Computational Model of the Cardiovascular System for Analysis of Spaceflight-Induced Orthostatic Intolerance

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Background:

- Cardiovascular problems following spaceflight have been encountered since the Mercury missions
- Drastically increased heart rates have been noted in upright tilt-table testing during the Gemini missions
- Post-spaceflight orthostatic intolerance was noted in Apollo astronauts for up to 3 days after landing
- Skylab (1970s) mission explored human physiology during long-term space missions
- Spacelab (1980s) provided a framework for studying human physiology with emphasis on various organs systems
- Neurolab (1998) explored several hypotheses regarding the the mechanisms underlying post-spaceflight OI.

⟶ OI still persists

Orthostatic Intolerance Syndrome:

Presenting symptoms:

- Lightheadedness
- Palpitations
- Fatigue
- Blurred Vision
- Dizziness
- Syncope

Clinical Findings:

- Drop in Mean Arterial Pressure
- DRAMATIC Increase in Heart Rate

… upon assumption of the upright posture.

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→ OI still persists

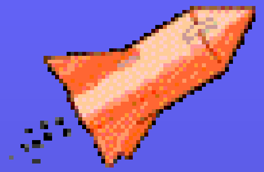
Problems:

- High variability in individual responses
- Small number of subjects studied
- Environmental effects unclear
- Conflicting experimental observations

Cardiovascular Problems Associated with Spaceflight:

- Orthostatic Intolerance upon Re-entry
- Arrhythmias
- Loss of Cardiac Mass
- Reduced Exercise Capacity
- Manifestation of Pre-Existing Cardiovascular Diseases

Transition from 1g to 0g:



Loss of gravitational gradients:

- Redistribution of volume
- Loss of intravascular volume
- Lack of regular exercise
- Lack of constant stimulation of reflex mechanisms

Hypotheses:

- Cardiac Atrophy
- Hypovolemia
- Downregulation of Effector mechanisms
- Muscle Atrophy / Changes in Properties of Leg Circulation
- ...

Rationale for Modeling:

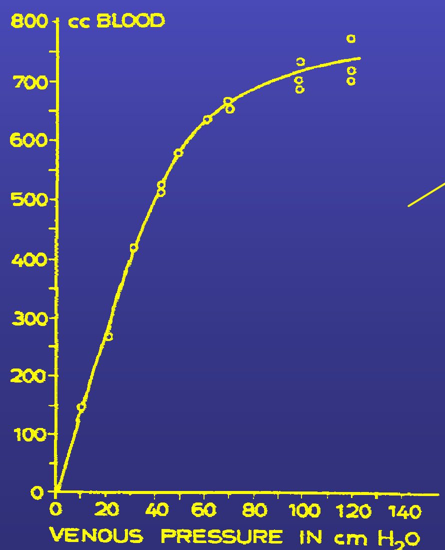
- Provides rational framework to interpret experimental results and test hypotheses
- Aids in predicting benefits of specific counter-measures

