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ATP metabolism in RBC as potential biomarker for post-exercise hypotension and a therapeutic target for cardiovascular drugs

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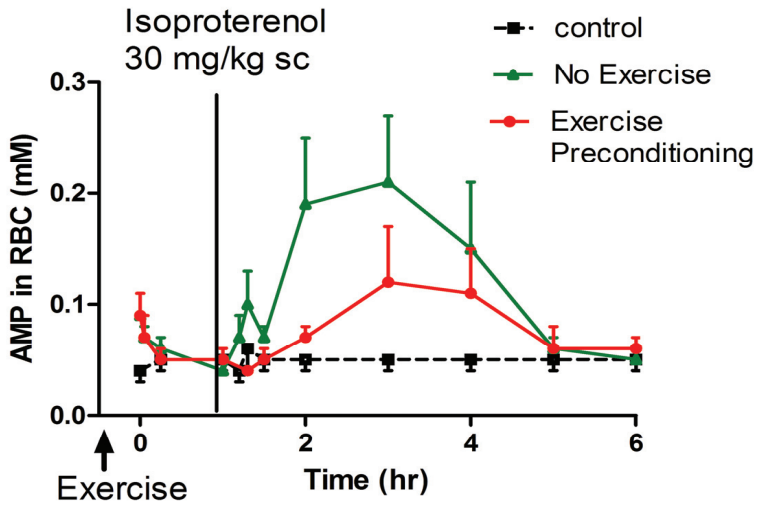
ATP metabolism in RBC as potential biomarker for post-exercise hypotension and a therapeutic target for cardiovascular drugs

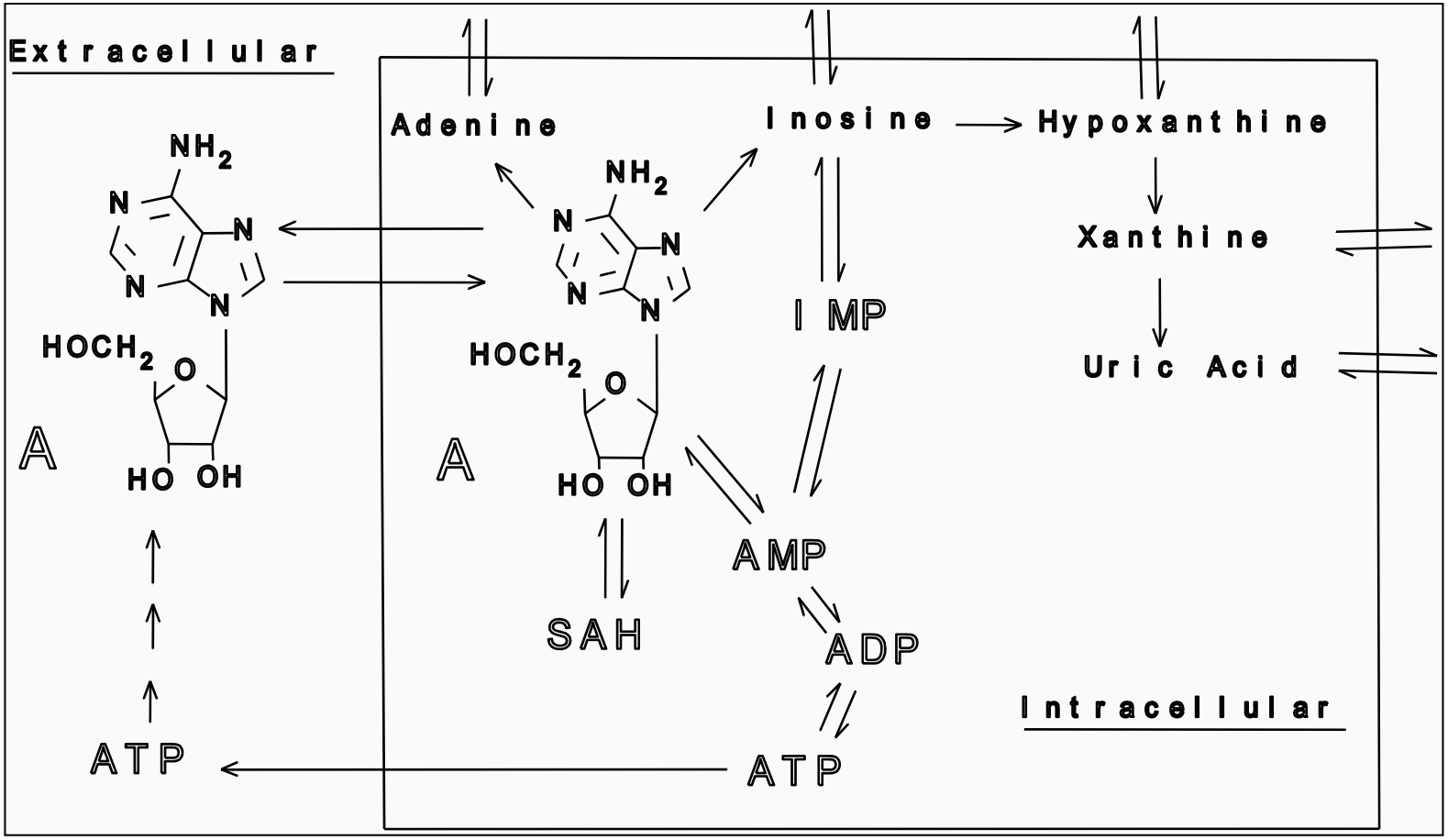


Effect of exercise pre-conditioning on AMP concentrations in RBC in an experimental rat model of acute MI in vivo

- **Breakdown of ATP to AMP in the RBC is a potential biomarker for serious cardiovasculcar toxicity and/or mortality**
- **Preserving ATP in the RBC is a potential drug target for cardiovascular protection**

