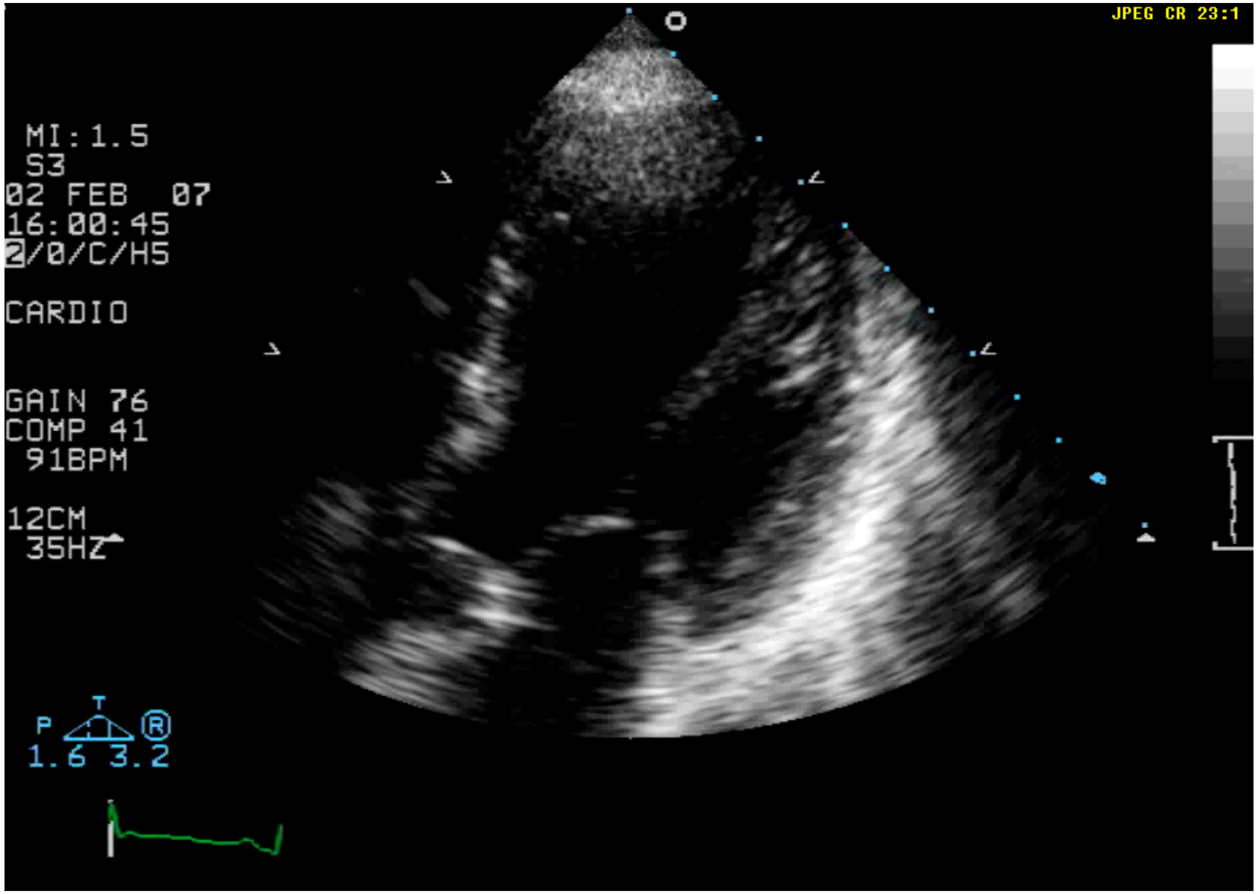


Clinical case (1)

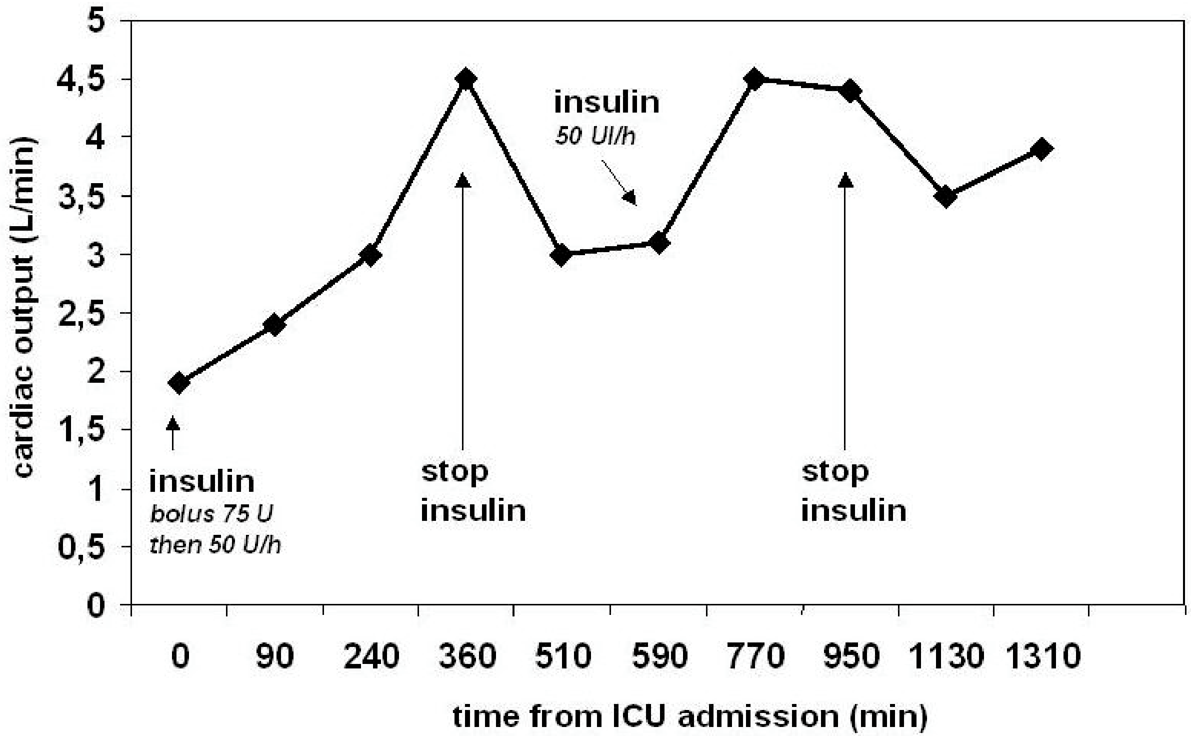


- Admission chest-X-ray
- FiO2: 0.6

Clinical case (1)



Clinical case (1)



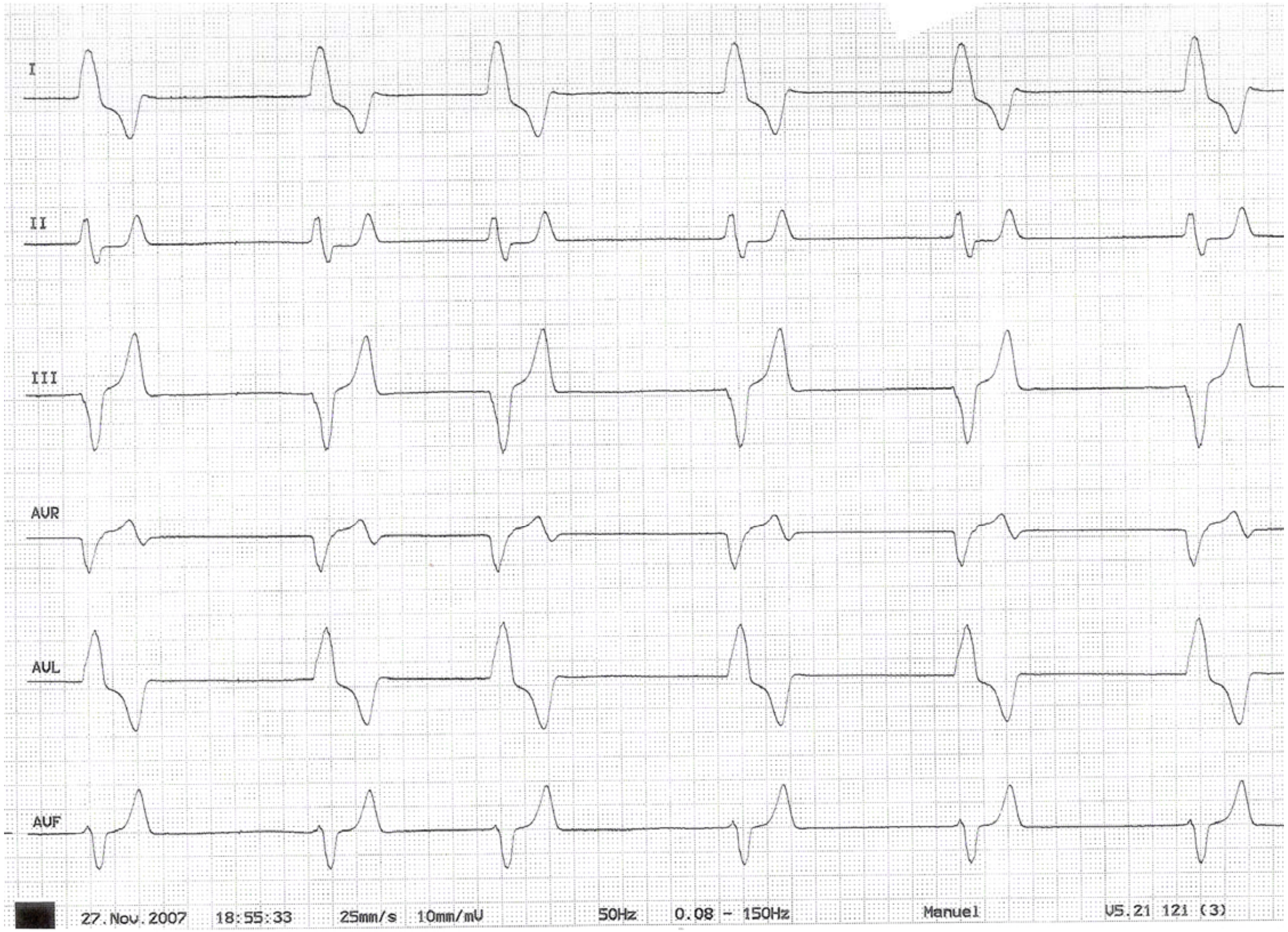
- How to treat?
  - Are catecholamines your first option?
  - SAH => « catecholamines storm »

(Hantson et al., J Neurosurg, 2008)