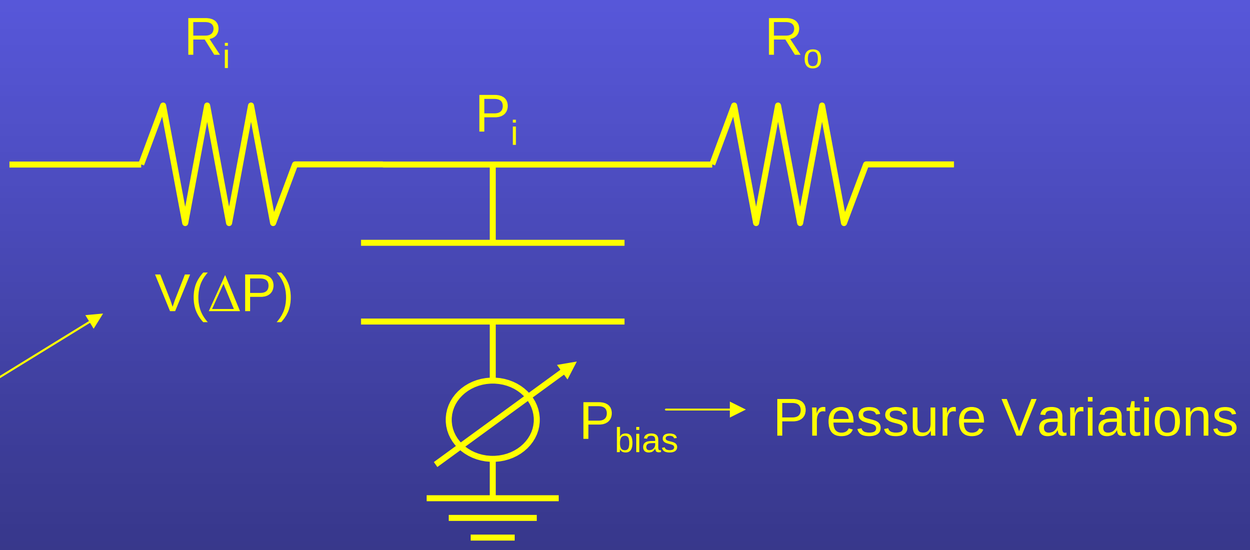
Goals:

- Simulate the short term (10 - 15 mins) response to orthostatic stress in normals and microgravity adapted individuals
- Test hypotheses concerning mechanisms of orthostatic intolerance
- Simulate effects of countermeasures

The Hemodynamic Model:

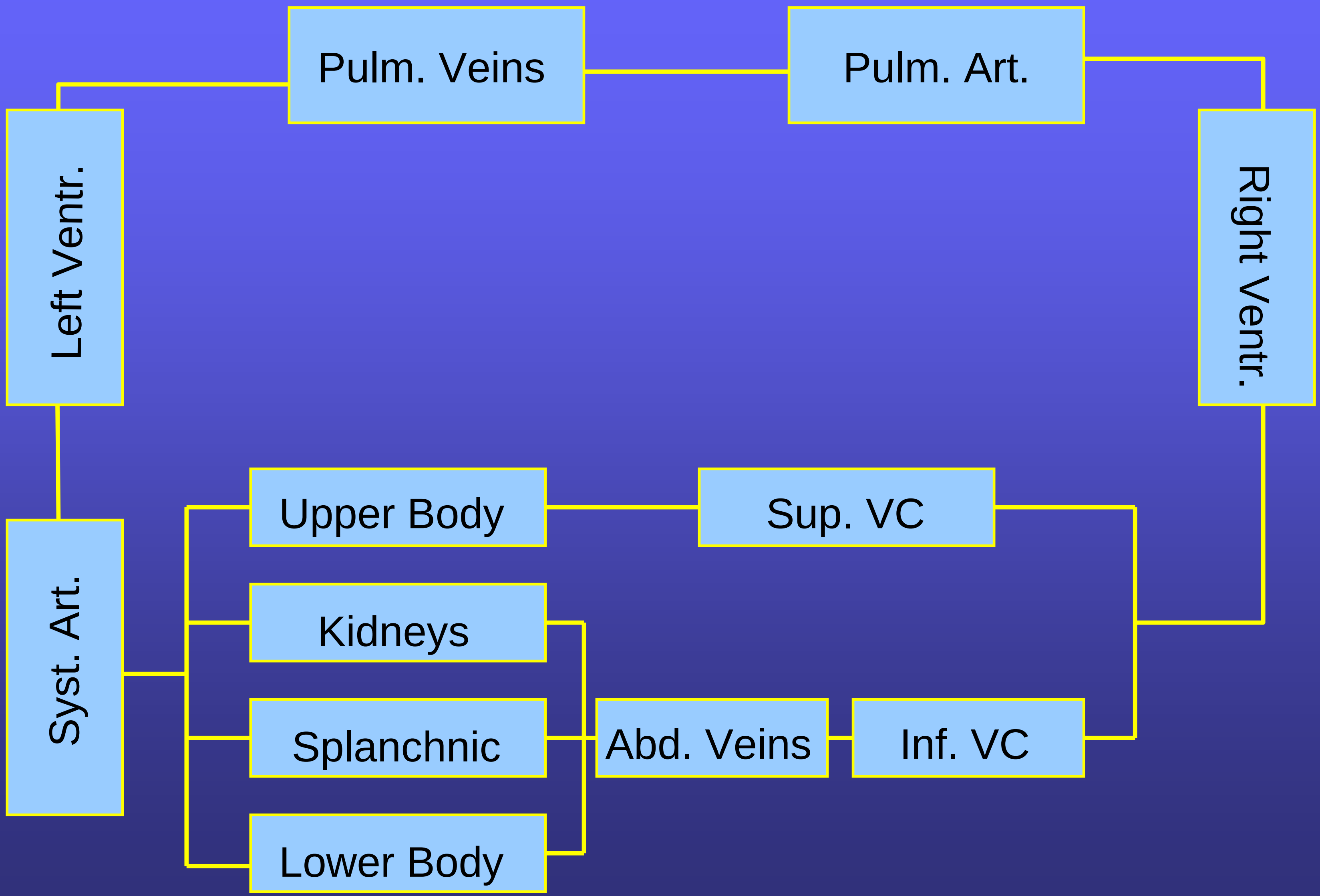
- Thirteen compartment lumped-parameter hemodynamic model