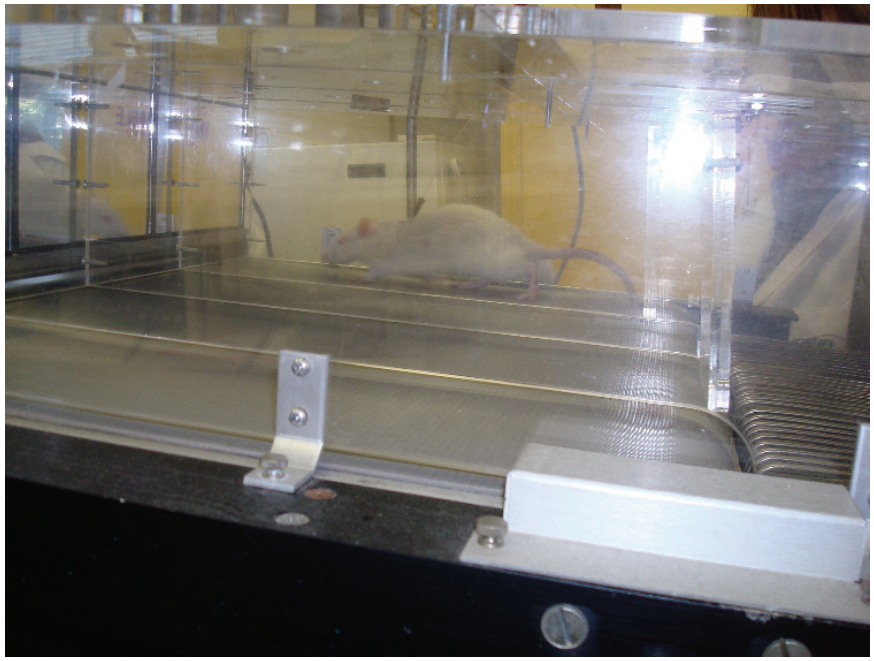
Adenosine /ATP Transport and Metabolism

Yeung, PKF et al. Effect of diltiazem on plasma concentrations of oxypurines and uric acid. Therap. Drug Monit. 1997; 19:286-291

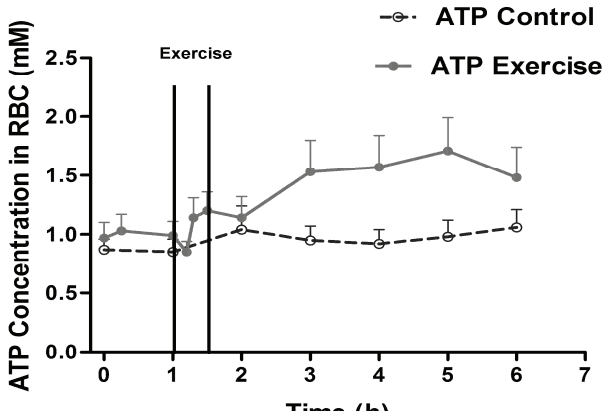


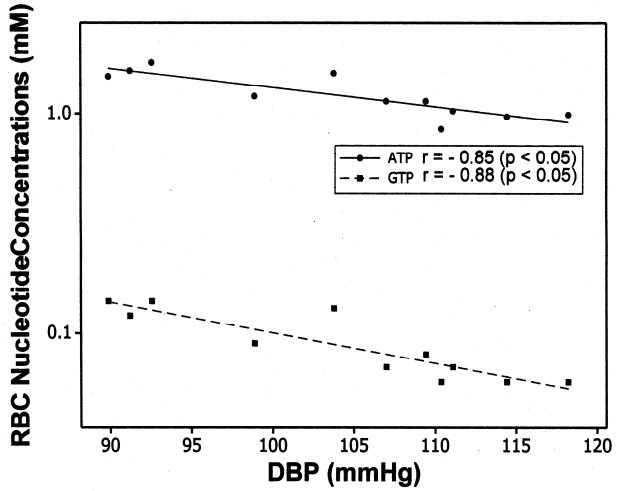
Effect of Exercise on ATP Metabolism in RBC

Yeung, P. K et al. Exercise improves hemodynamic profiles and increases red blood cell concentrations of purine nucleotides in a rodent model. Ther Adv Cardiovasc Dis. 2010; 4(6)341-7.



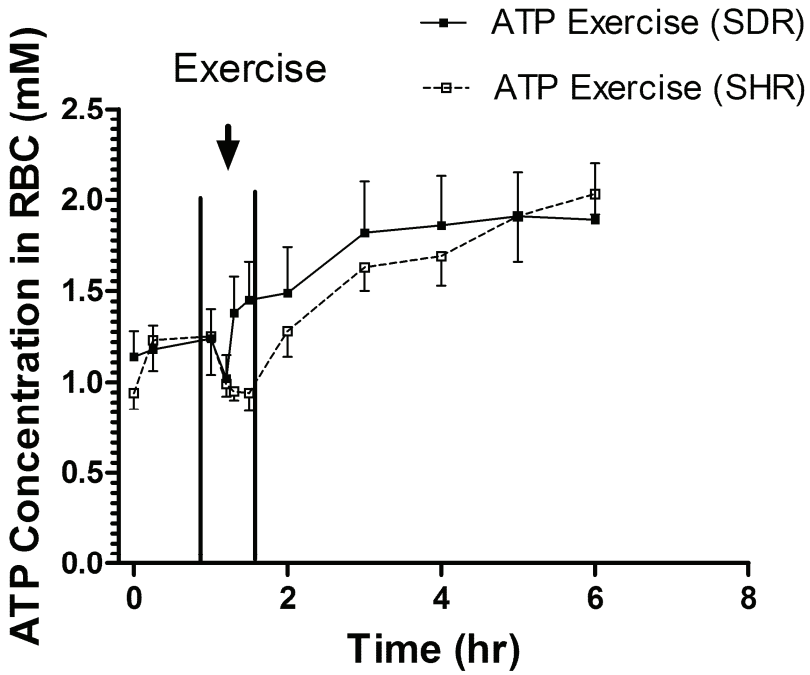
Treadmill exercise 15 min at a speed of 10 m/min and 5% grade

