

The Case of POTS

Jesper Mehlsen

Syncope Center

Bispebjerg & Frederiksberg Hospitals

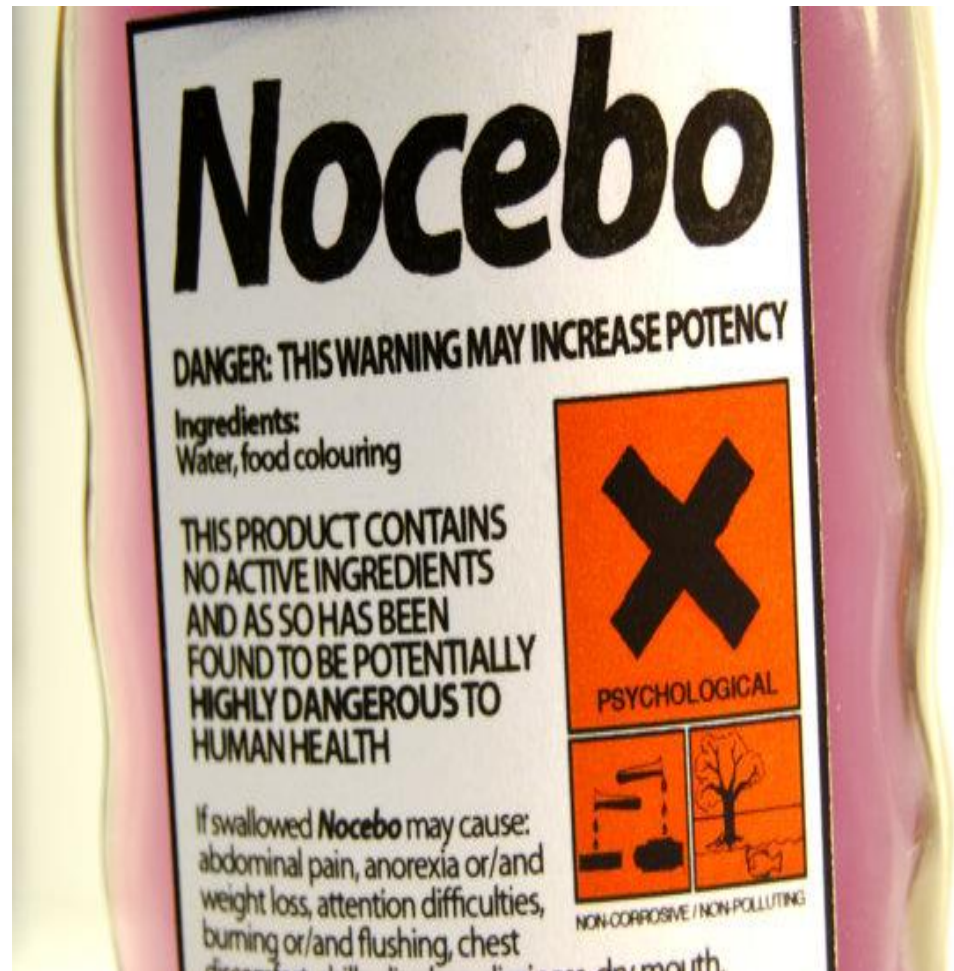
Case Report

- 18-year-old woman previously player on a national team
- Developed burning pain and muscle weakness within 7 days
- After 6 months progressive muscle weakness and a chronic, severe headache
- Gradually developed: orthostatic intolerance; fatigue; exercise intolerance; cognitive dysfunction; widespread involuntary muscle activity and severe pain
- Quit her studies. Lost weight (6 kg – BMI 19.5))
- Dependent on help 24/7
- Diagnosed with POTS

Is it Nocebo?

Despite containing no active ingredients whatsoever, Nocebo can cause a wide range of undesirable effects, from nausea to diarrhea, that is because it's potency lies entirely inside the human brain!

Nocebo merely suggests that it is bad for you, your brain and body does the rest!



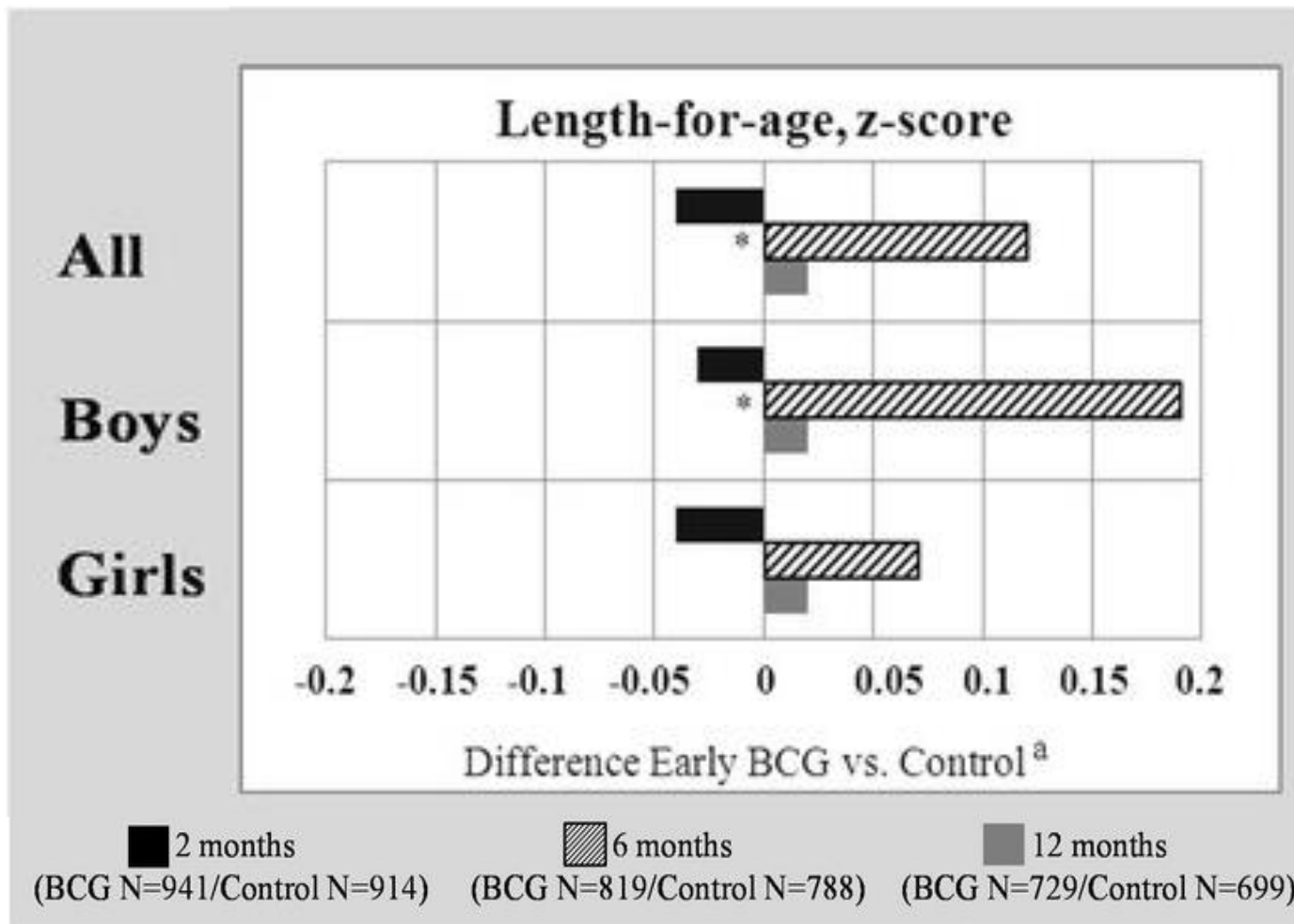
Or are there non-specific effects of vaccines?