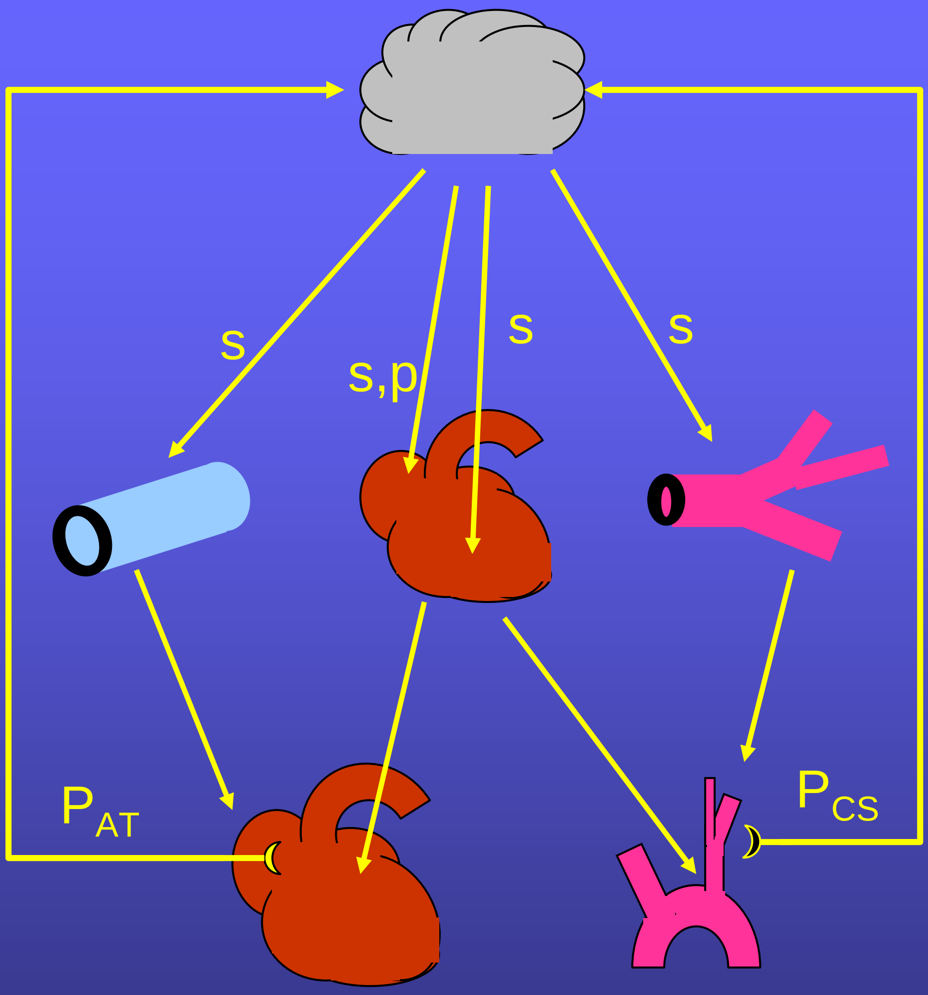
From:Gauer et al. in: Handbook of Physiology.