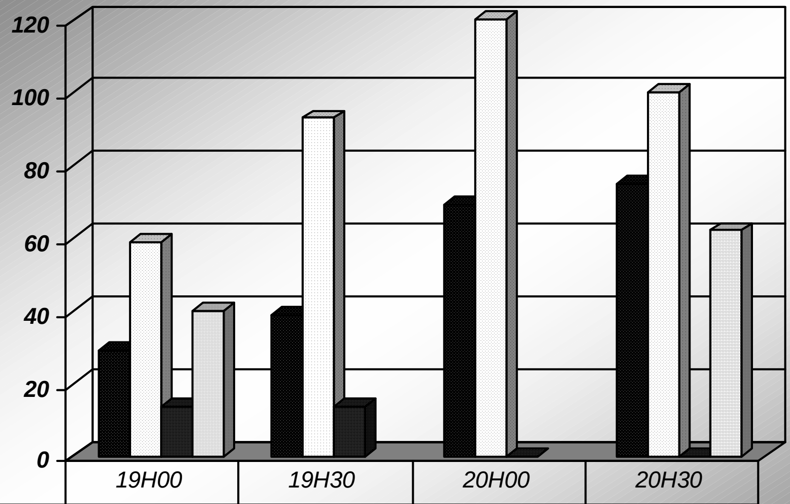
Clinical case (2)

- 52-y-old man, 70 kg weight
  - Child C alcoholic cirrhosis
  - Chronic renal failure with preserved diuresis
  - Type 2 diabetes, insulin started recently
  - Hypertrophic obstructive cardiomyopathy
  - Treated by lactulose, ranitidine and insulin
  - Received 120 mg SR verapamil (Loxidal) for HOC with intraventricular gradient
  - Admitted with severe bradycardia, shock, lactic acidosis and oliguria
  - Refractory to atropine, calcium salts, epinephrine and norepinephrine

Clinical case (2)



Clinical case (2)

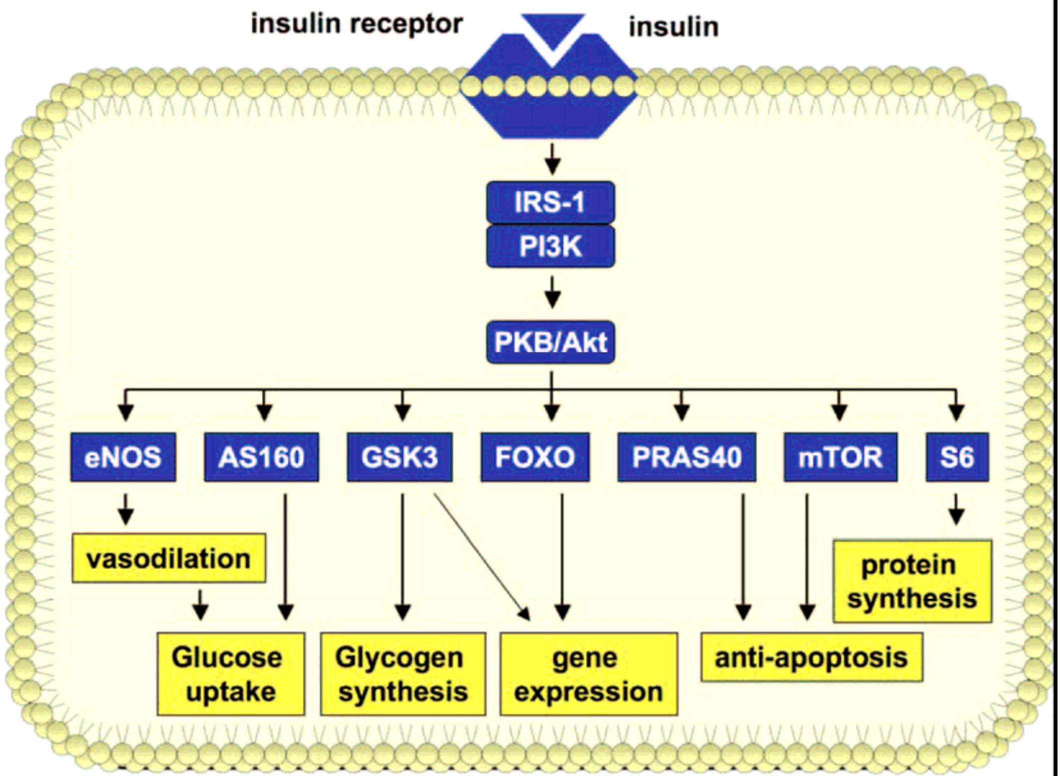


	19H00	19H30	20H00	20H30
HR (bpm)	29	39	69	75
SBP (mmHg)	59	93	120	100
Nor-E (µg/min)	13,3	13,3	0	0
ScvO2	40			62

Insulin 70 IU bolus → 45 IU/hr for 28 hr

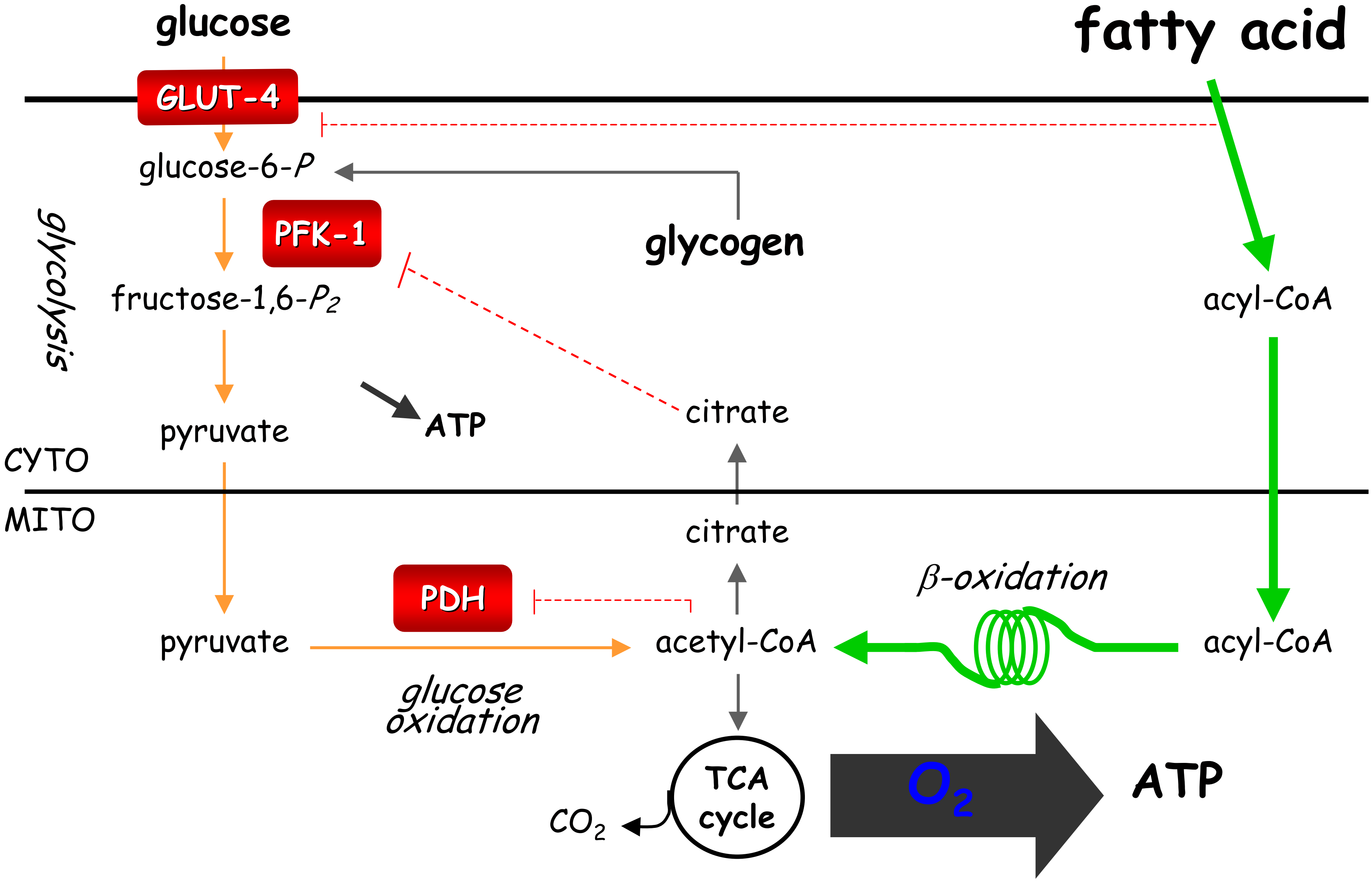
- Recovery of sinus rhythm within 30 min, rapid improvement in blood pressure, ScvO2 and diuresis, complete withdrawal of catecholamines

