



UiT The Arctic University of Norway

Treatment of rewarming shock with PDE-inhibitors - Temperature dependent effects on transport and metabolism of cAMP and cGMP

Selli AL, Kalasho A, Smaglyukova N, Kondratiev T, Lyså R, Sager G, Tveita T, Ravna AW, Dietrichs ES

Experimental and Clinical Pharmacology Research Group, Department of Medical Biology, UiT The Arctic University of Norway, Tromsø, Norway

Introduction

- Hypothermia – below 35°C
- Rewarming shock contributing to 25-40% mortality
- Accidental and therapeutic hypothermia
- cAMP and cGMP modulates cardiovascular function

	cAMP	cGMP
Metabolizing enzyme	PDE3	PDE5
Extrusion pump	ABCC4	ABCC5



Ullstinden December 8th 2018, -13°C

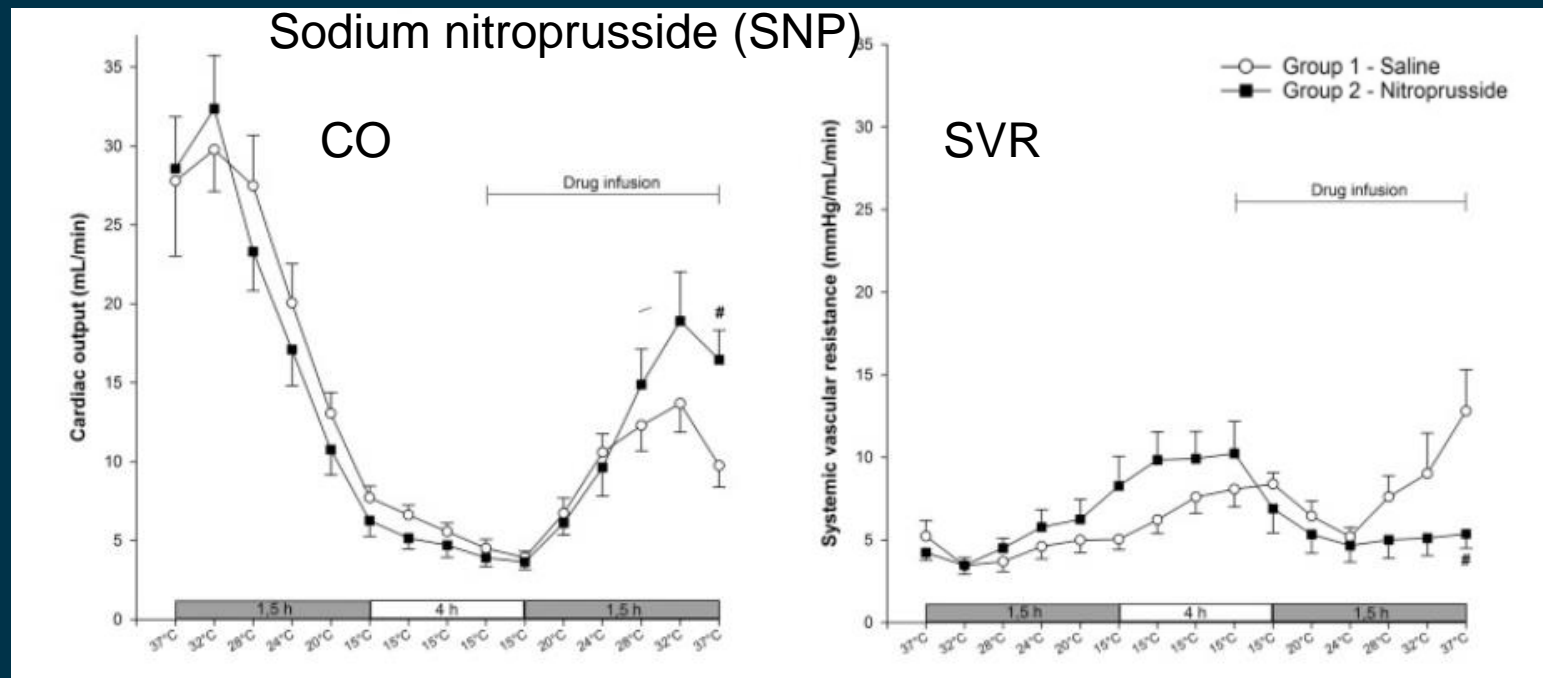
Objectives

- Pharmacokinetic properties of 6 PDE-inhibitors during hypothermia
- Cellular extrusion, PDE-inhibition and intracellular access
- Sildenafil (Viagra), Milrinone, Levosimendan, Amrinone, Pentoxifylline, Vardenafil
- Clinical relevance