The Hemodynamic Model:

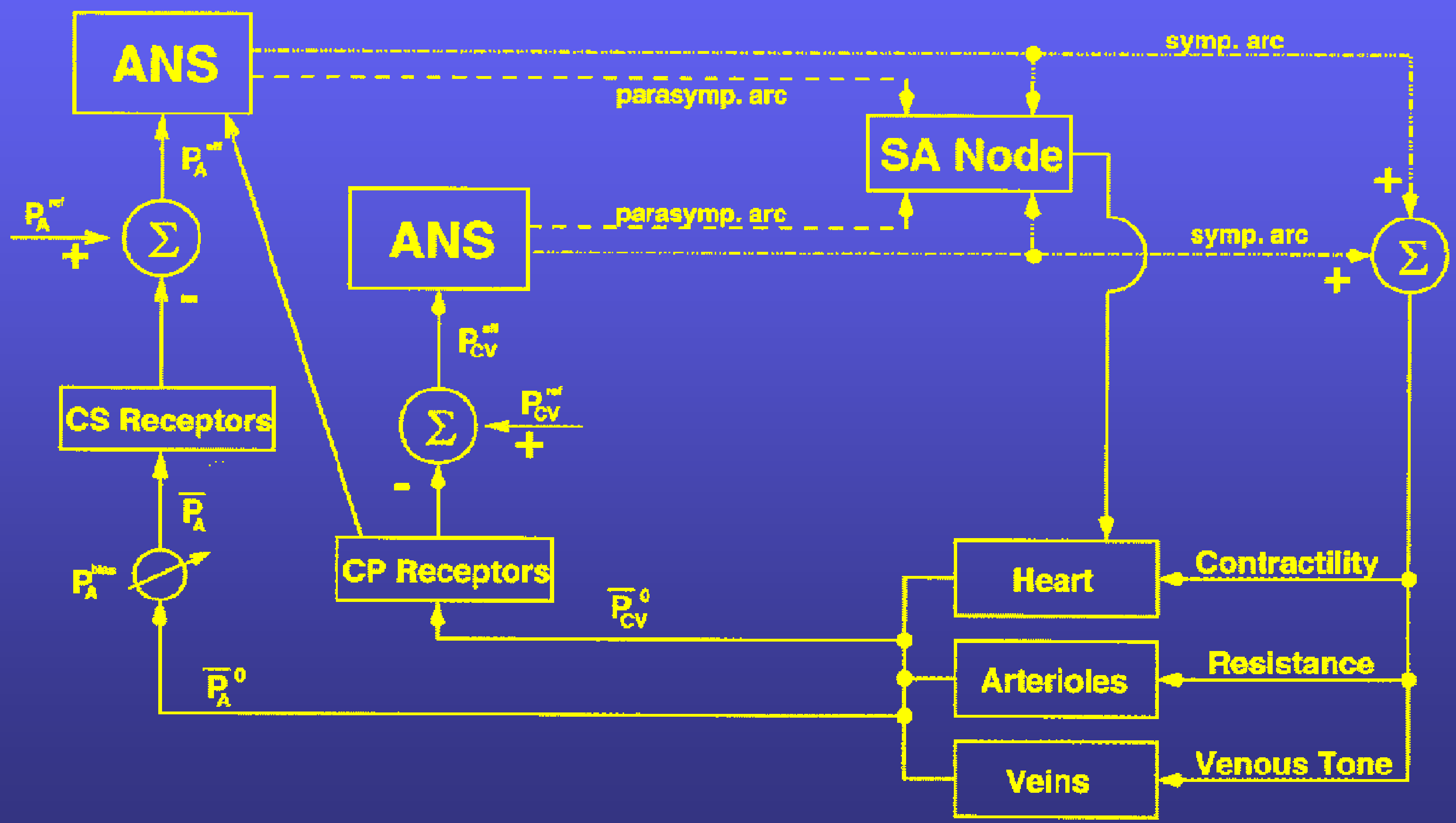


Control System:

- Arterial Baroreflex
- Cardiopulmonary reflex;
- Individual gains adjustable
- Effector mechanisms:
  heart rate, venous tone,
  cardiac contractility, and
  arteriolar resistance

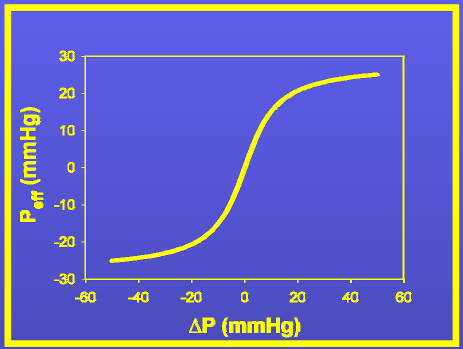


Control System:

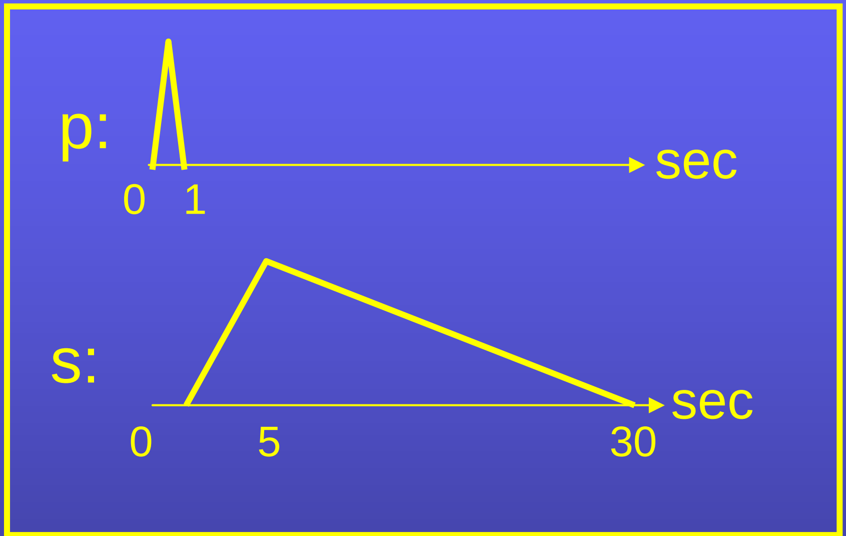


Control System:

$\Delta P = P_{trans} - P_{set}$



$\rightarrow P_{eff} \rightarrow$



$\int P_{eff}(t-k)\ \{\alpha\ p(k) + \beta\ s(k)\}\ dk$

- Heart Rate
- Contractility
- Venous Tone
- Art. Resistance

Model Performance:

Parameter	Model	Normal Value*
Pressures (mm Hg)		
LVP	131/6	130/7
ABP	130/80	130/70
CVP	5/3	7/5
RVP	28/1	24/4
Stroke Vol. Ind. (ml/beat per m^2)	50	47
Cardiac Index (l/min per m^2)	3.2	3.4

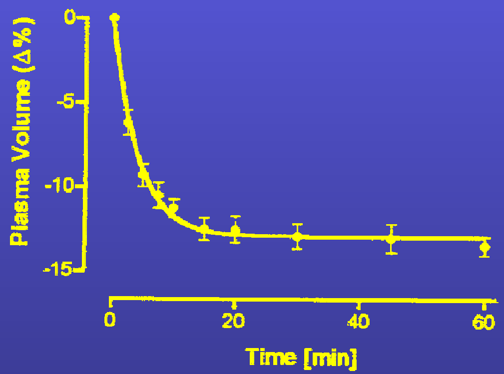
* Based on: Hurst's The Heart, RW Alexander (ed.), vol.1, 9th ed.