Insulin signaling

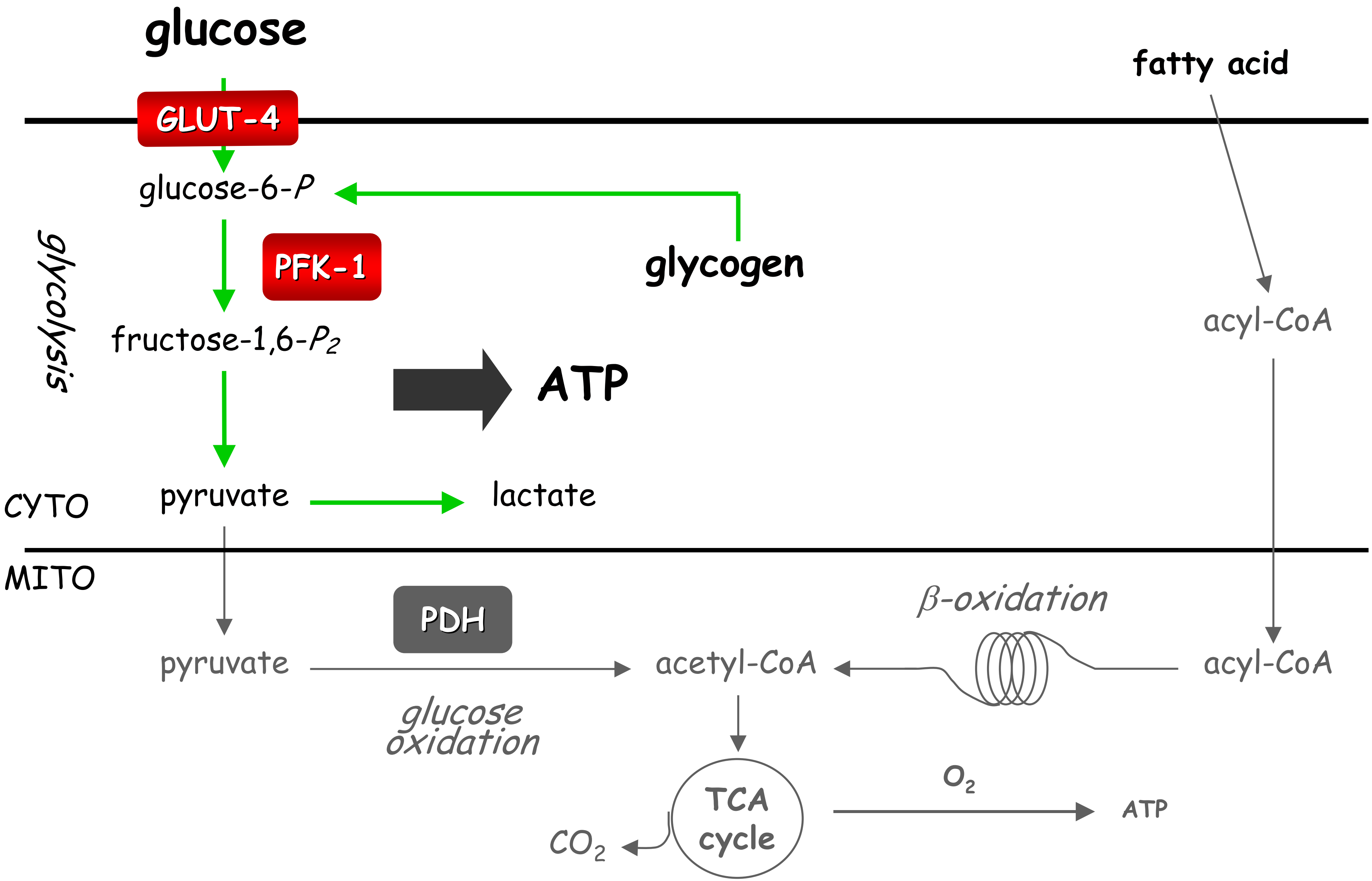


(Ouwens et al., Arch Physiol Biochem, 2007)