Off-target effects of vaccines?

The heterologous effects of vaccines suggest that they can affect the immune response to organisms other than their pathogen-specific intended purpose. These effects are increasingly recognized as important biological processes by a growing group of immunologists and epidemiologists.

M. Saadatian-Elahi et al: Vaccine 2016 34:2923-30

Effect of early BCG-vaccination



Possible Nonspecific Effects of Diphtheria-Tetanus-Pertussis Vaccine.

P Aaby, H Ravn, CS Benn. Pediatr Infect Dis J 2016;35:1247–1257

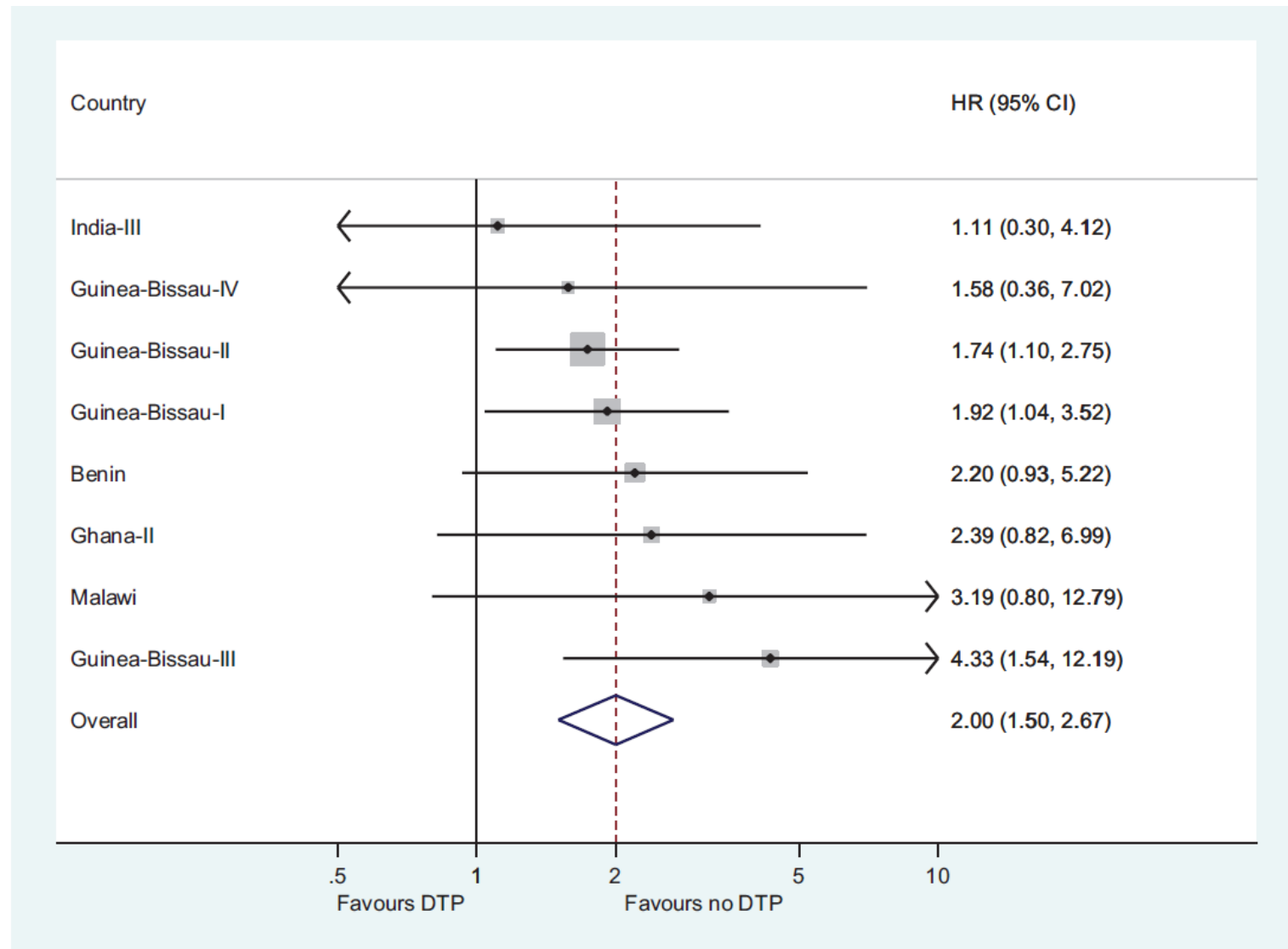


FIGURE 3. The mortality rate ratio for DTP-vaccinated versus DTP-unvaccinated children in studies with no survival bias. full color online