Tilt Table Simulation:

• Account for fluid shifts into dependent venous compartments by varying bias pressures at C_{LL} and C_{AB}

$$P_{bias} = P_0 \sin(\alpha(t))$$

• Account for blood plasma leakage from capillaries by reducing overall blood volume over time

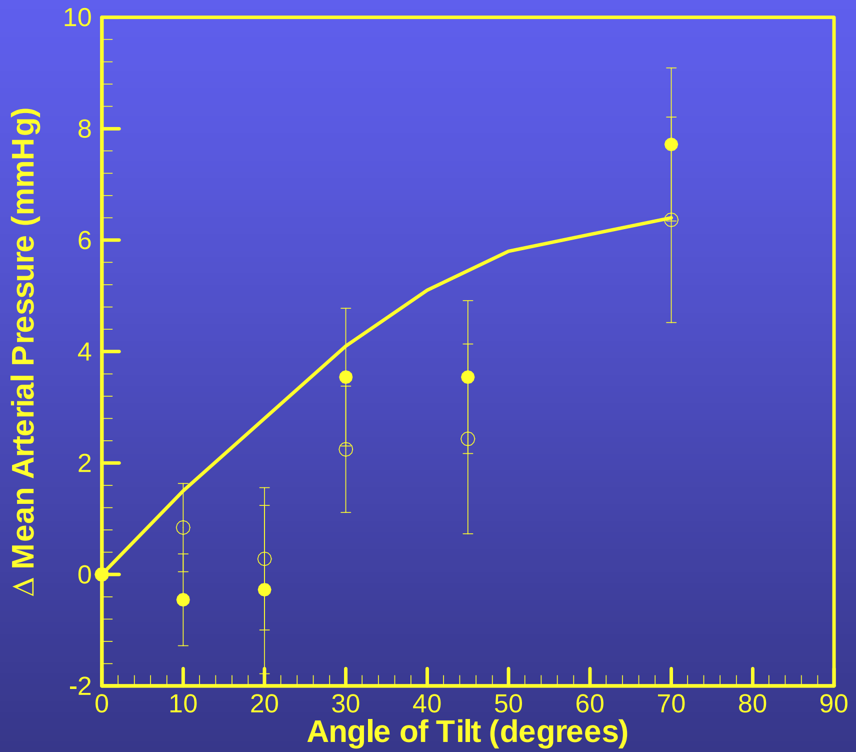


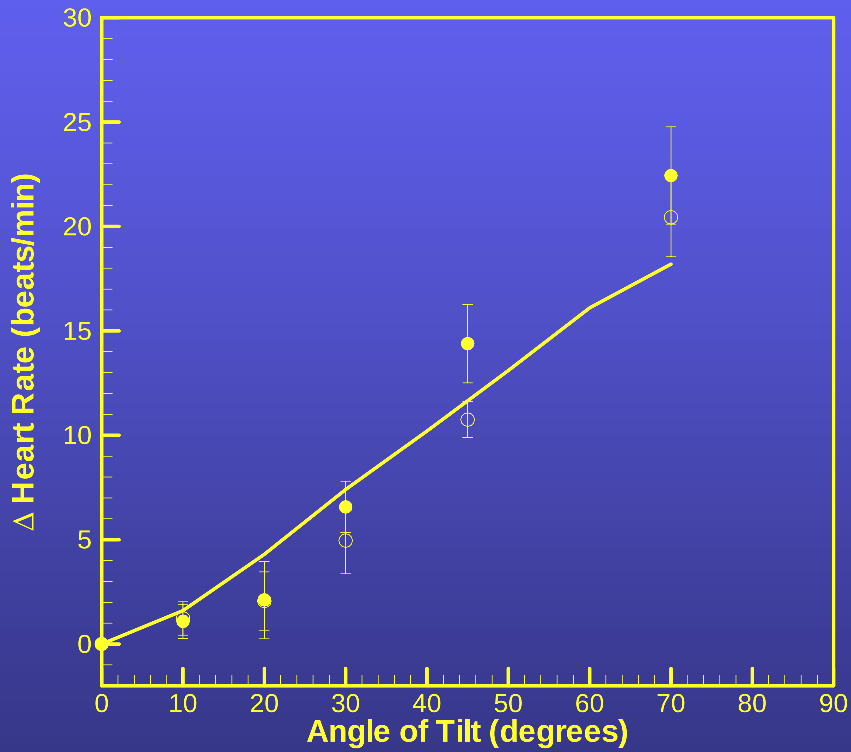
• Account for gravitational effect on sensed carotid sinus pressure