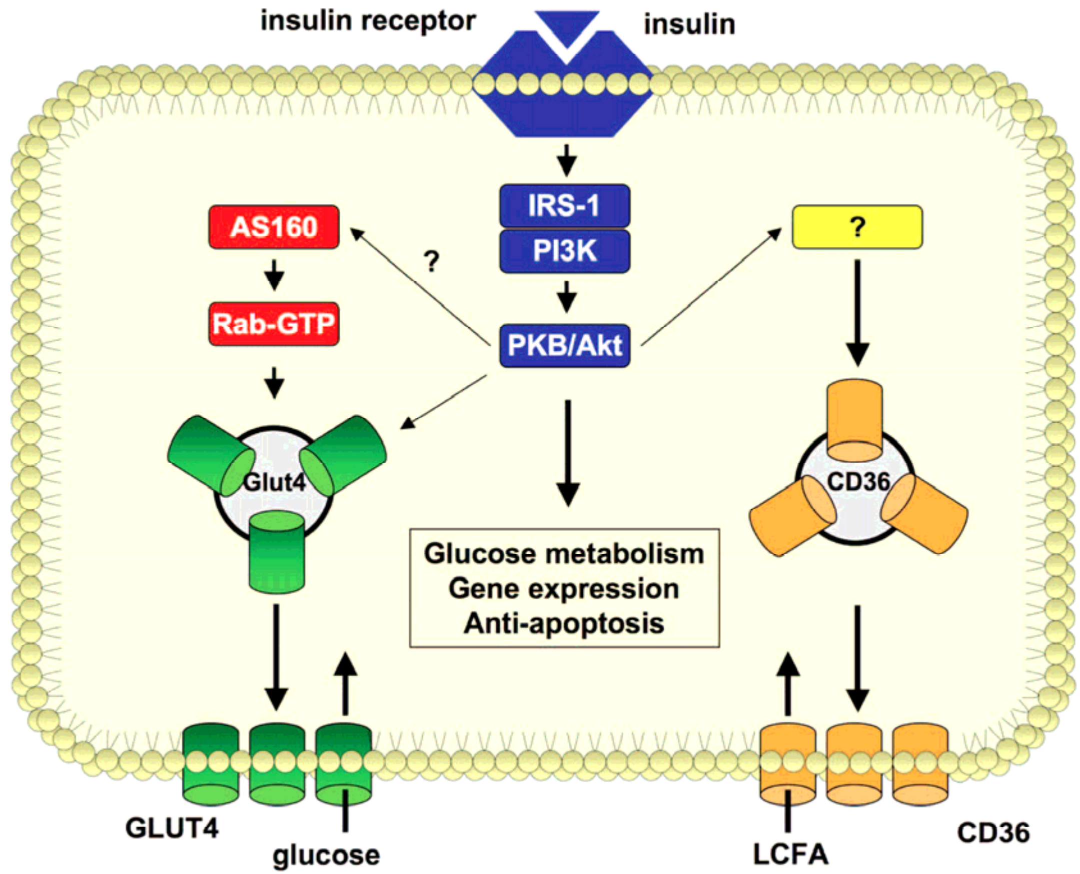
Energy metabolism in the aerobic heart



Energy metabolism in the ischemic heart

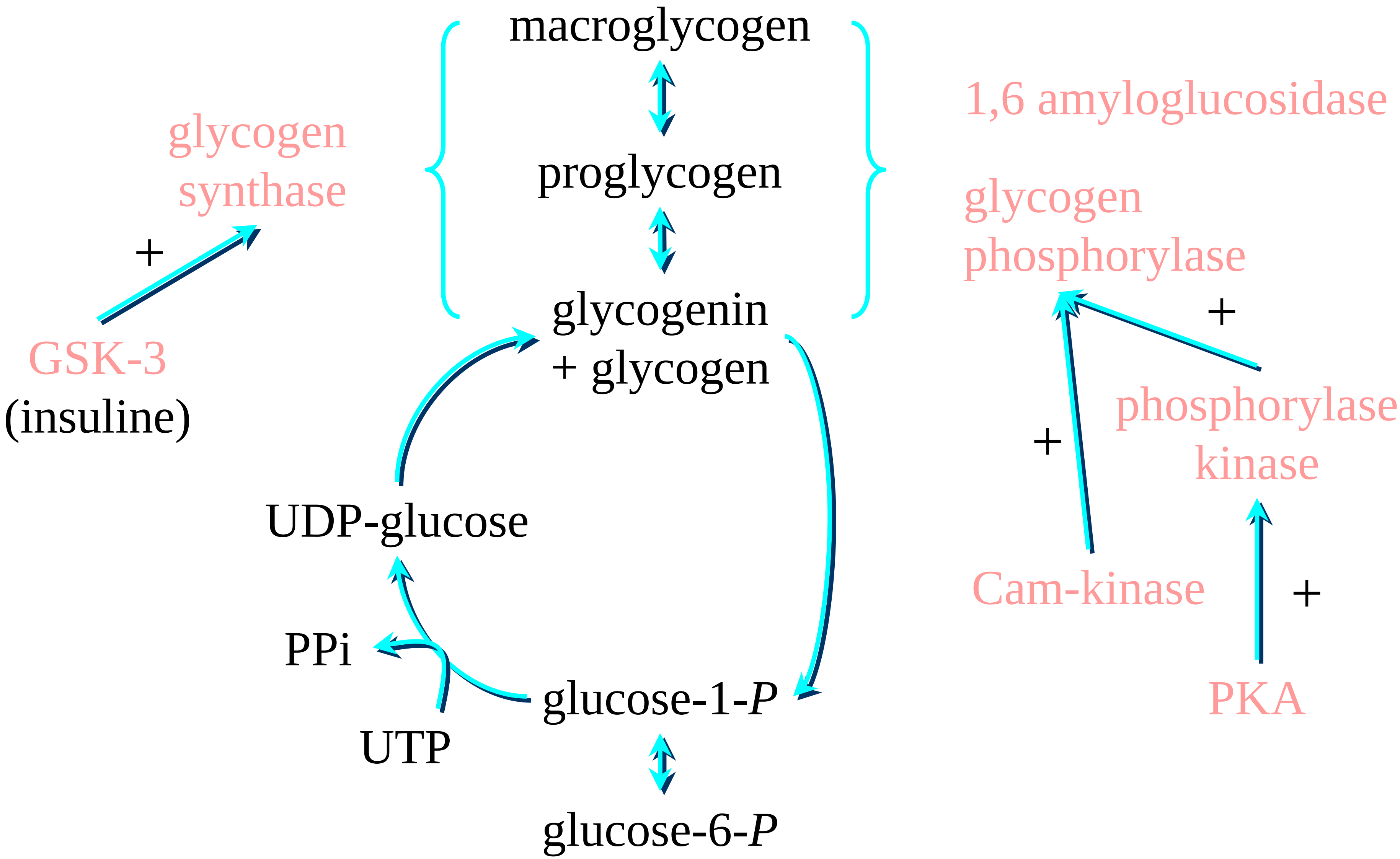


Regulation of glucose uptake

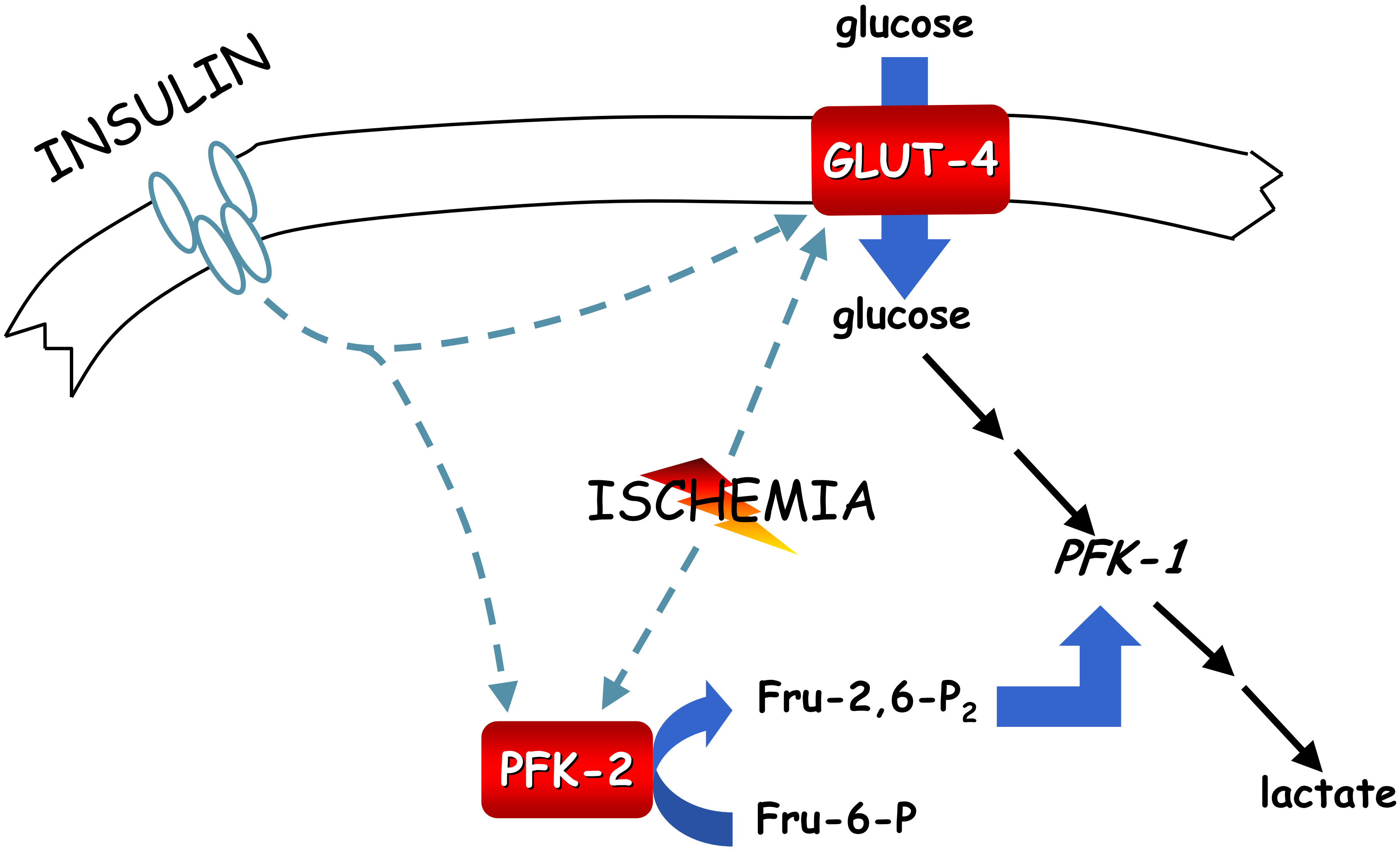


(Ouwens et al., Arch Physiol Biochem, 2007)