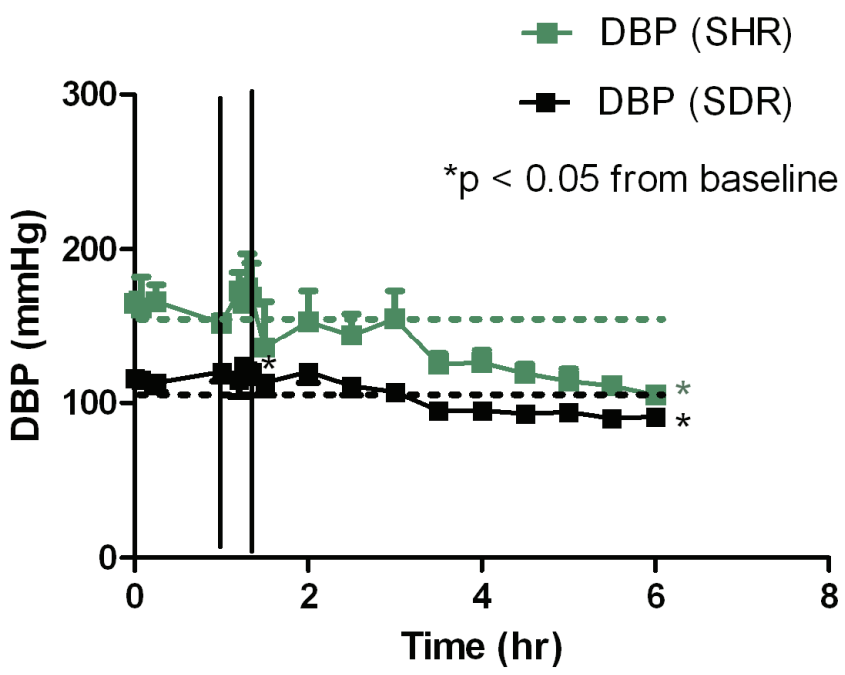




Effect of Exercise in SDR vs SHR

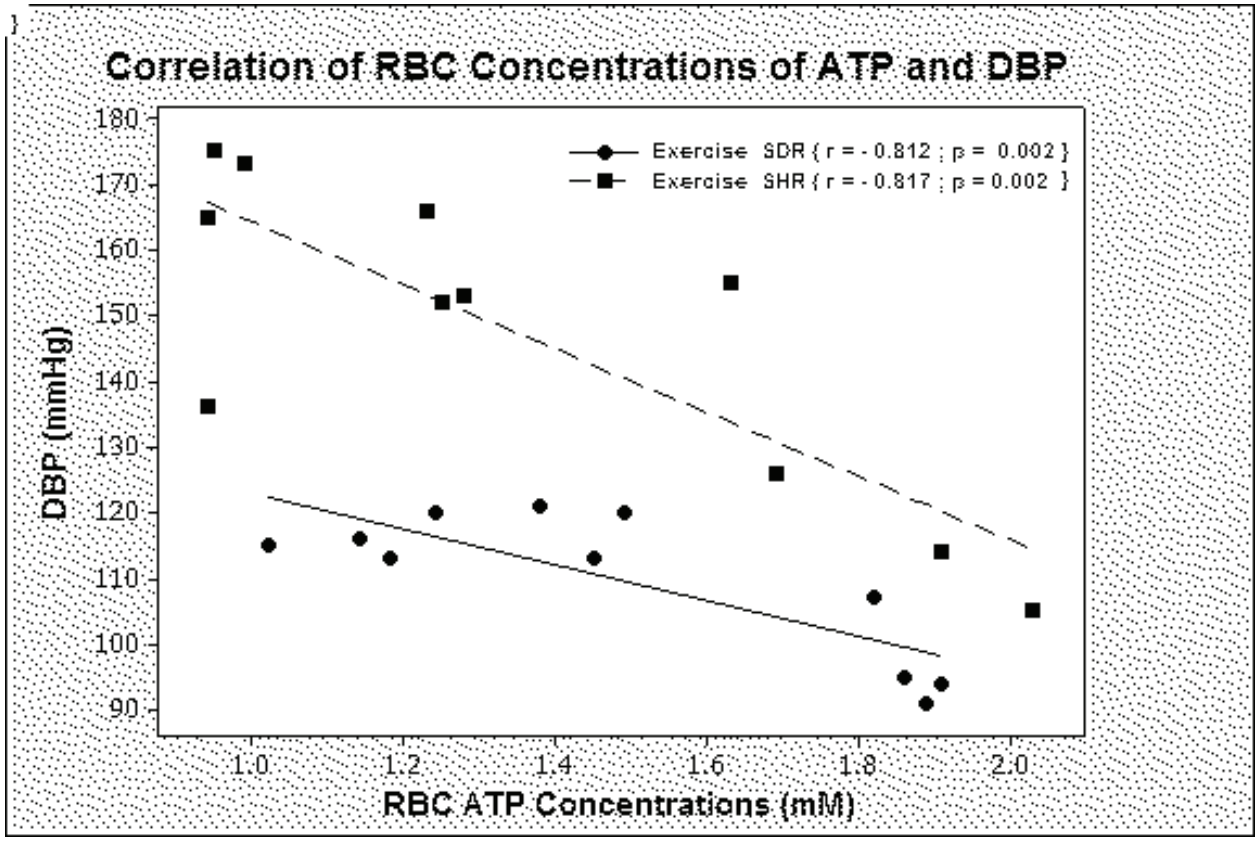
Yeung, P. K et al. Effect of acute exercise on cardiovascular hemodynamic and red blood cell concentrations of purine nucleotides in hypertensive compared with normotensive rats. Therapeutic Advances in Cardiovascular Disease 7(2):63-74, 2013.