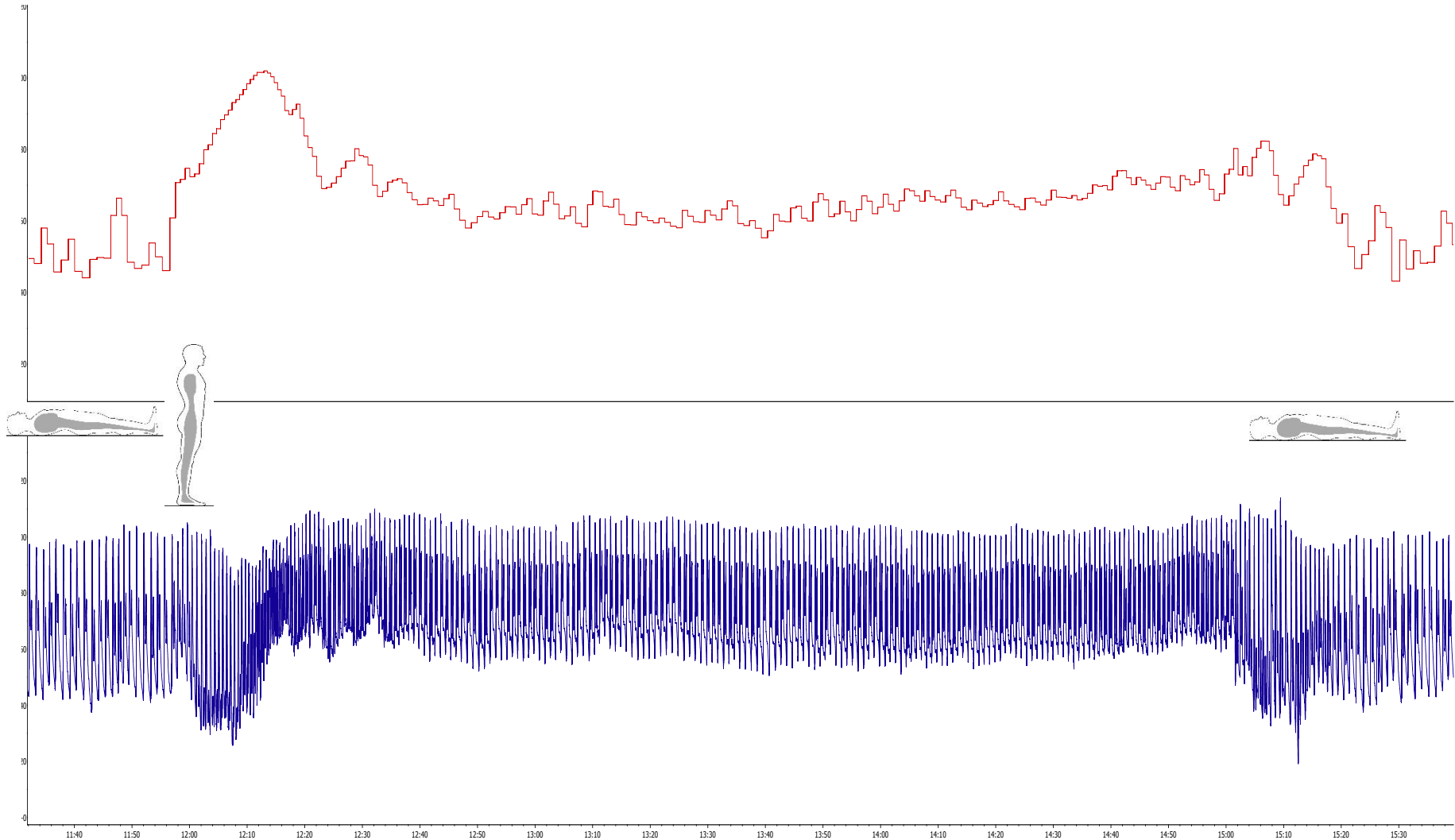
What have we seen?

- 782 patients referred for possible side-effects
- Age: 23 ± 8 years – range 12 - 73 years
- 689 seen so far
- Main symptoms:
 - Orthostatic intolerance
 - Headache
 - Fatigue/fatigability
 - Nausea/abdominal pain
 - Dysaesthesia
 - Involuntary muscular contractions