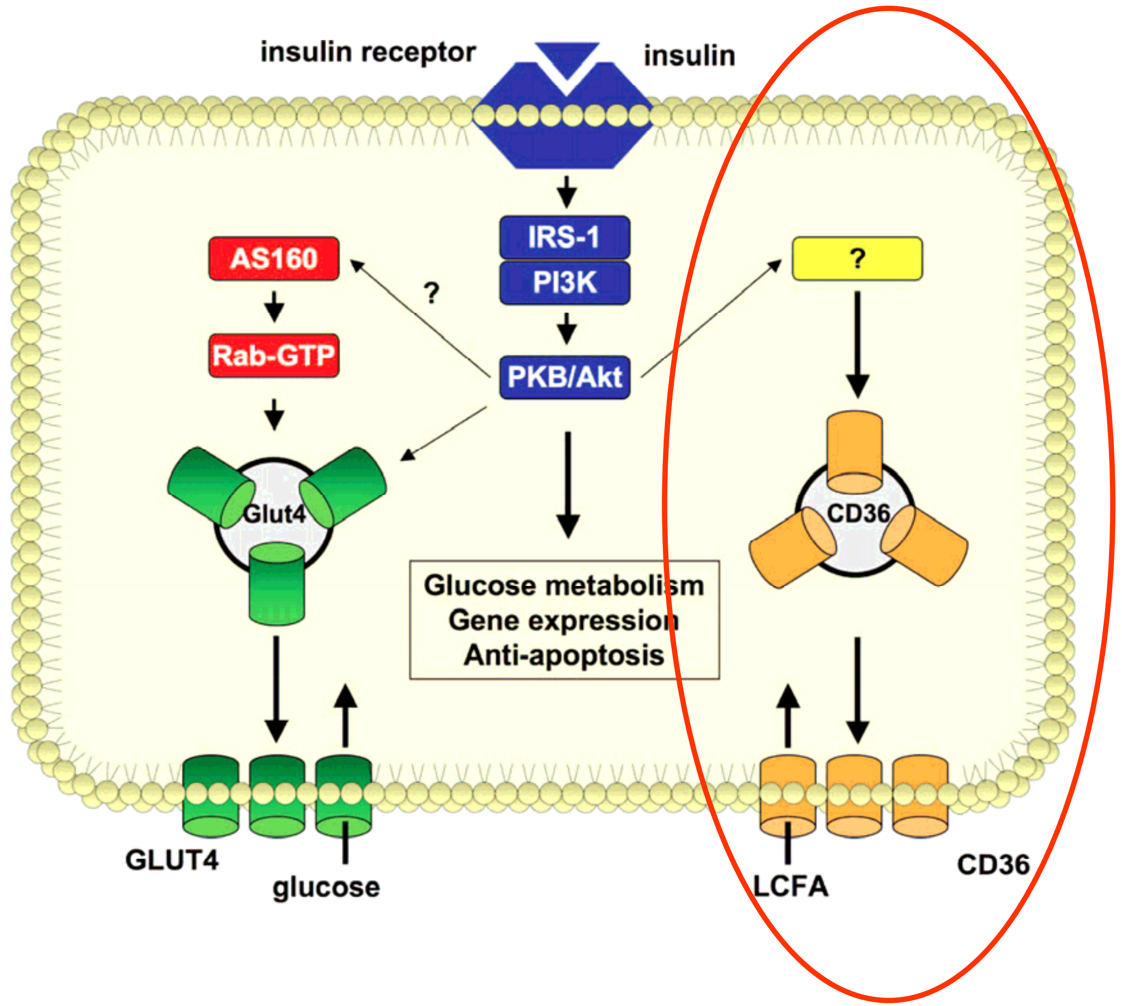
Regulation of glycogen synthesis



Regulation of glycolysis

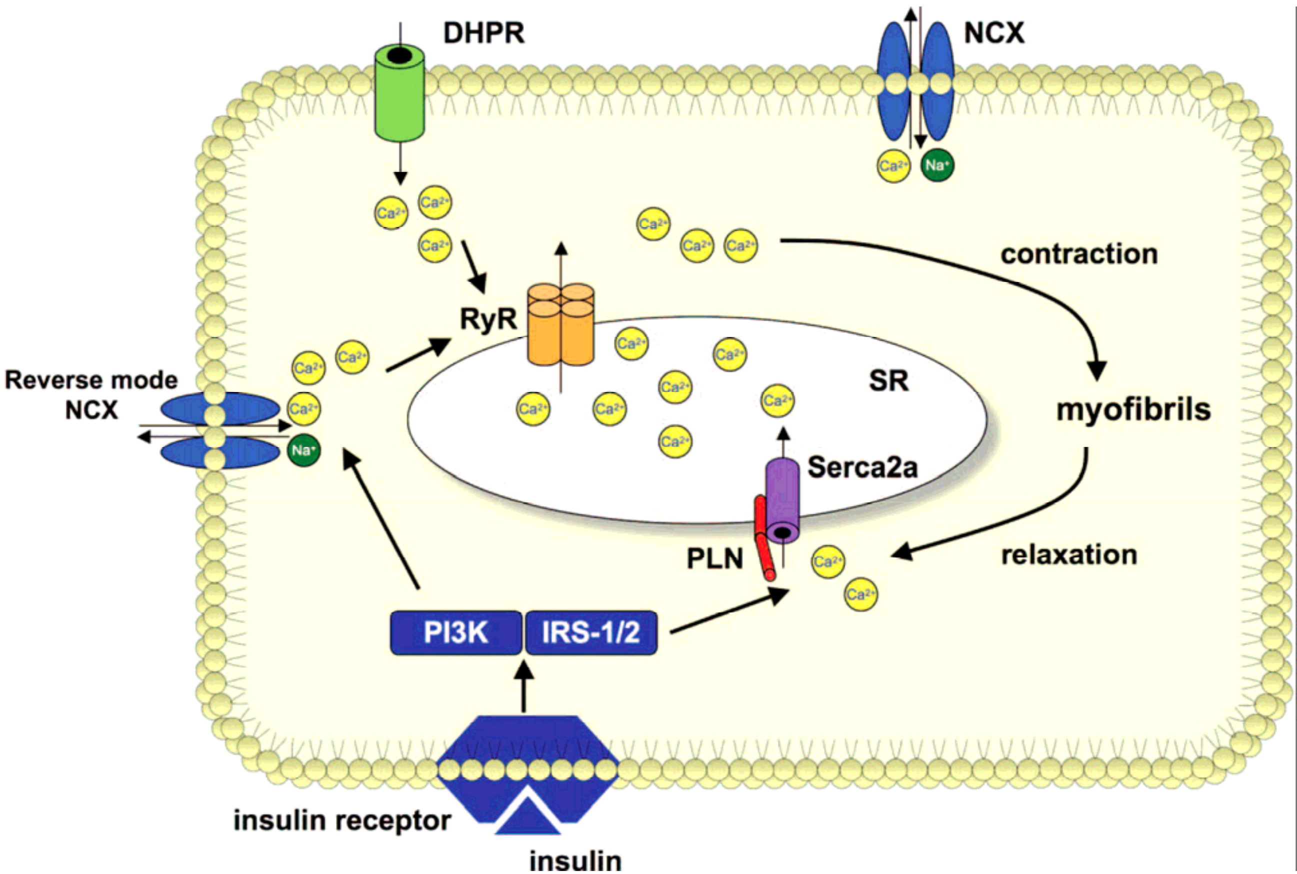


Influence of insulin on lipid metabolism



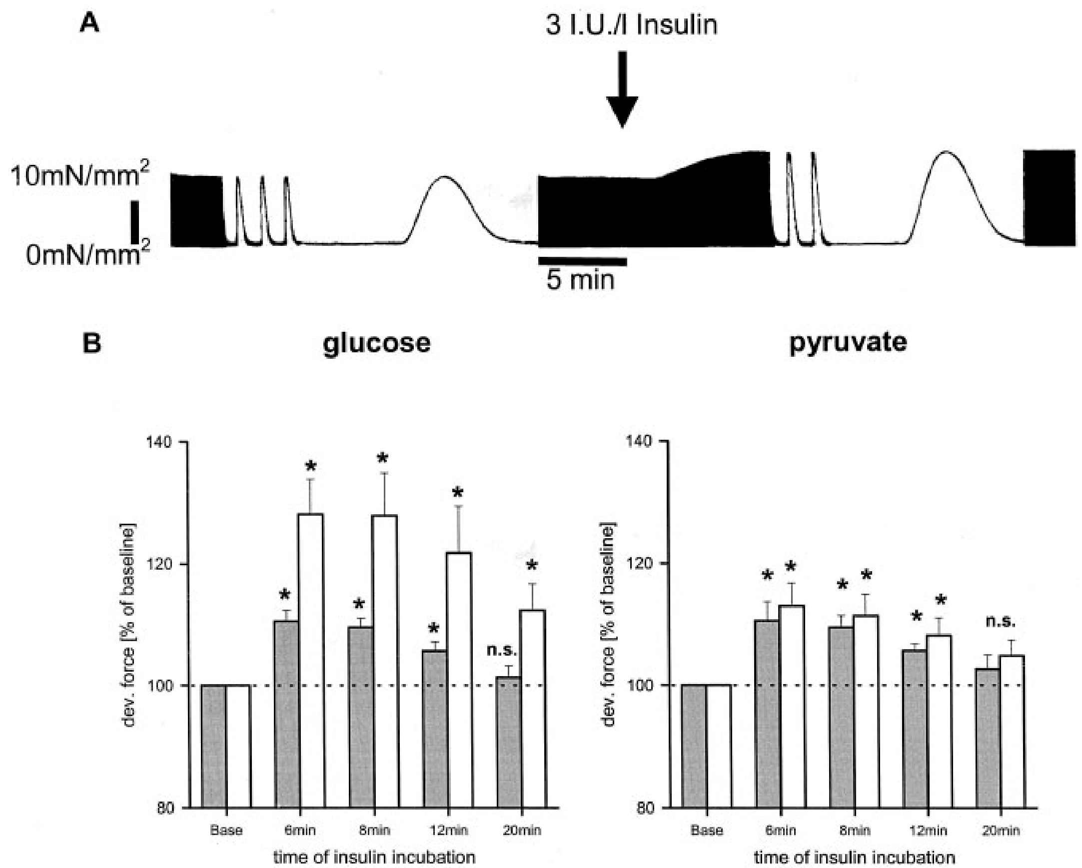
(Ouwens et al., Arch Physiol Biochem, 2007)

Regulation of contractile force development and calcium metabolism



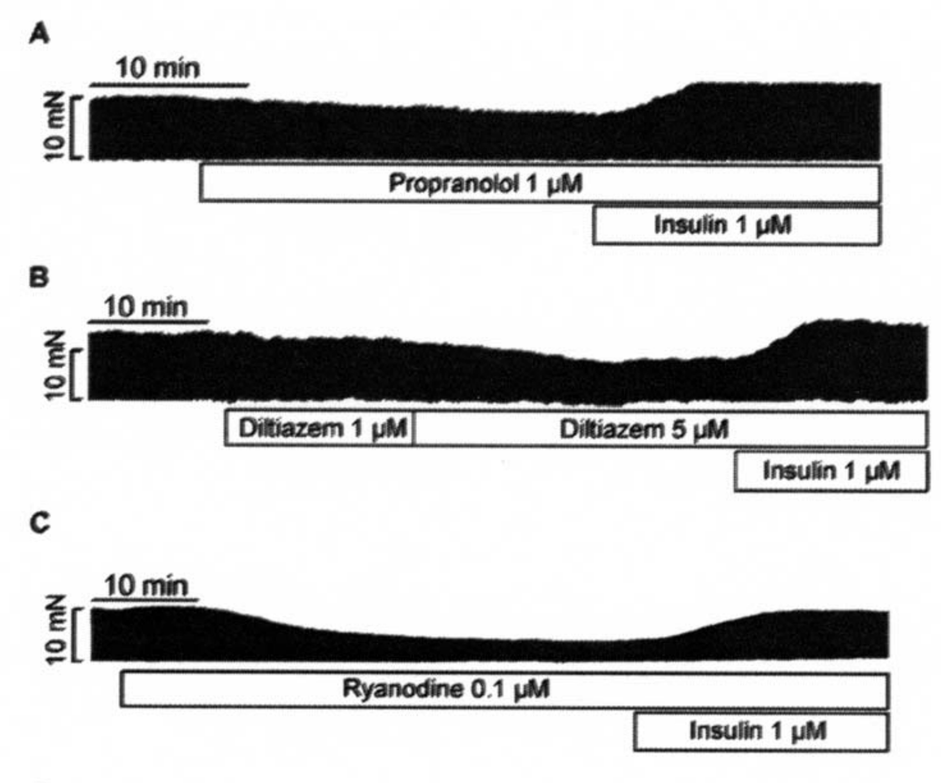
(Ouwens et al., Arch Physiol Biochem, 2007)

Inotropic effects of insulin in failing human myocardium



(von Lewinski et al., 2005)

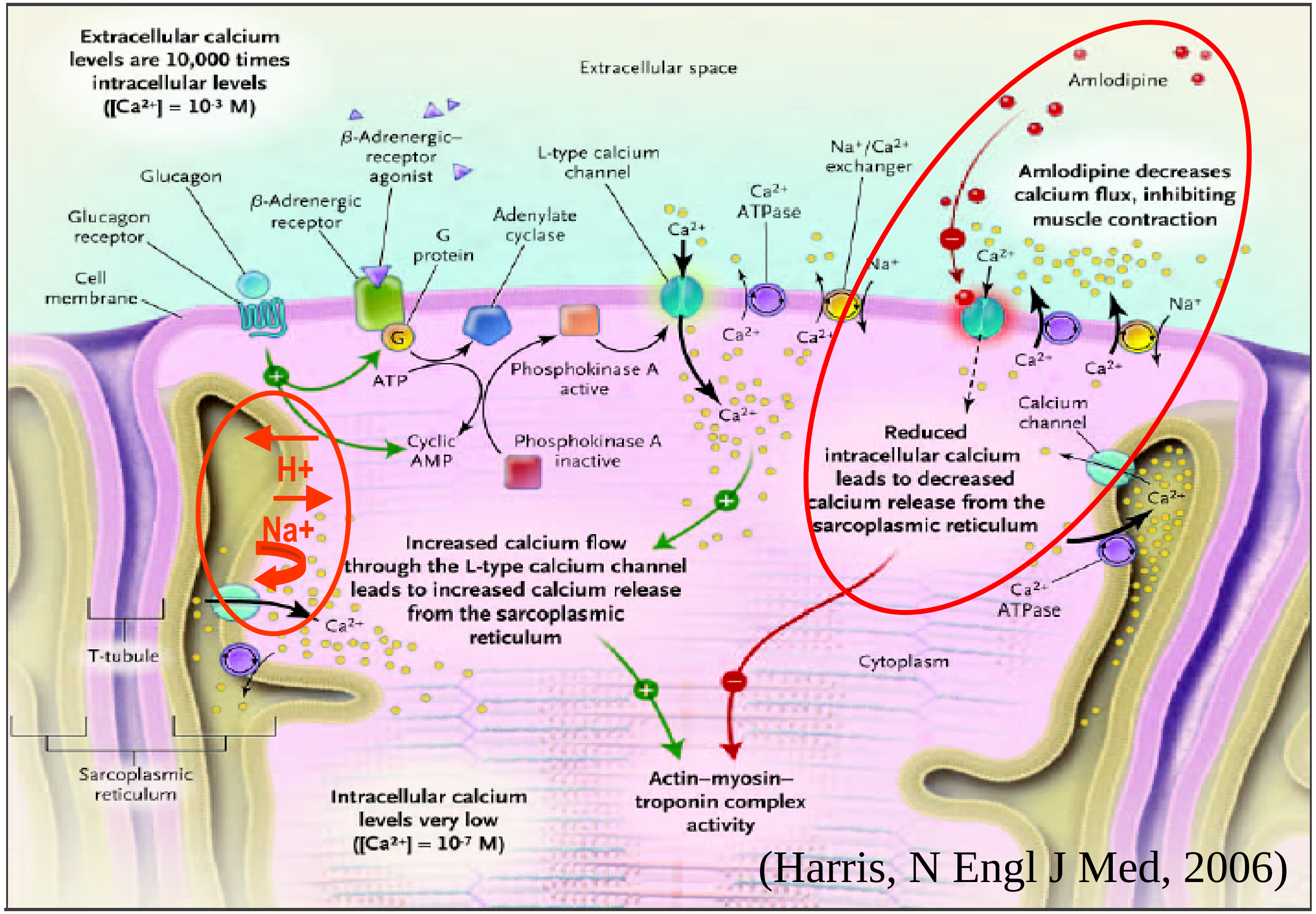
Inotropic effects of insulin in failing human myocardium



(Hsu et al., J Heart Lung Transplant, 2007)

- the positive inotropic effects of insulin are partially preserved in the absence of glucose
- not modified by preincubation with propranolol or diltiazem
- complex relationships with Ca $^{2+}$ handling
  - direct Ca $^{2+}$ sensitizing effects
  - indirect effects

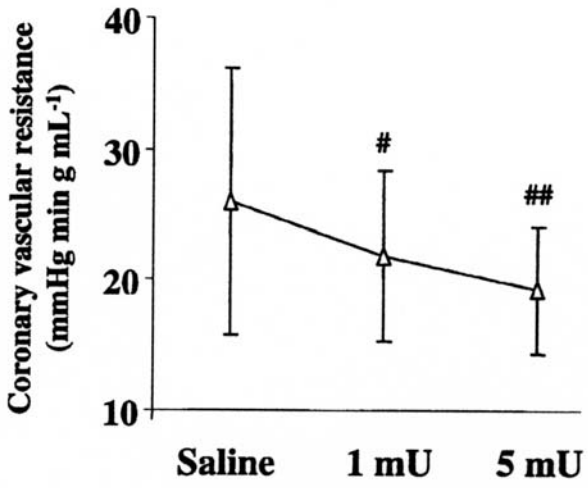
Link between improved glycolytic activity and calcium-related contractility?