Correlations between RBC [ATP] and DBP post exercise

Yeung, P. K et al. Effect of acute exercise on cardiovascular hemodynamic and red blood cell concentrations of purine nucleotides in hypertensive compared with normotensive rats. Therapeutic Advances in Cardiovascular Disease 7(2):63-74, 2013.



Effect of exercise on RBC adenine nucleotide concentrations in healthy subjects

Dudzinska et al. Adenine, guanine and pyridine nucleotides in blood during physical exercise and restitution in healthy subjects. Eur J Appl Physiol. 2010 Dec; 110(6)1155-62.

Table 3 Concentrations of adenine nucleotides (ATP, ADP, AMP) and inosine nucleotides (IMP) in red blood cells before exercise, after exercise and 30 min of recovery

	Before exercise	After exercise	30 min of recovery
ATP (µmol/l RBC)	1,797.00 ± 158.83	1,777.80 ± 130.52	1,808.522 ± 155.26
ADP (µmol/l RBC)	227.42 ± 40.49	220.13 ± 42.30	189.18 ± 39.57*
AMP (µmol/l RBC)	14.25 ± 2.94	13.21 ± 3.09	9.77 ± 2.43***,§§
TAN (µmol/l RBC)	2,038.59 ± 172.87	2,010.73 ± 154.92	2,006.79 ± 171.29
AEC	0.93 ± 0.01	0.93 ± 0.01	0.94 ± 0.009**,§
IMP (µmol/l RBC)	7.16 ± 1.35	8.43 ± 1.86*	6.82 ± 2.00§
ATP/ADP (µmol/l RBC)	8.13 ± 1.54	8.41 ± 1.53	9.91 ± 1.96*,§
ADP/AMP (µmol/l RBC)	16.06 ± 1.13	16.95 ± 1.84	19.56 ± 1.67***,§§§

Concentrations of ATP, ADP, AMP, TAN and IMP are expressed as µmol/l RBC

Values are given as mean ± SD; $n = 22$

TAN (total adenine nucleotides) = [ATP] + [ADP]) + [AMP]

AEC (adenylate energy charge) was evaluated according to the formula by Atkinson

AEC = ([ATP] + 0.5[ADP])/([ATP] + [ADP] + [AMP])

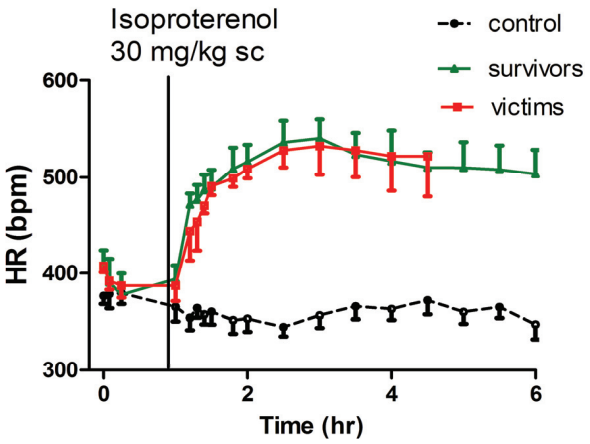
* $P < 0.01$; **$P < 0.006$; ***$P < 0.0001$, significantly different from before exercise

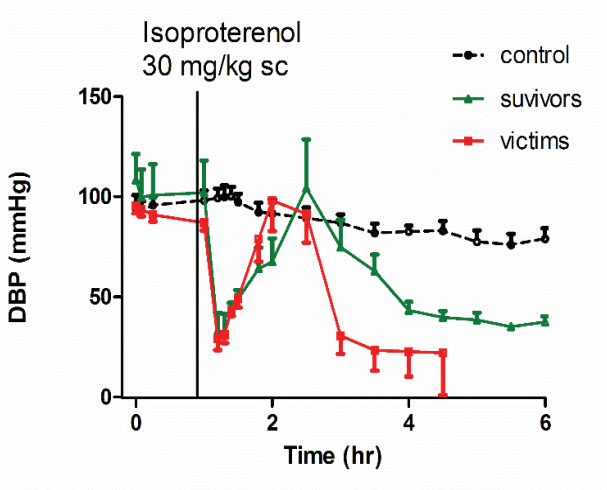
§ $P < 0.01$; §§$P < 0.001$; §§§$P < 0.0001$, significantly different from after exercise

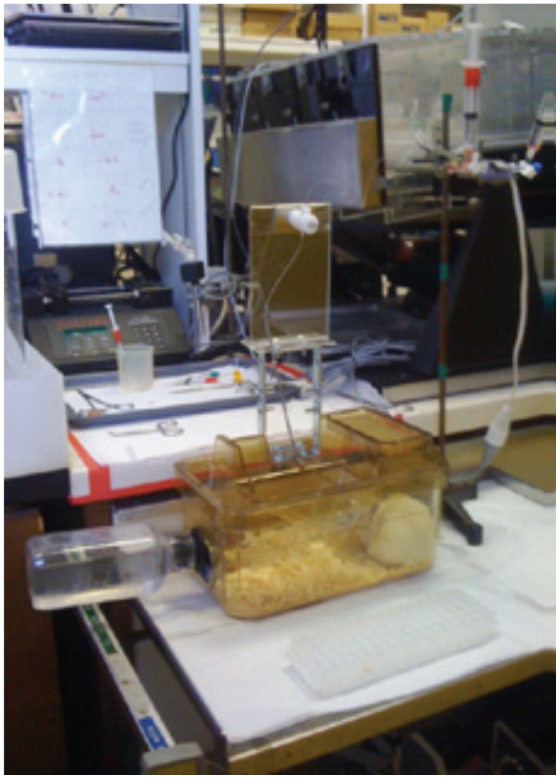
The examined individuals were subjected to a continuous effort test with progressively increasing intensity (up to a refusal) on a cycloergometer.