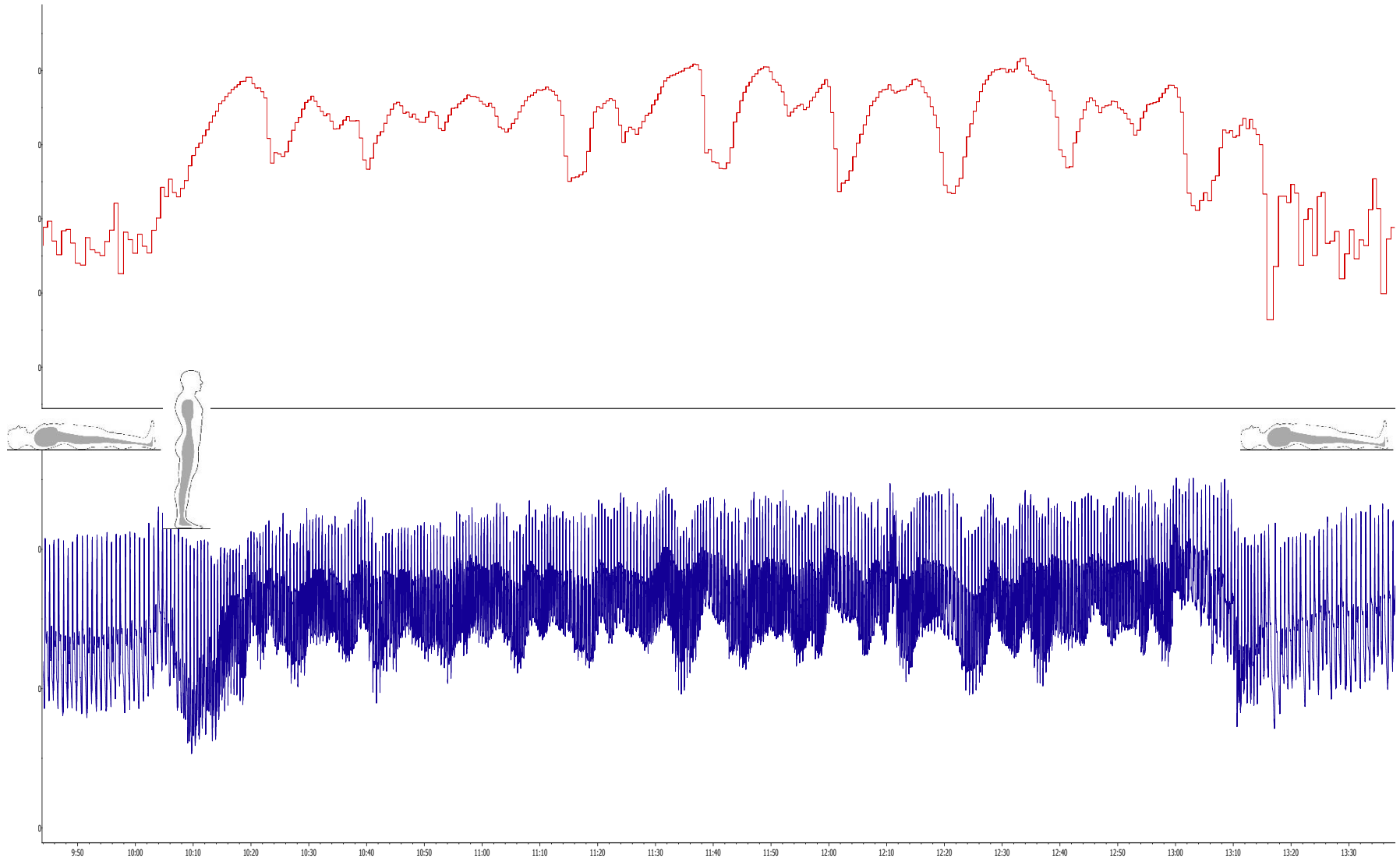
Characteristics in the publicized cohort

Diagnoses of POTS:	47%
Height:	168 cm
Body weight:	61 kg
BMI:	21,9
Symptoms after 1. vaccination	40%
Symptoms after 2. vaccination	35%
Symptoms after 3. vaccination	25%
Time to onset of symptoms:	11 days (0-58 days)
Physical activity level:	
Elite	63%
Medium	31%
Low	6%

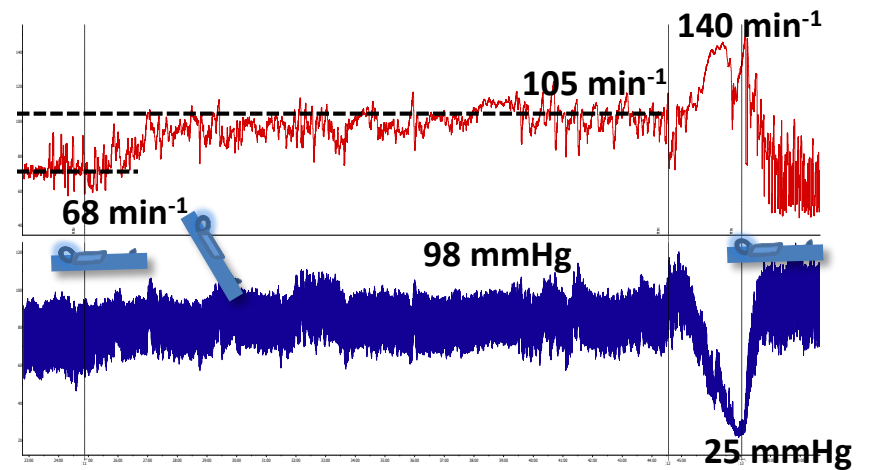
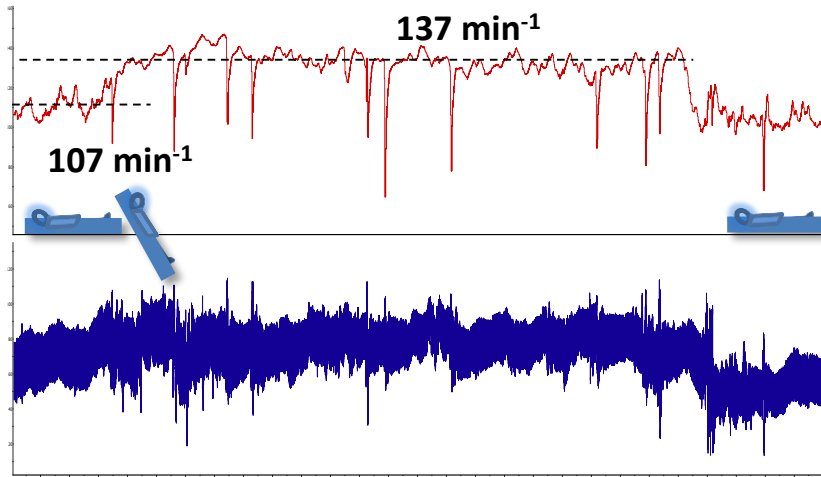
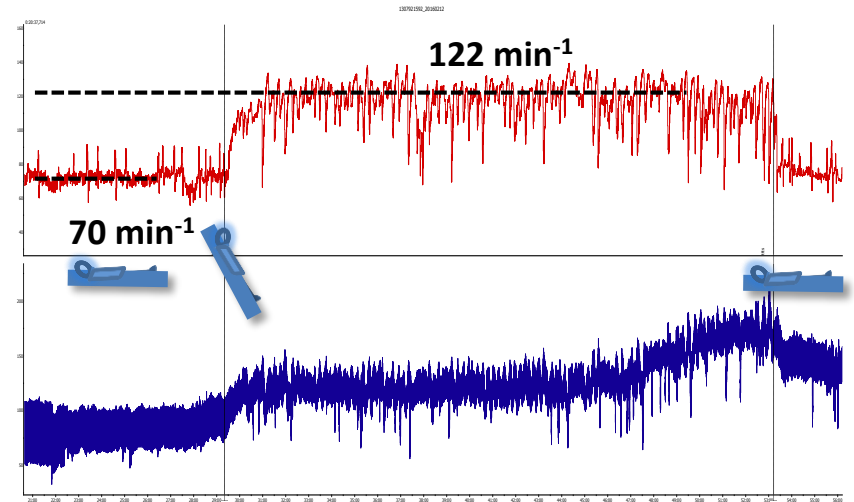
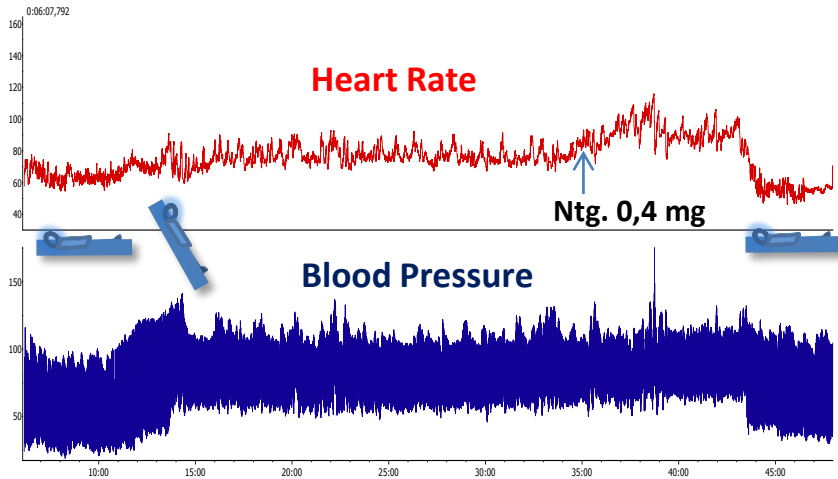
Active stand – Normal Subject