cGMP increase

- Vasodilation, reducing afterload
- Shown beneficial effects on cardiac output

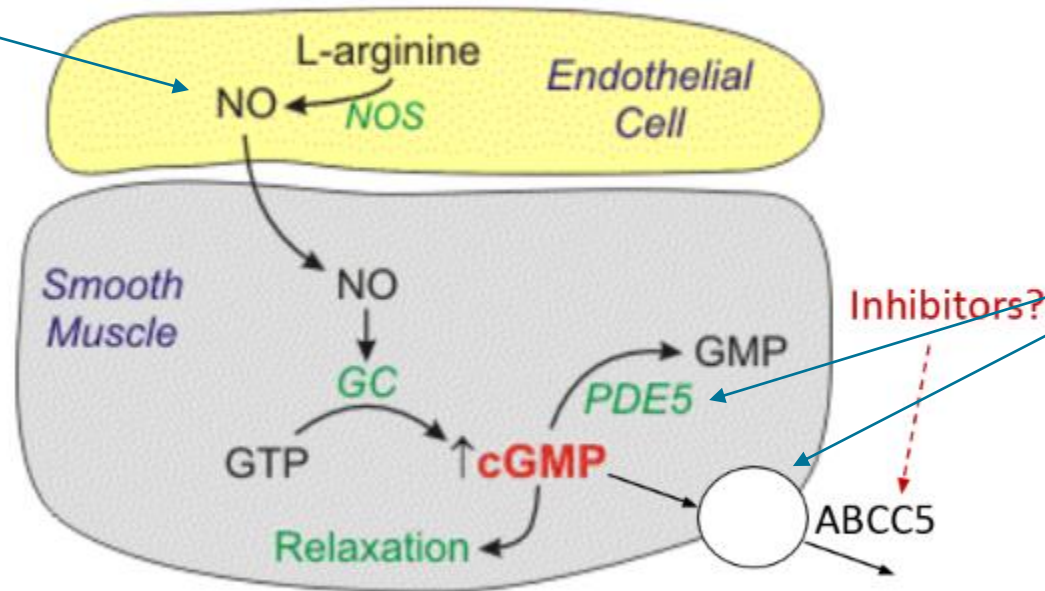


Håheim B, Kondratiev T, Dietrichs ES, Tveita T: The beneficial hemodynamic effects of afterload reduction by sodium nitroprusside during rewarming from experimental hypothermia. *Cryobiology* 2017, 77:75.

The role of cGMP

SNP

Vascular smooth muscle



Sildenafil

Abbreviations: NO, nitric oxide; NOS, nitric oxide synthase; GC, guanylyl cyclase; PDE5, cGMP-dependent phosphodiesterase (type 5)