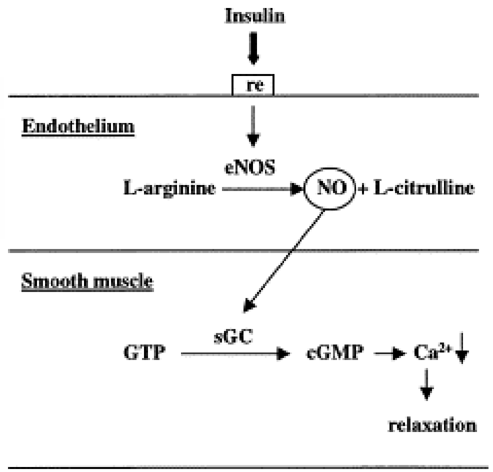


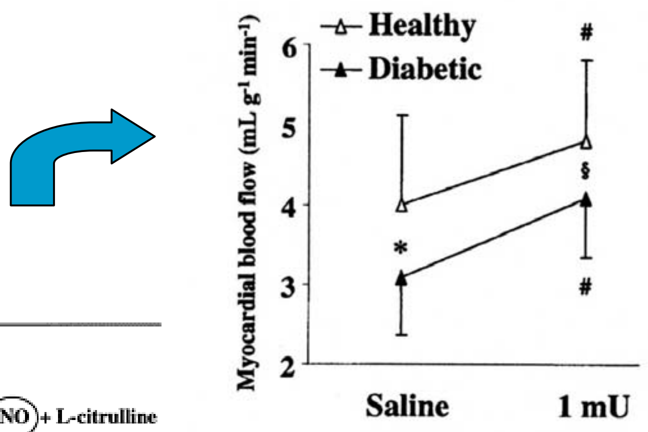
(Harris, N Engl J Med, 2006)

Effects on myocardial blood flow

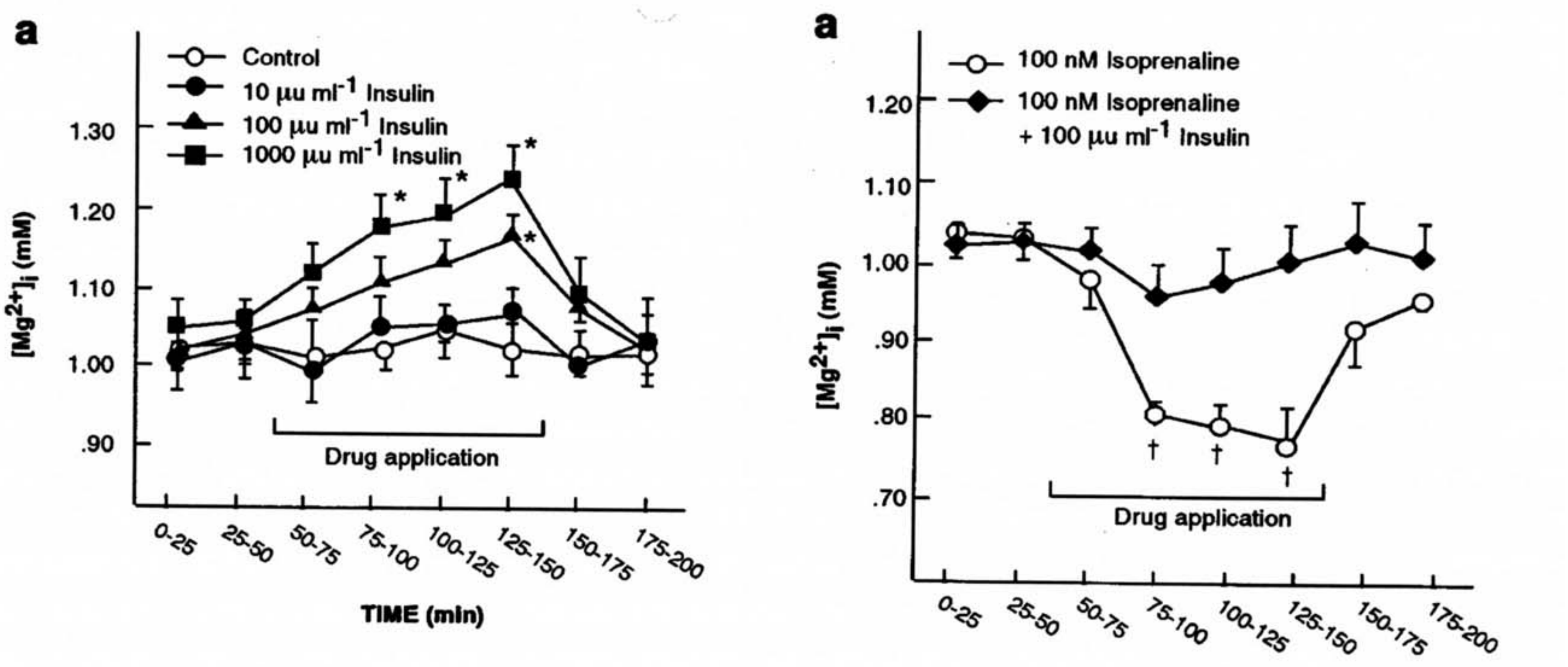
- Insulin decreases coronary vascular resistance and increases myocardial blood flow, not only in healthy subjects
- Mechanisms: induction of eNOS, decrease in $Ca^{2+}{}_i$





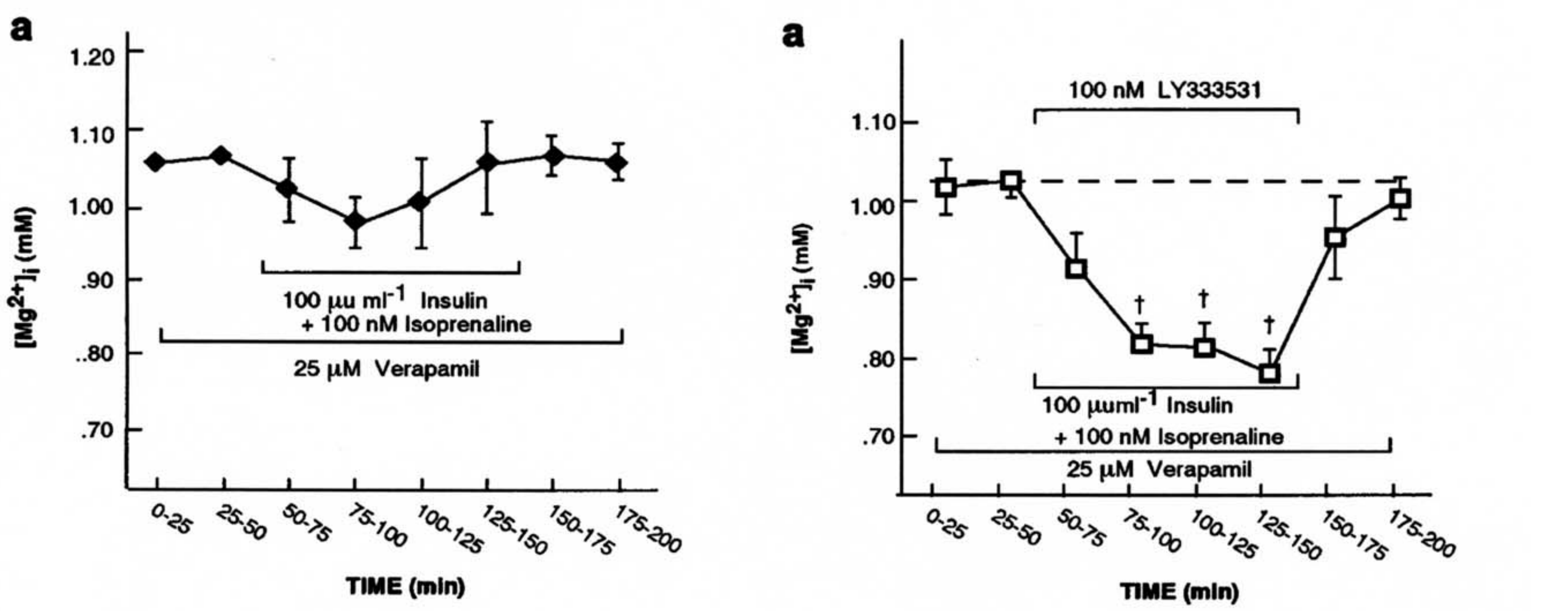


Insulin modulation of intracellular Mg^{2+}



(Amano et al., Br J Pharmacol, 2000)

Insulin modulation of intracellular Mg^{2+}



(Amano et al., Br J Pharmacol, 2000)

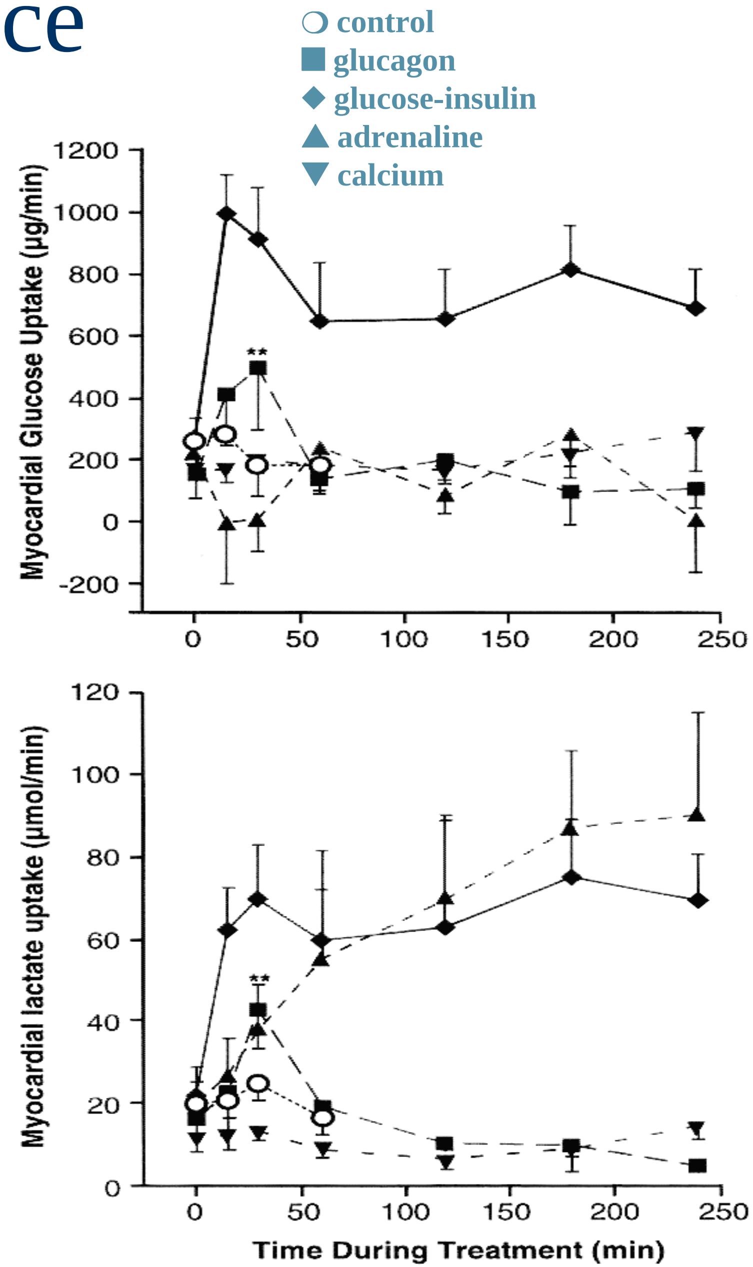
Chronotropic effects of insulin?