Active stand – POTS-patient



Head-up Tilt Test

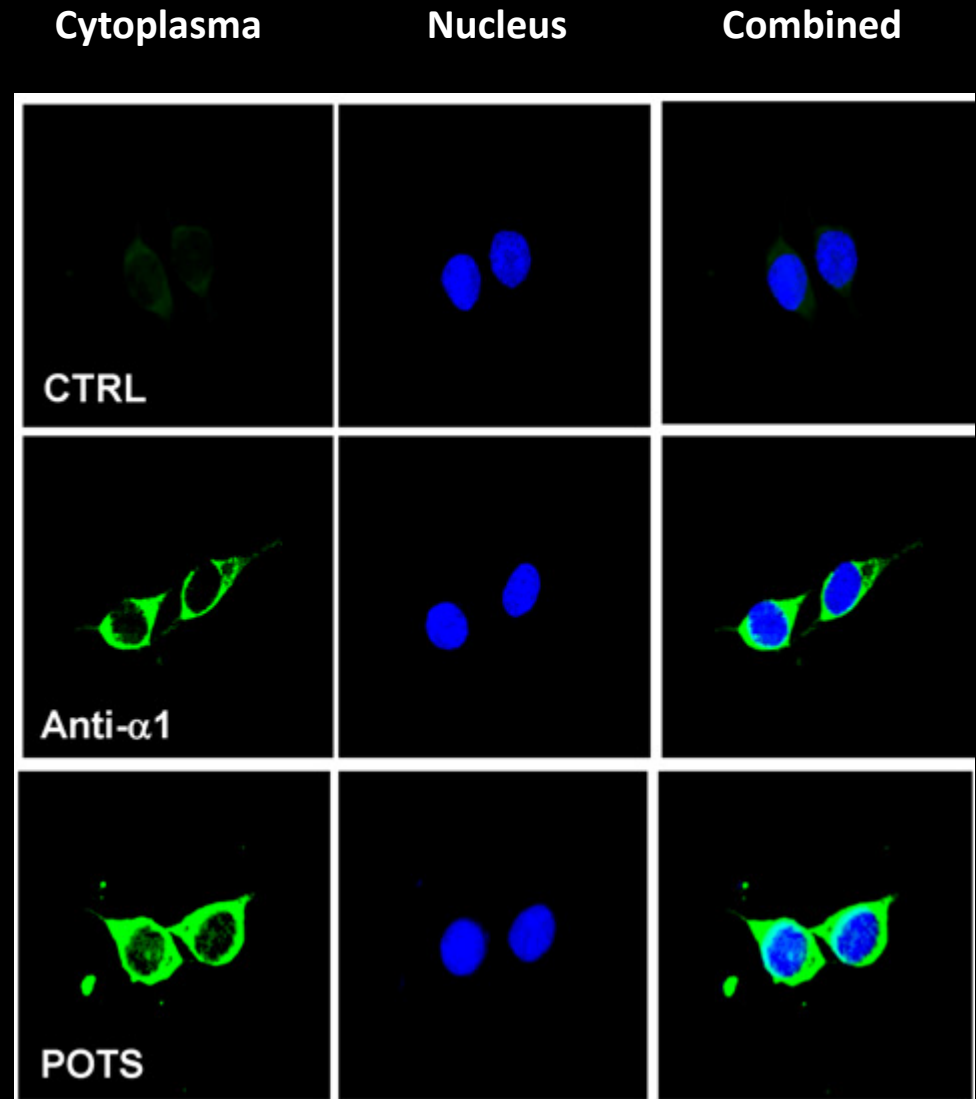


POTS and Vascular Alpha-1-receptors

Controls:
Weak coloring of cytoplasm (green)
Nucleus coloring (blue)

Addition of alpha-1-antibody:

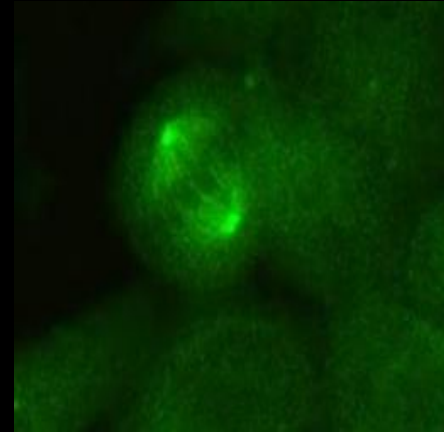
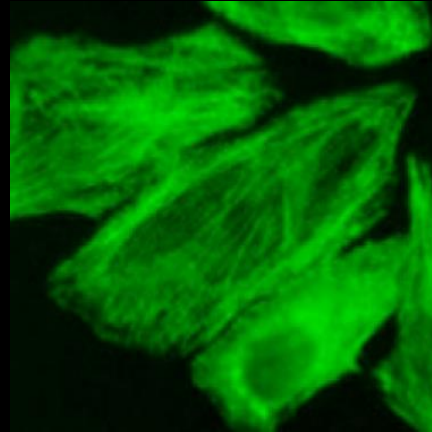
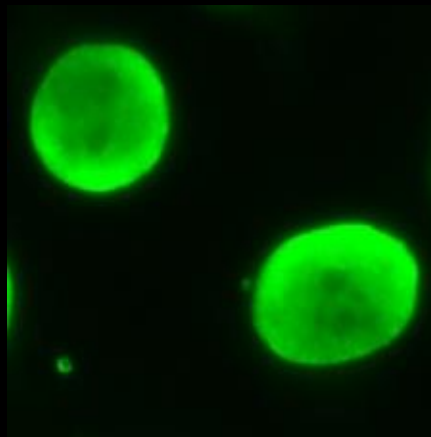
Addition of IgG from POTS-patient:



Autoimmune Disorder?

Antinuclear
antibodies (ANA)

Total &
Fractionated

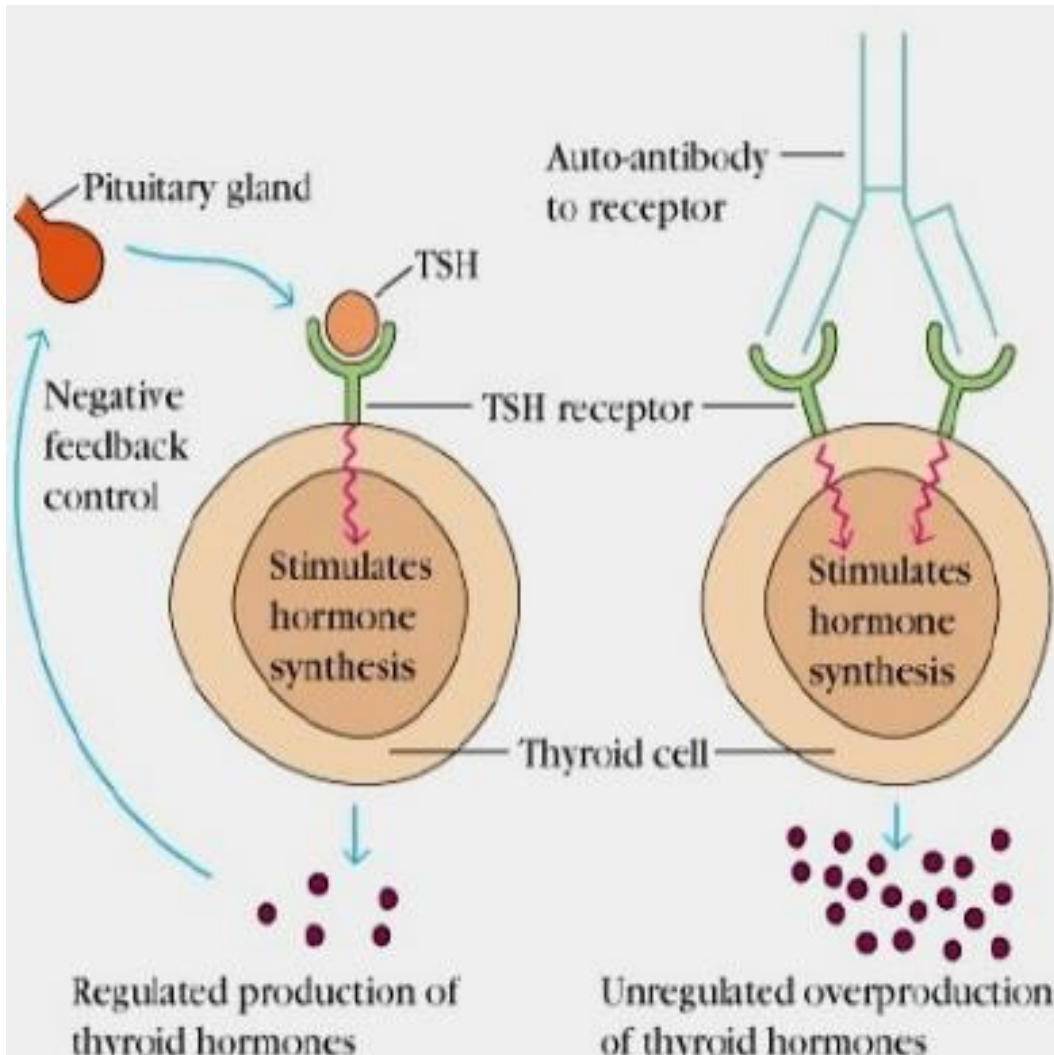


HPV vs Blood Donors

Samples	Positive	Antinuclear	Anticytoplasmic	Antimitotic
HPV (n=83)	59%	29%	10%	28%
Blood donors (n=289)	25%	20%	2%	2%
Fisher's test	***	ns	**	***
	p<0.0001	p=0.1339	p=0.0073	p<0.0001

Agonistic autoantibodies?