Illustration by Erik Sveberg Dietrichs

Methods

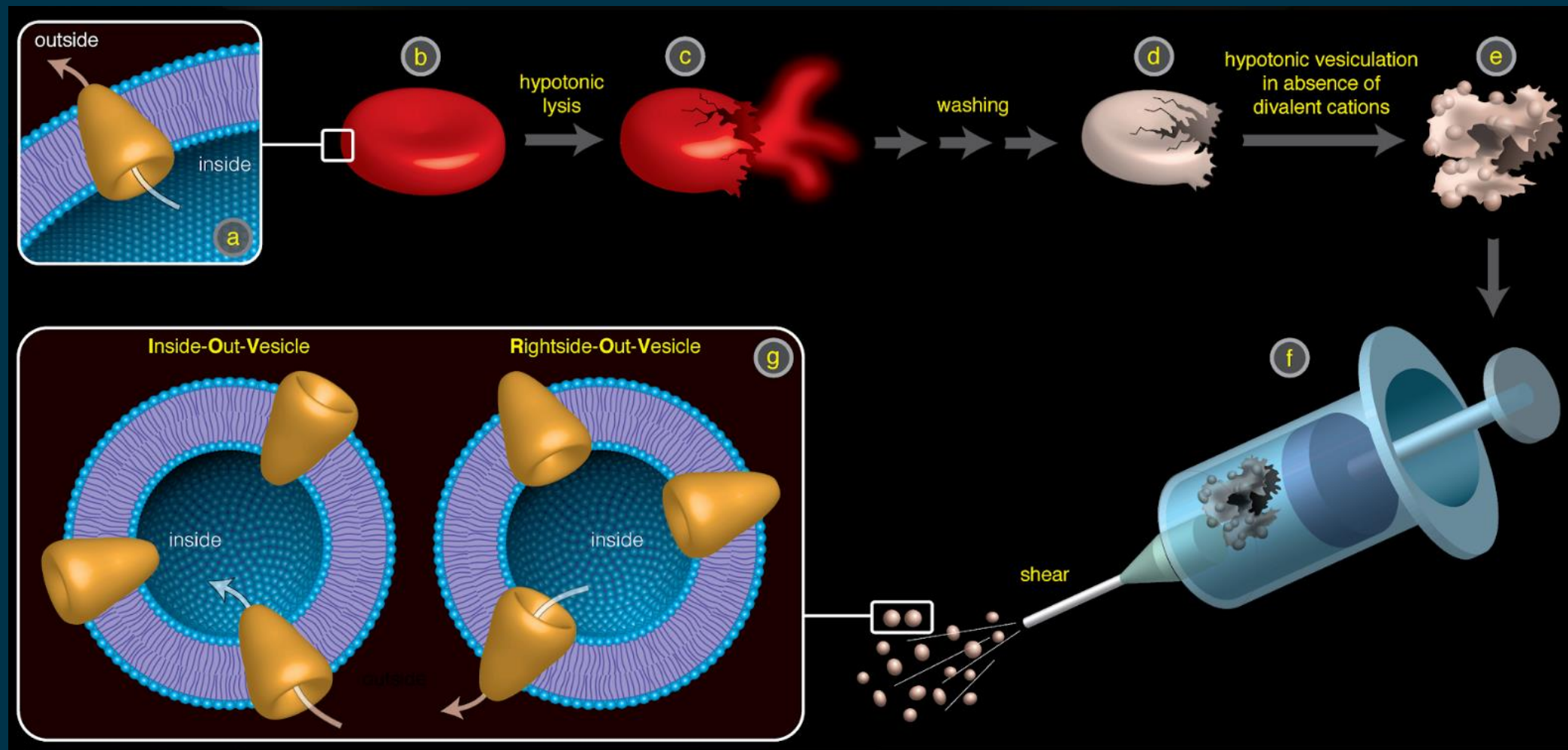