	Normal solution T25-50 min	Drug application T75-100 min	Drug application T125-150 min	Washout T175-200 min
Control ($n=5$)				
HR (b.p.m.)	263±5	263±5	261±5	262±5
LVDP (mmHg)	154±4	155±6	153±5	156±5
10 μu ml^{-1} Insulin ($n=5$)				
HR (b.p.m.)	255±6	267±5	261±8	258±4
LVDP (mmHg)	157±7	166±9	163±6	154±5
100 μu ml^{-1} Insulin ($n=5$)				
HR (b.p.m.)	261±3	285±6*	281±5*	265±4
LVDP (mmHg)	150±5	176±7*	175±7*	153±6
1000 μu ml^{-1} Insulin ($n=5$)				
HR (b.p.m.)	258±5	297±7*	296±8*	252±6
LVDP (mmHg)	155±6	188±10*	185±7*	144±7

- Blocked by LY333531, a protein kinase C inhibitor, but not by propranolol

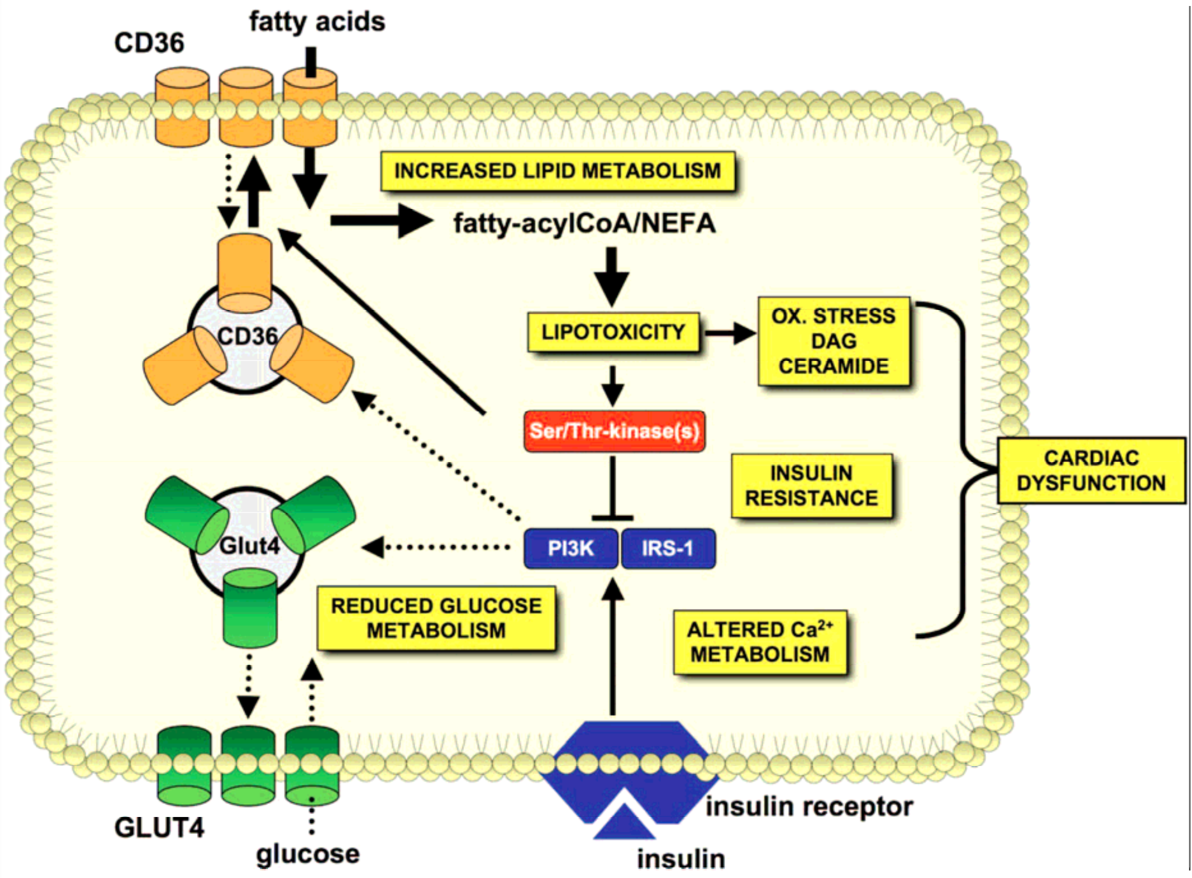
Experimental evidence

- Animal models with calcium channel blockers or bêta-blockers toxicity
  - insulin improves myocardial glucose and lactate uptake
  - better performance, without increased oxygen consumption



(Kline et al, CCM, 1995)

Some common features



« Stressed » myocardium

↓

glucose preference

Insulin resistance

↓

impaired glucose and calcium metabolism

Conclusions

- Positive inotropic effects of insulin
  - have been demonstrated both *in vitro* and *in vivo*
  - are not mediated by the release of catecholamines and subsequent activation of β-adrenergic receptors
  - are partially preserved in the absence of glucose
  - could be related to an increase of the intracellular calcium transients
  - could be of interest for the management of β-blockers or calcium channel blockers overdoses, preferably from an early stage

Experimental evidence

Critical Care Medicine:Volume 23(7)July 1995pp 1251-1263

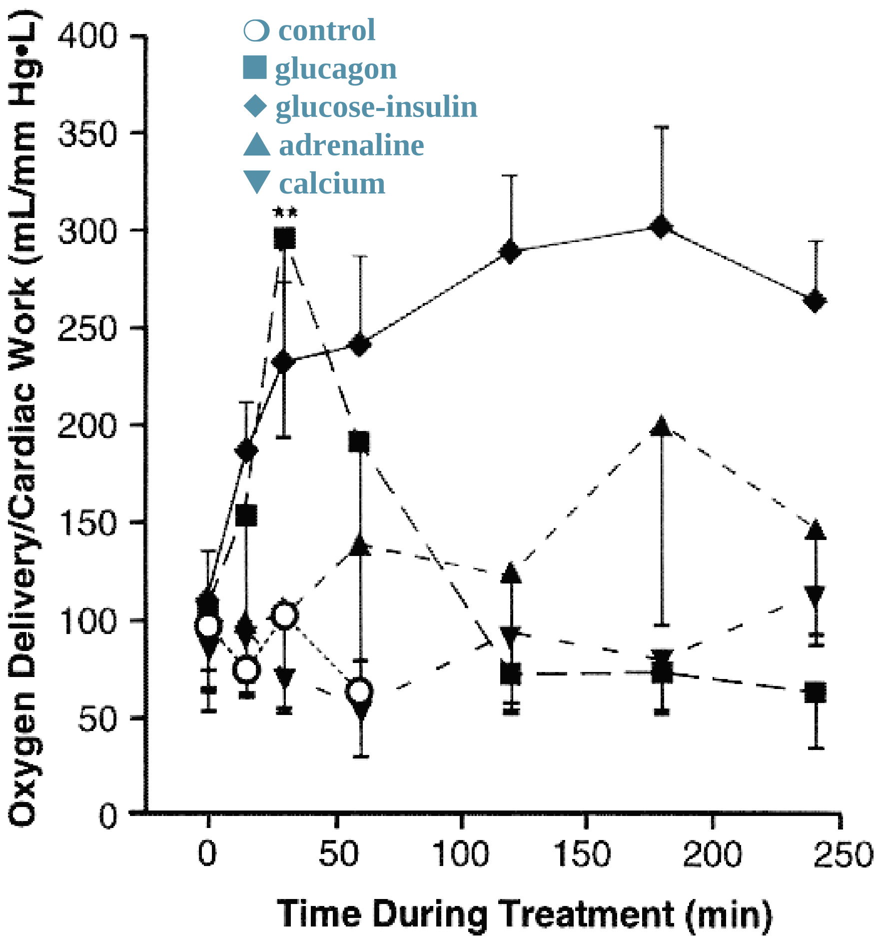
Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine [Laboratory Investigation]

Kline, Jeffrey A. MD; Leonova, Elena MS; Raymond, Richard M. PhD

- 30 dogs intoxicated by i.v. verapamil, randomized to control, or to one of four treatment protocols
  - calcium chloride (20 mg/kg), then 0.6 mg/kg/hr
  - hyperinsulinemia-euglycemia (4.0 U/min) with arterial glucose +/- 10 mg/dl
  - epinephrine starting at 1 µg/kg/min
  - glucagon 0.2 mg/kg bolus, then 150 µg/kg/h

Experimental evidence

- Glucose-insulin: ⇑ ratio O2 delivery/cardiac work
- Biphasic action of glucagon: ⇑ then ⇓
- No significative changes with calcium or epinephrine

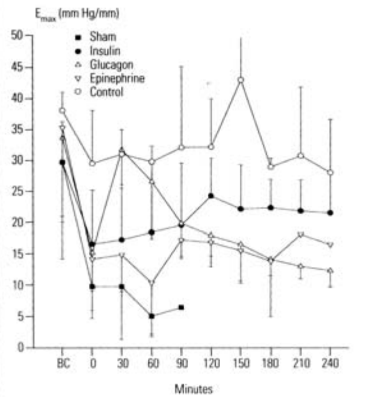


(Kline et al, CCM, 1995)

Experimental evidence

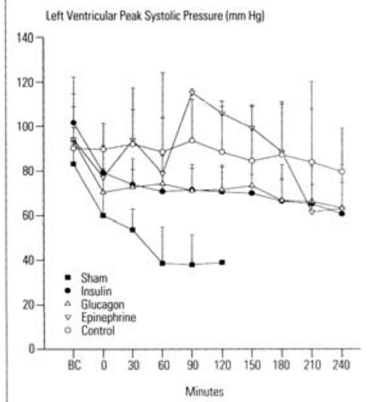
- Extension of the benefit of hyperinsulinemia-euglycemia to bêta-blocker toxicity
- Increased myocardial glucose uptake

Figure 3.
Contractility (E_{max}).