Acute MI Model induced by Isoproterenol

Yeung, PK and Seeto, D. A study of the effect of isoproterenol on red blood cell concentrations of adenine nucleotides in a freely moving rat model in vivo. Cardiovascular Pharmacology : Open Access 2 (1): 102 , 2013.







- Isoproterenol (30 mg/kg) by sc injection
- 10 blood samples taken (0.3 mL each) for measurement of biomarkers
- 50 % mortality

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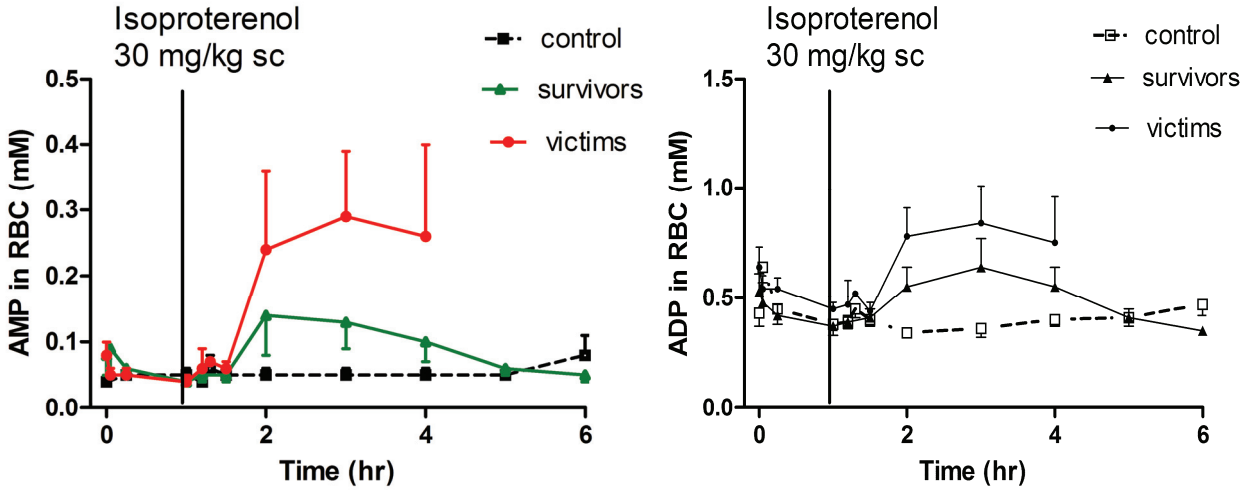

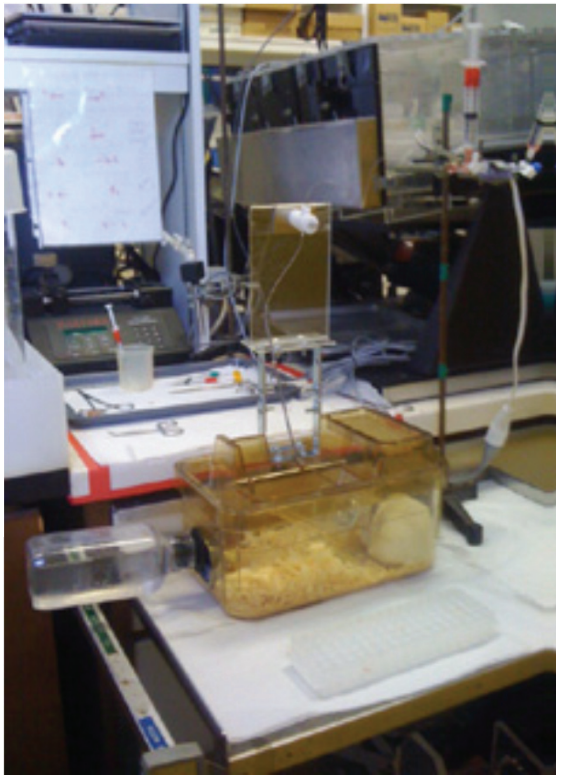

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Effect of Cardiovascular Injury on ATP and Adenosine Metabolism in RBC

Yeung, P. K. et al. Effect of Cardiovascular Injury on Catabolism of Adenosine and Adenosine 5-Triphosphate in Systemic Blood in a Freely Moving Rat Model In Vivo. Drug Metabolism Letters. 2016; 10(3)219-226.

Baseline Concentrations

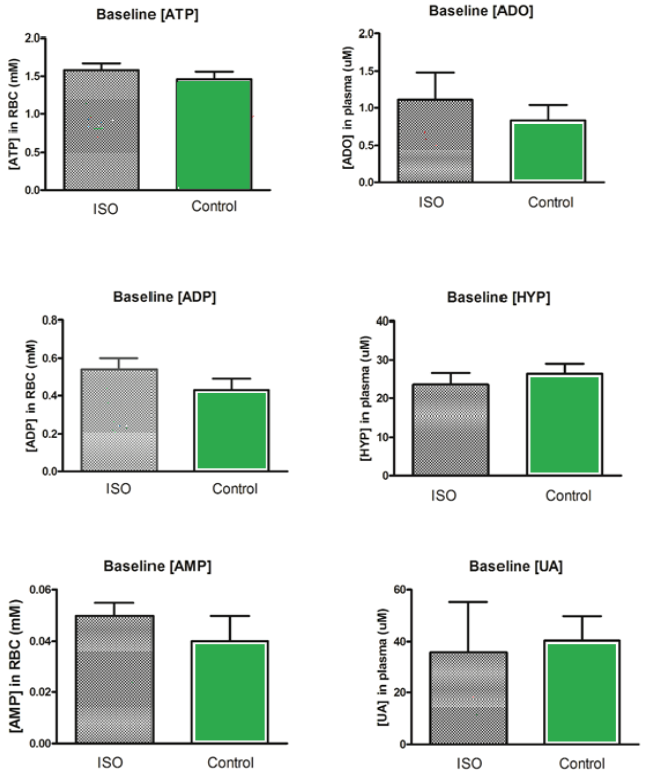


Figure1A. Baseline concentrations of ATP and its catabolites

After Isoproterenol Injection (30 mg/kg ip)