Ex: Graves Disease



Other condition with agonistic autoantibodies:

- Dilated cardiomyopathy
- Chaga's disease
- Preeclampsia
- Complex Regional Pain syndrome
- POTS
- Chronic Fatigue Syndrome

Agonistic Autoantibodies against G-protein coupled receptors

Receptor type	Disease	Prevalence (%)
Alpha ₁ -R	Hypertension	44
β ₁ -R	Dilated cardiomyopathy	80
β ₁ -R	Myocarditis	80
β ₁ -R	Chagas' disease	29
β ₂ -R	Chagas' disease	12
β ₂ -R	Allergic rhinitis	ND
AT ₁ -R		0
AT ₁ -R		33
AT ₁ -R		D
Muscarinic M ₂ -R		7
Muscarinic M ₂ -R	Dilated cardiomyopathy	25
5HT ₄ -R	Systemic lupus erythematosus	ND
Nicotinic AcCh-R	Myasthenia gravis	90
Glutamate receptor	Rasmussen's encephalitis, noninflammatory focal epilepsy, catastrophic epilepsy	ND
TSH-R	Grave's disease	>95

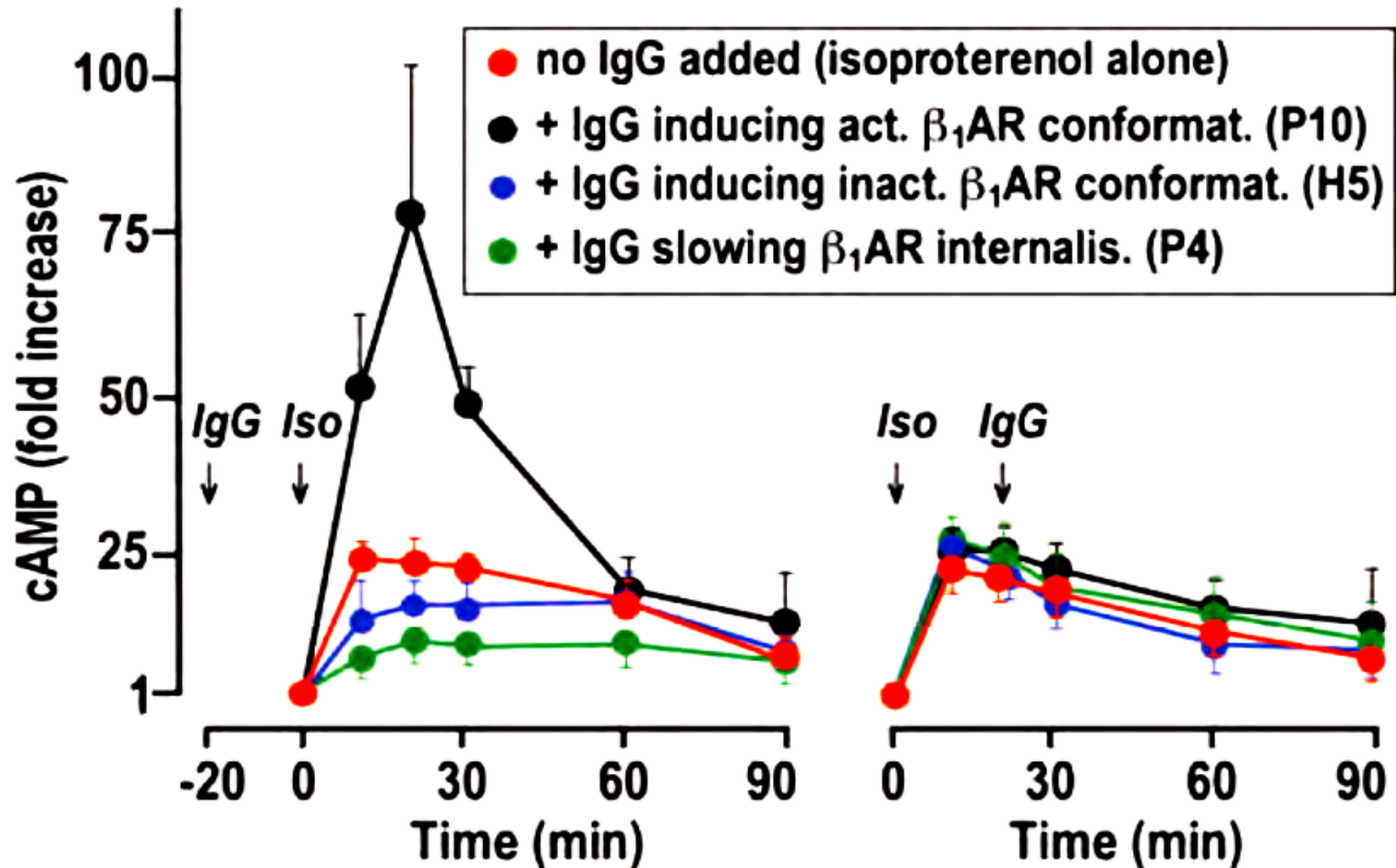
Our patients

β₂-R 54/56 97%

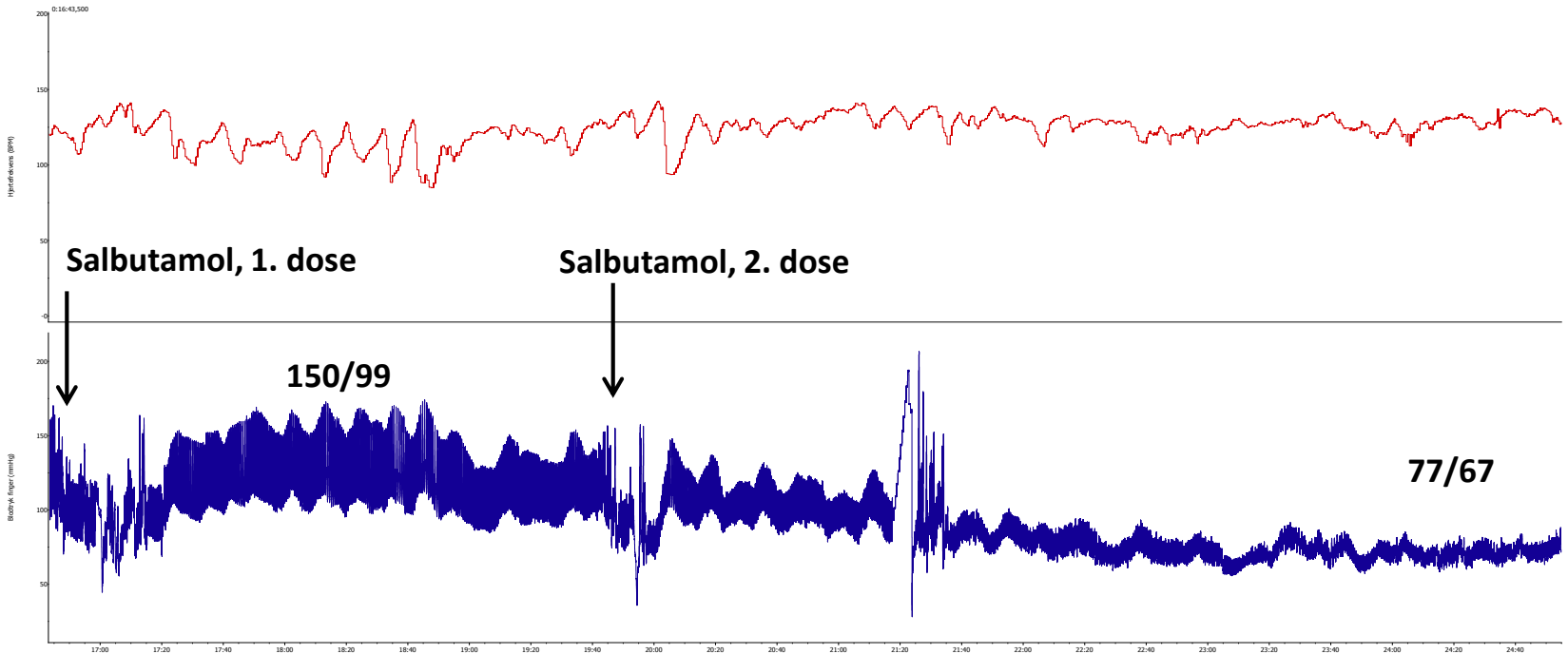
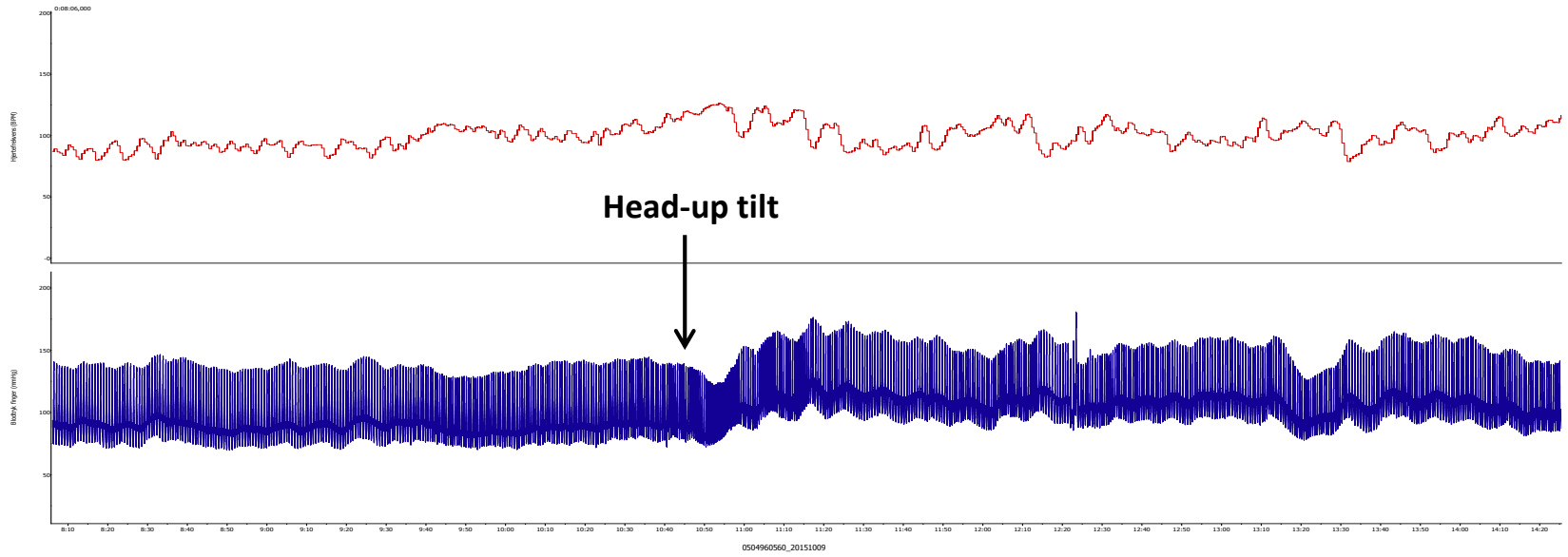
M₂-R 51/56 91%

Agonistic antibodies

Mechanism of Action



0504960560_20151009



Rearranging the Symptoms

- Stimulation of the sympathetic nervous system:
 - palpitation, shortness of breath, orthostatic intolerance
 - headache/migraine, visual disturbances
 - fatigue, cognitive dysfunction
 - disturbed sleep/insomnia
- Stimulation of the parasympathetic nervous system:
 - nausea
 - postprandial abdominal pain
 - hyperactive bladder dysfunction

Treatment

Current

- Propranolol to block beta-2-receptors
- Midodrine (Gutron) to stimulate alfa-1-receptors
- Fesoterodine (Toviaz) to block M2-receptors in the bladder
- Metoclopramide to block pyloric M2-receptors
- Salt and fluid to stabilize the orthostatic intolerance

Future

- Immune adsorption (Aferesis)
- Infusion of aptamer (BC007)
- Immuno-supression (Steroid, Rituximab)

Research Program

- Genetics and Autoantibodies
- Mitochondrial dysfunction
 - Based on fatigue, autonomic dysfunction, and pain
- Neuroinflammation
 - Based on headache, autonomic and sensory dysfunction, and involuntary muscular contractions
- Small fibre disease
 - Based on sensory and autonomic dysfunction

Conclusion

- Our preliminary studies point to an autoimmune condition occurring in a temporal association with HPV-vaccination
- The condition may not be specific for HPV-vaccination and may require additional genetic/environmental factors
- The autoimmunity seems to be directed against receptors in the autonomic nervous system



Thank you for your attention