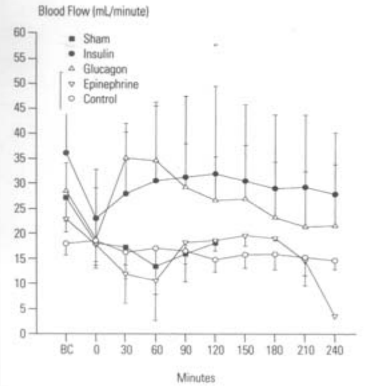
After exposure to propranolol, animals in all groups demonstrated decreased E_{max} (P=.024 versus control) before experimental treatment was started at 0 minutes. Insulin produced a consistent increase in E_{max} (no difference versus control group at 120 minutes). Glucagon transiently increased E_{max} during the first 30 minutes (P=.0007 versus insulin and epinephrine groups). Although two sham-treated animals remained alive at 120 minutes, cardiac function was so depressed that E_{max} could not be determined.

Figure 4.
Left ventricular peak systolic pressure.



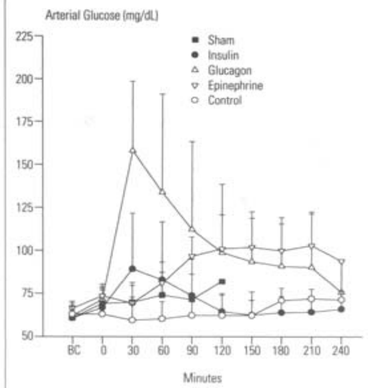
Left ventricular peak systolic pressure decreased progressively in the sham-treated group (P=.011 versus control group by 0 minutes). Insulin and glucagon prevented the decline in left ventricular pressure (P=.0002 versus sham-treatment group by 90 minutes). Peak left ventricular pressure during epinephrine treatment occurred at 90 minutes (P=.0002 versus all other groups).

Figure 7.
Coronary artery blood flow.



Experimental treatment with glucagon transiently increased coronary artery blood flow compared with that in the sham, control, and epinephrine groups early in the experiment (P=.0012 at 30 minutes). Coronary artery blood flow in the sham, insulin, and epinephrine groups was not different than that for the control group.

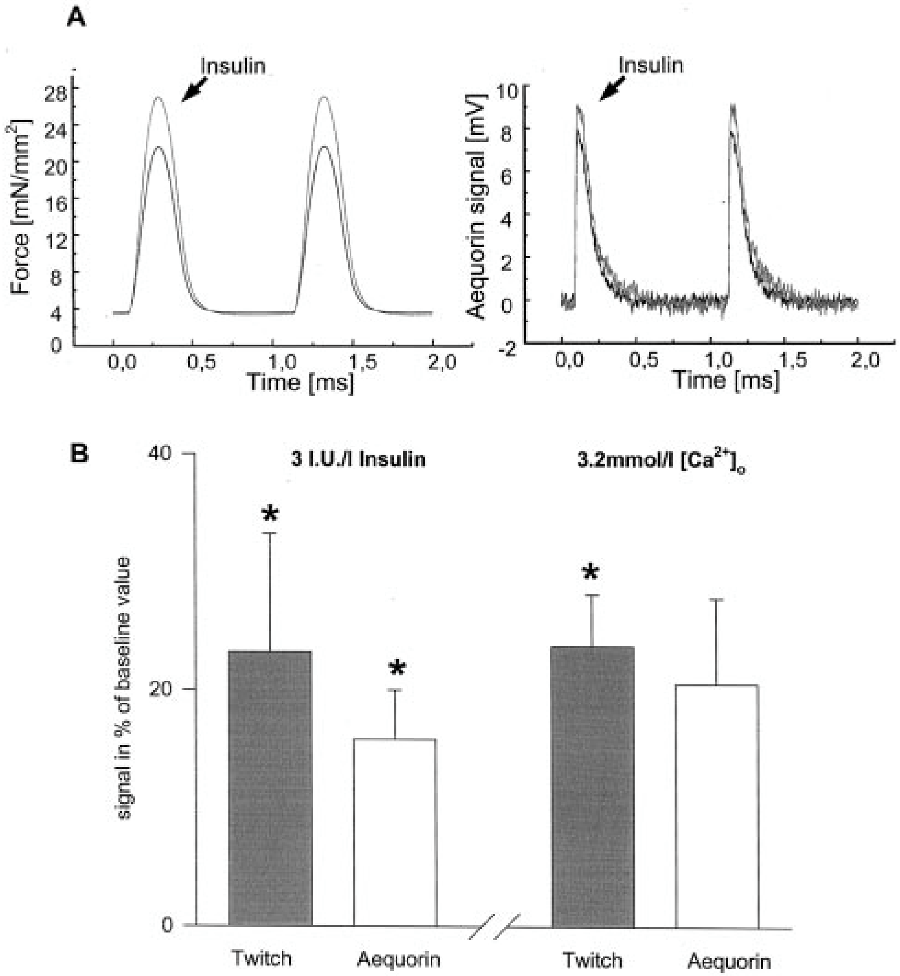
Figure 8.
Arterial glucose concentration.



After glucagon treatment, arterial glucose concentration increased from baseline and peaked at 30 minutes (P=.0001 versus all other groups). Thereafter, glucose concentration returned to control values. The sham, insulin, and epinephrine groups did not differ from the control group during the study.

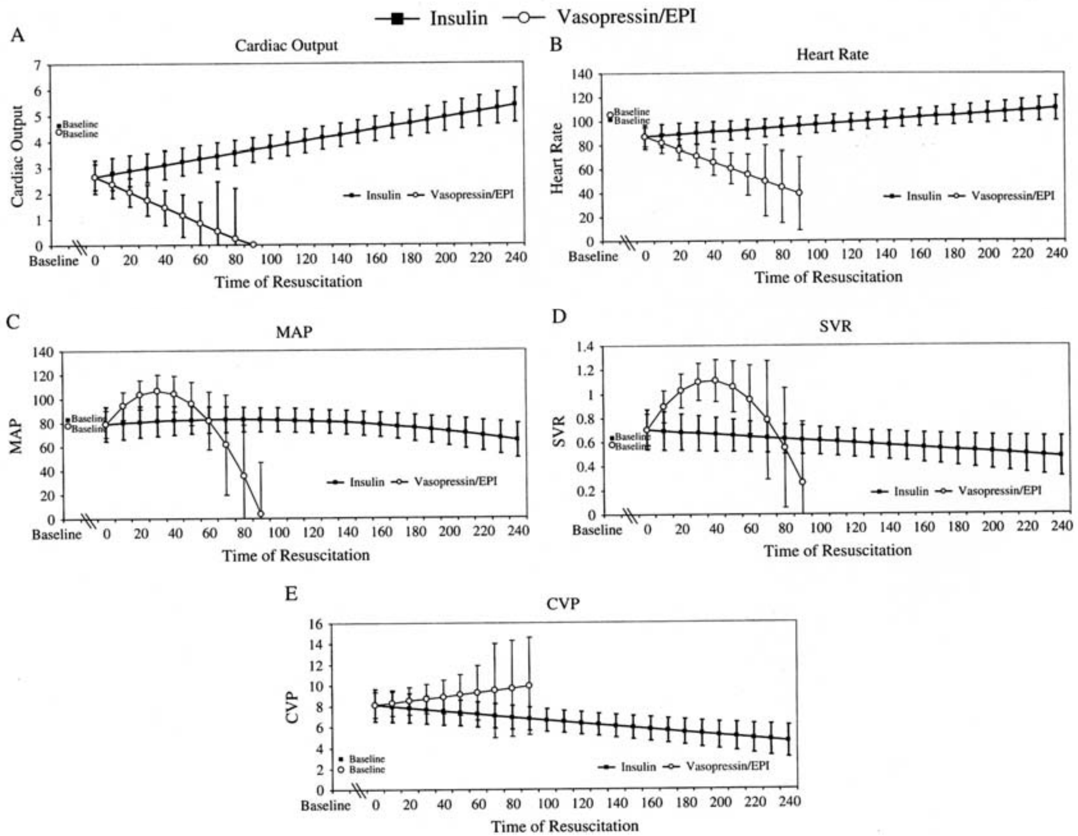
(Kerns et al., Ann Emerg Med, 1997)

Inotropic effects of insulin in failing human myocardium



Experimental evidence

- Pig model of β-blocker toxicity: comparison insulin-glucose versus vasopressin-epinephrine



Holger, Joel S., Engebretsen, Kristin M., Fritzlar, Sandy J.,Patten, Lane C., Harris, Carson R. and Flottemesch, Thomas J. (2007). Insulinversus vasopressin and epinephrine to treat β-blocker toxicity. Clinical Toxicology,45:4, 396 - 401

Cardiac contractile dysfunction in insulin-resistant rats

Table 1 In vivo cardiac characteristics of rats before and after 8 weeks on an HFD or a LFD

	Start (n=24)	LFD (n=8)	HFD (n=16)
Physiological parameters			
Body weight (g)	295±4	476±8*	463±8*
Left ventricular mass (mg)	637±15	890±18*	882±32*
LV diastolic parameters			
Posterior wall thickness (mm)	1.63±0.03	1.80±0.07	1.71±0.05
Lumen diameter (mm)	6.92±0.07	7.55±0.20*	7.68±0.10*
Interventricular septum wall thickness (mm)	1.37±0.03	1.67±0.08*	1.54±0.04*
Ventricular diameter (mm)	9.80±0.06	10.86±0.13*	10.89±0.12*
LV systolic parameters			
Posterior wall thickness (mm)	2.93±0.06	3.45±0.12*	3.00±0.08**
Lumen diameter (mm)	3.41±0.10	3.32±0.25	4.07±0.12*,**
Interventricular septum wall thickness (mm)	2.51±0.05	2.85±0.09*	2.67±0.06
Ventricular diameter (mm)	8.81±0.07	9.82±0.12*	9.81±0.10*
Fractional shortening (%)	50.8±1.3	56.3±2.4*	47.1±1.7*,**
Ejection fraction (%)	87.5±1.0	91.1±1.4	84.9±1.0*,**

Data are means±SE
*$p<0.05$ vs start
**$p<0.01$ vs LFD

(Ouwens et al., 2007)