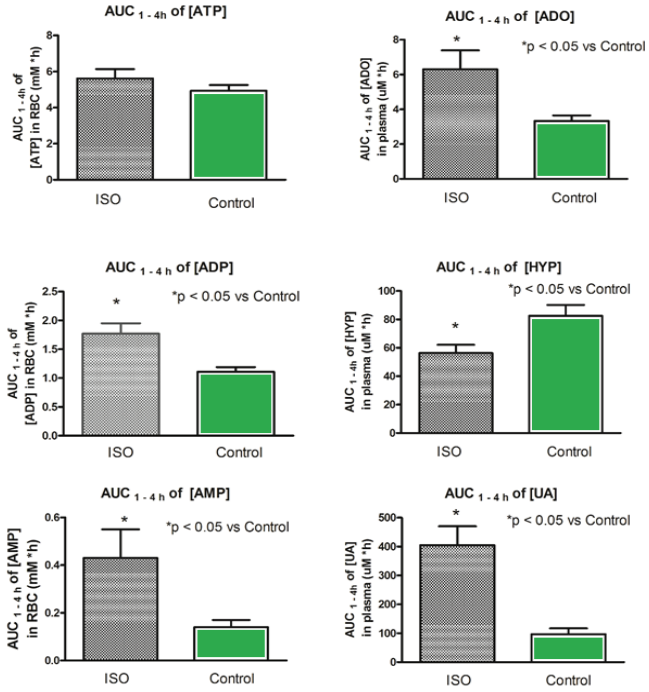


Figure 1B. Area under the curves (AUCs) of ATP and its catabolites after isoproterenol

Effect of Cardiovascular Injury on ATP and Adenosine Metabolism in RBC

Yeung, P. K. et al. Effect of Cardiovascular Injury on Catabolism of Adenosine and Adenosine 5-Triphosphate in Systemic Blood in a Freely Moving Rat Model In Vivo. Drug Metabolism Letters. 2016; 10(3)219-226

- **Tmax of adenosine (ADO) and uric acid (UA) after isoproterenol was shorter (ca 1hr) than the Tmax of ADP and AMP after isoproteremol (ca. 2 hr)**
- **ADO and UA in the plasma pool were produced from other sites in addition to the RBC**

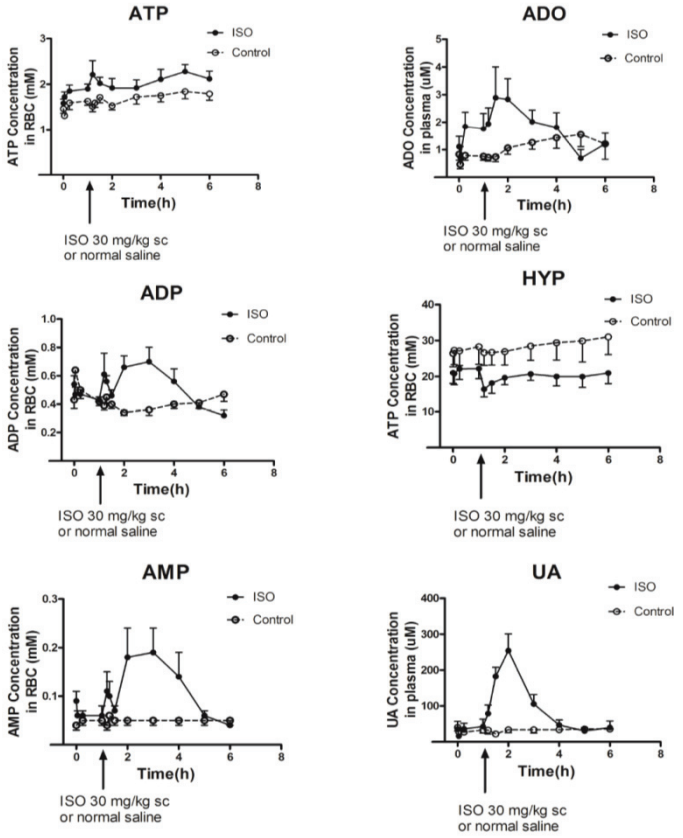
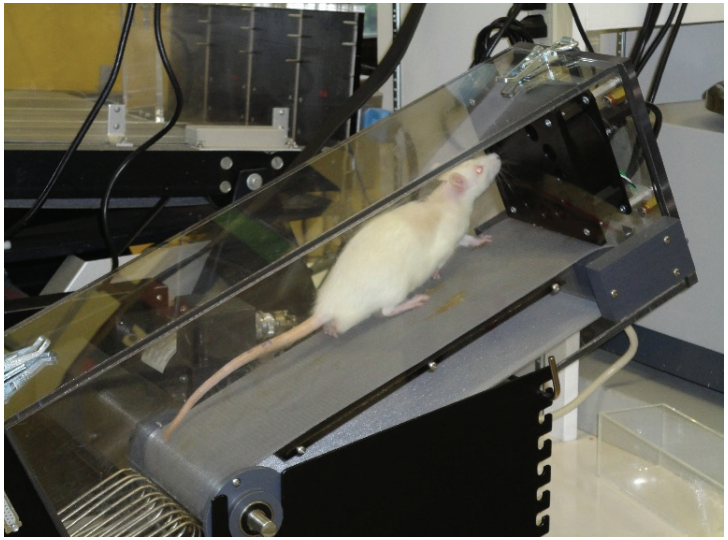


Figure 3. Circulating concentrations of ATP and its catabolites in response to isoproterenol (ISO). Values shown are mean and S.E.M.