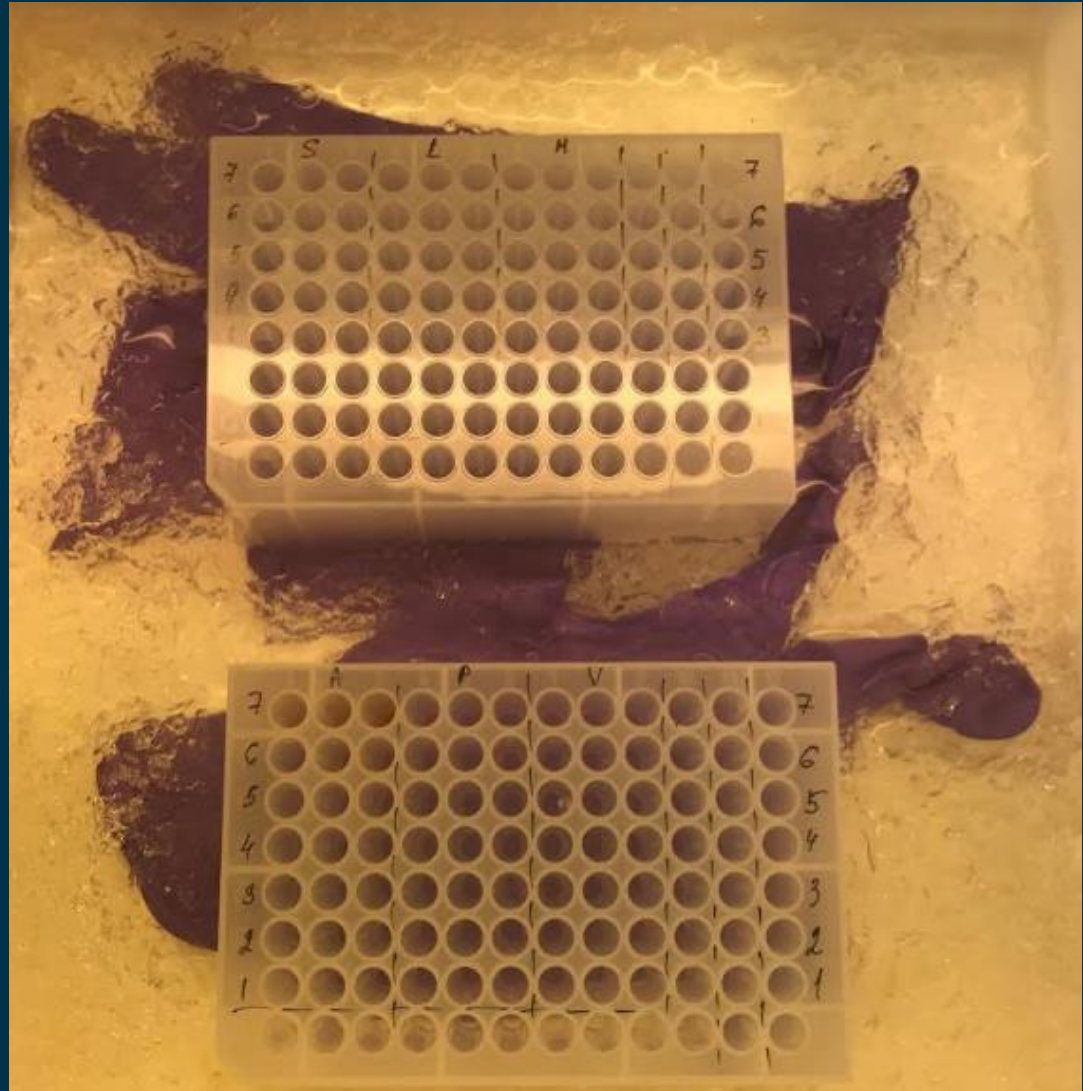
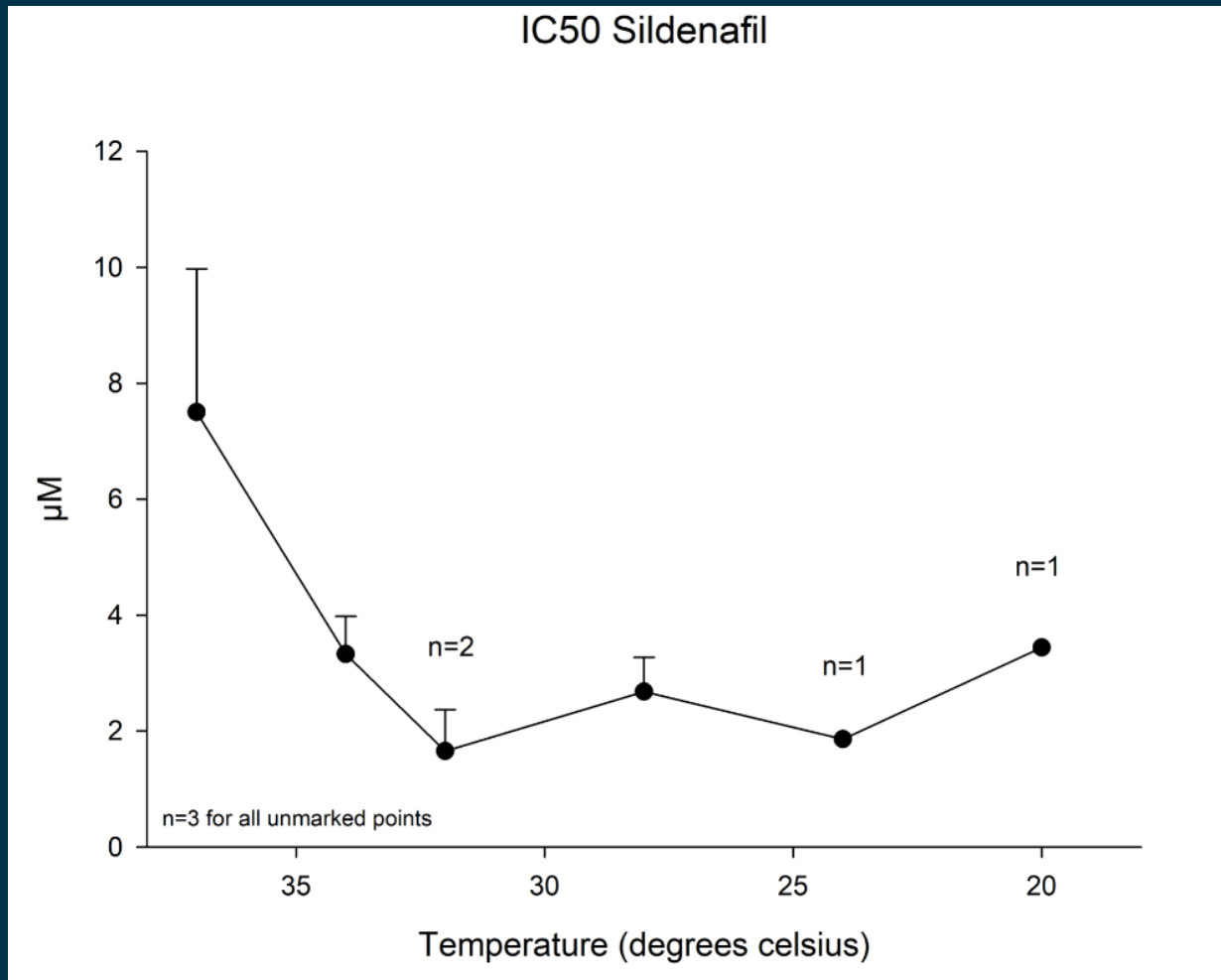