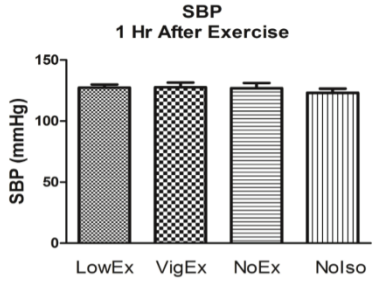
Rat Model for Exercise Preconditioning Study

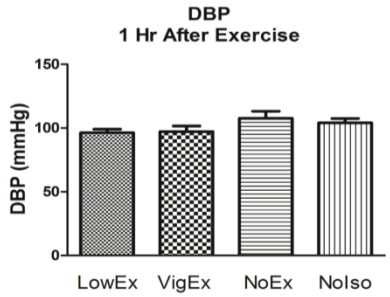
Effect of Exercise Pre-conditioning on Cardiovascular Hemodynamics and ATP Metabolism in RBC

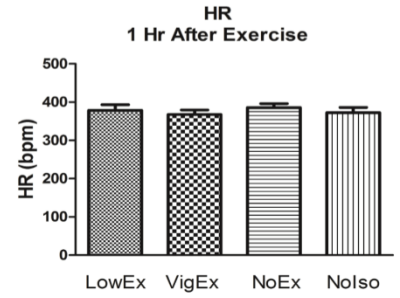
Yeung, P. K et al. A Pilot Study to Assess Adenosine 5′-triphosphate Metabolism in Red Blood Cells as a Drug Target for Potential Cardiovascular Protection. Cardiovasc Hematol Disord Drug Targets. 2016; 15(3)224-32.

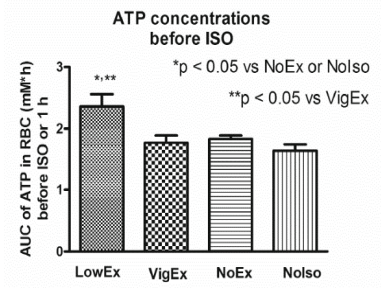


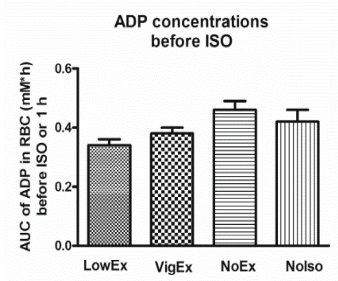
LowEx = 15 min at 10 m/m and 10% grade
Mortality = 2 of 7
VigEx = 15 min at 14 m/min and 22% grade
Mortality = 2 of 8
NoEx Mortality = 5 of 10
NoIso Mortality = 0 of 10

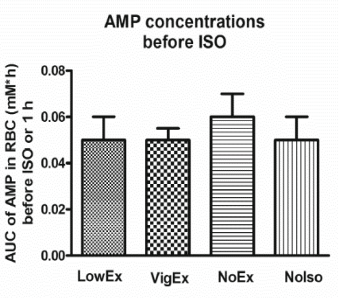






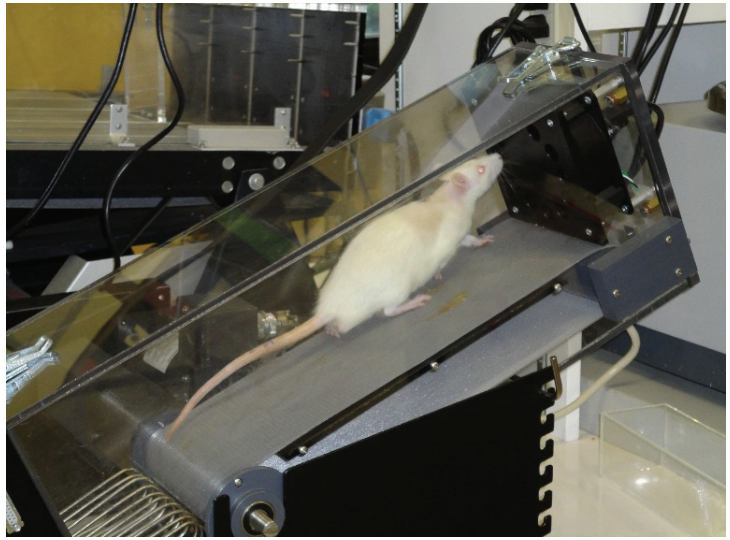


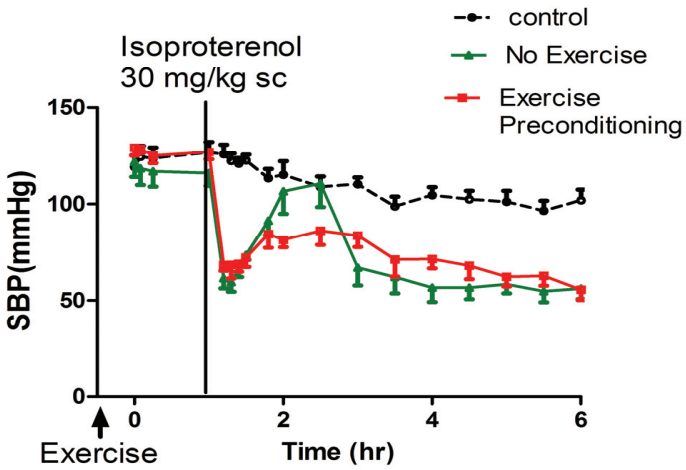


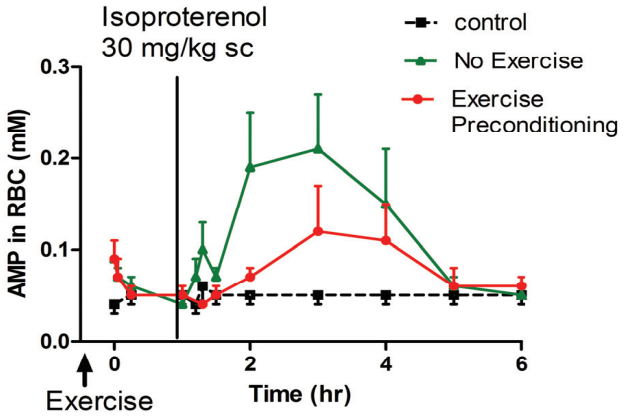


Effect of Exercise Preconditioning (VigEx) on Cardiovascular Protection

Yeung, P. K et al. A Pilot Study to Assess Adenosine 5'-triphosphate Metabolism in Red Blood Cells as a Drug Target for Potential Cardiovascular Protection. Cardiovasc Hematol Disord Drug Targets. 2016; 15(3)224-32.