Illustration of inside-out-vesicles by Roy Lysaa

Cellular extrusion



IC-50 values



Mean IC-50 values for Sildenafil

IC-50: concentration at which the drug has reduced cGMP transport through the efflux pumps by 50%.

Conclusion

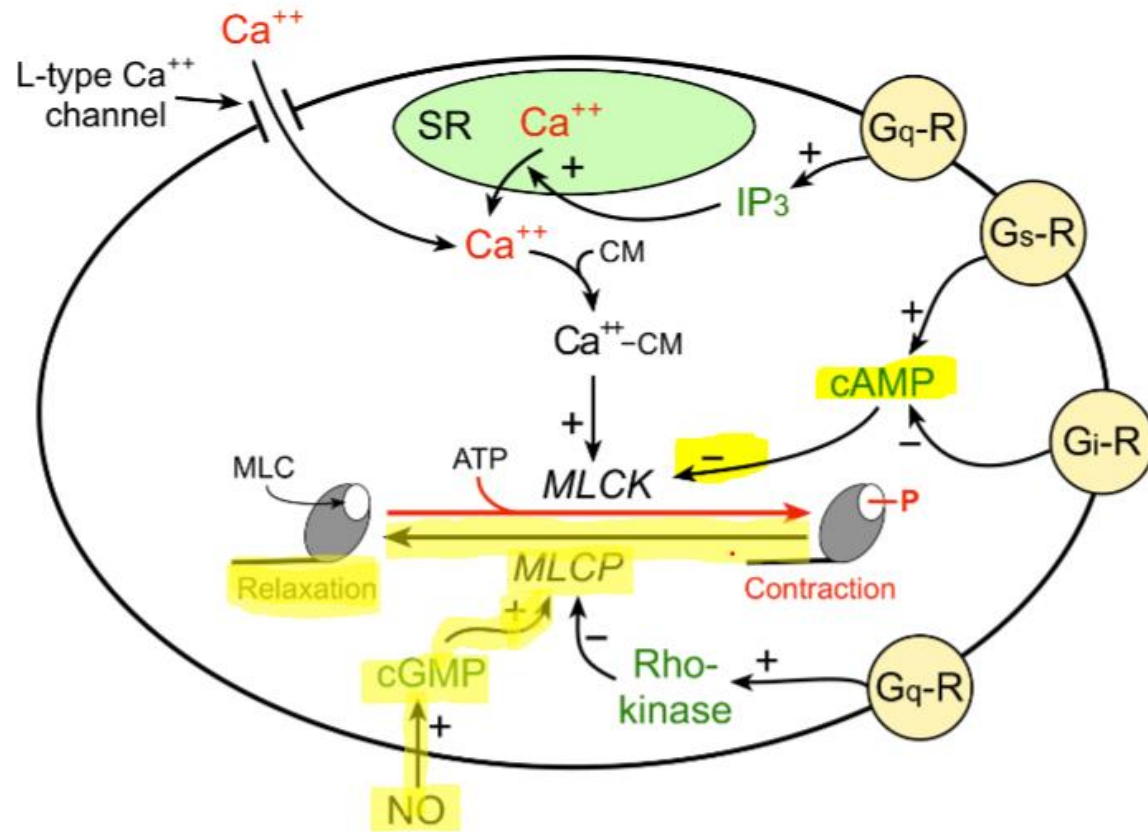
- Preliminary results
- Lower IC-50 values at lower temperatures?
- Further investigation
- PDE-inhibition and intracellular access

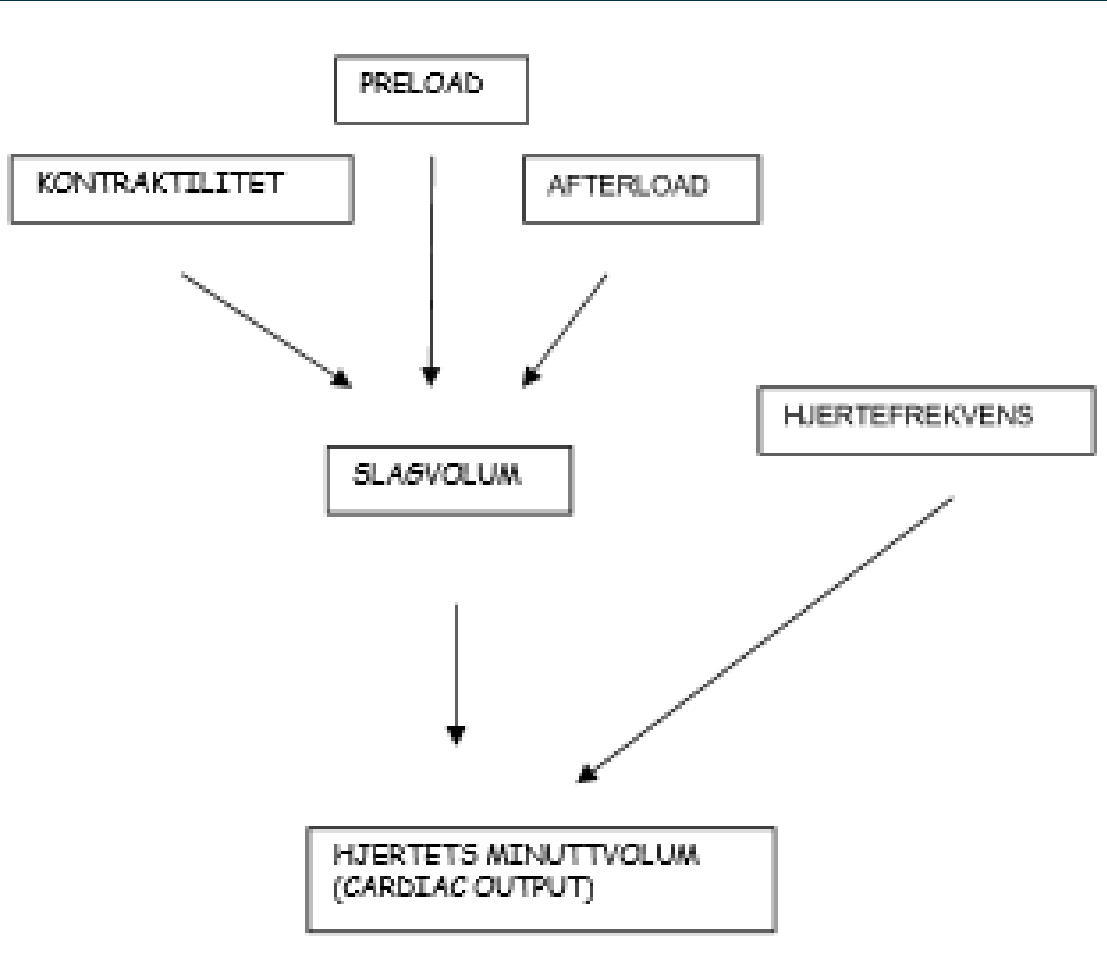
Acknowledgements

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- Erik Sveberg Dietrichs



- Har studiedesignet noen begrensninger?
- Er det noen svakheter?
- Er det noe vi ikke har gjort eller inkludert i studien som kunne vært relevant?
- Hva slags konsekvenser vil mine forskningsresultater kunne ha?





- PDE5-inhibitors: Sildenafil and Vardenafil
- PDE3-inhibitors: Milrinone, Amrinone and Levosimendan (calcium sensitizer)
- Unselective PDE-inhibitor: Pentoxifylline