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VigEx = 15 min at 14 m/min and 22% grade
Mortality = 2 of 8
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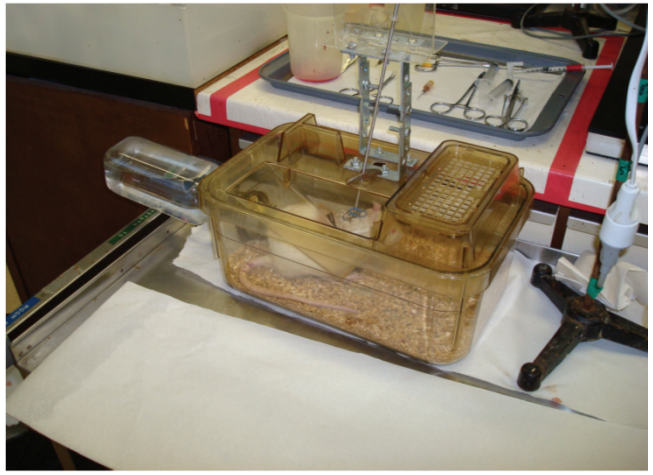
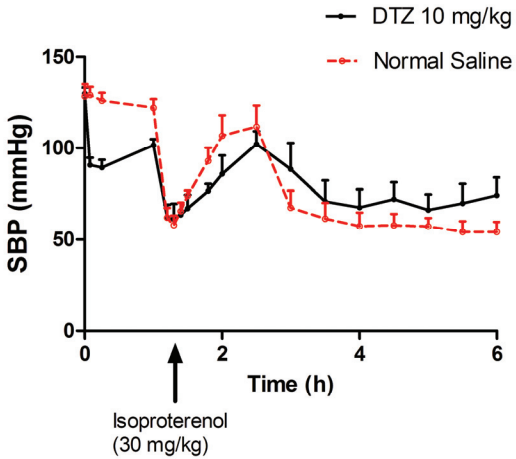
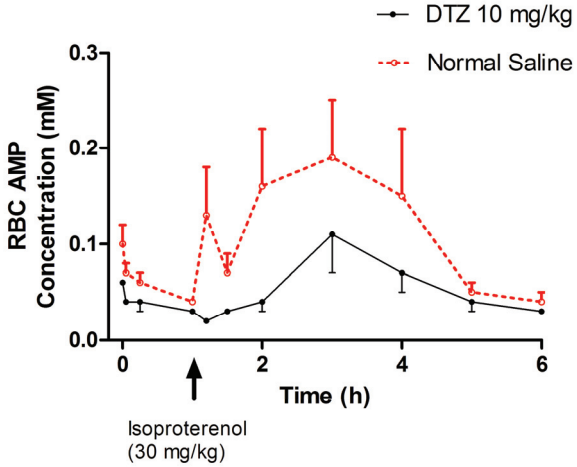
Effect of Diltiazem (DTZ) on cardiovascular toxicities induced by isoproterenol

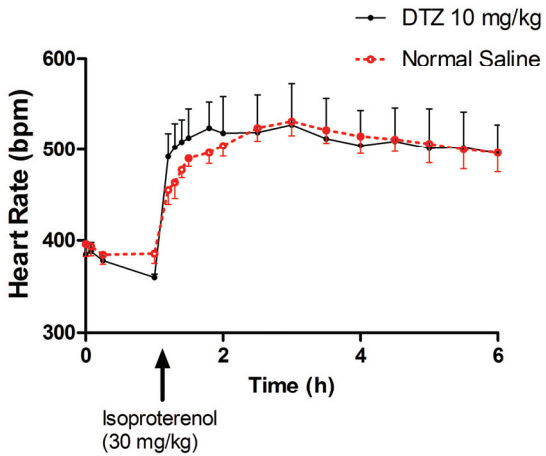
Yeung, PK.et al. Diltiazem Reduces Mortality and Breakdown of ATP in Red Blood Cell Induced by Isoproterenol in a Freely Moving Rat Model in Vivo . Metabolites. 2014; 4(3)775-789.





Mortality (Control) = ca 50%





Mortality (DTZ) = < 20%

Conclusions

- **ATP metabolism in RBC is potential biomarker for post-exercise hypotension**
- **Breakdown of ATP in the RBC is a potential biomarker for serious cardiovasculcar toxicity and/or mortality**
- **Rebound of blood pressure induced by isoproterenol is a potential biomarker for serious cardiovascular toxicity**
- **Preserving ATP in the RBC is a potential drug target for cardiovascular protection**

Challenges and Opportunities for ATP metabolism as Biomarker target

Challenges

- Instability of ATP and adenosine in blood samples.
- Blood samples need to be collected carefully to avoid damage to blood cells.
- Blood samples need to be processed immediately after collection using a suitable "Stopping Solution"

Opportunities

- Disease and health management:
  - May be a measure of "Inner Energy", "Reserves", and "Cardiovascular homeostasis"
  - Cardiovascular and metabolic diseases, cancer, aging, stroke and other neurodegenerated diseases.
- Drug development:
  - Cardiovascular protective agents (ARB, ACEI, CCB, rennin and thrombin inhibitor, anti-platelet agent, B-blocker, ant-coagulant, NHP, and others)
  - Anti-cancer agents and cardiovascular toxicities
  - Antibiotics and anti-inflammatory agents
- Complementary medicine:
  - Natural health products.
  - Traditional Chinese medicines
  - Energy supplements

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Pharmacokinetics & Metabolism Laboratory

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