$$P_{CS} = \rho g h \sin(\alpha(t))$$

Tilt Table Simulation:

Sudden tilts from horizontal
Mean values (3-5 min) after tilt





● Young males (20-29 y), N=15

○ Older males (40-49 y), N=16

Data taken from: Smith et al. Physiologist, **27**, 210, 1984.

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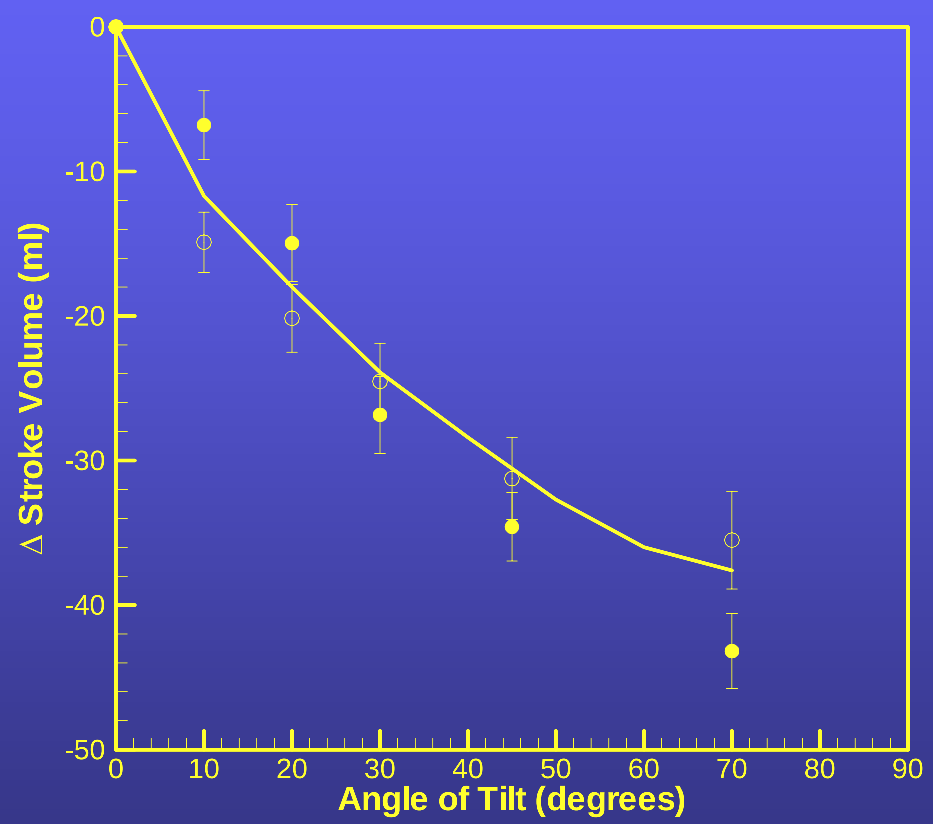

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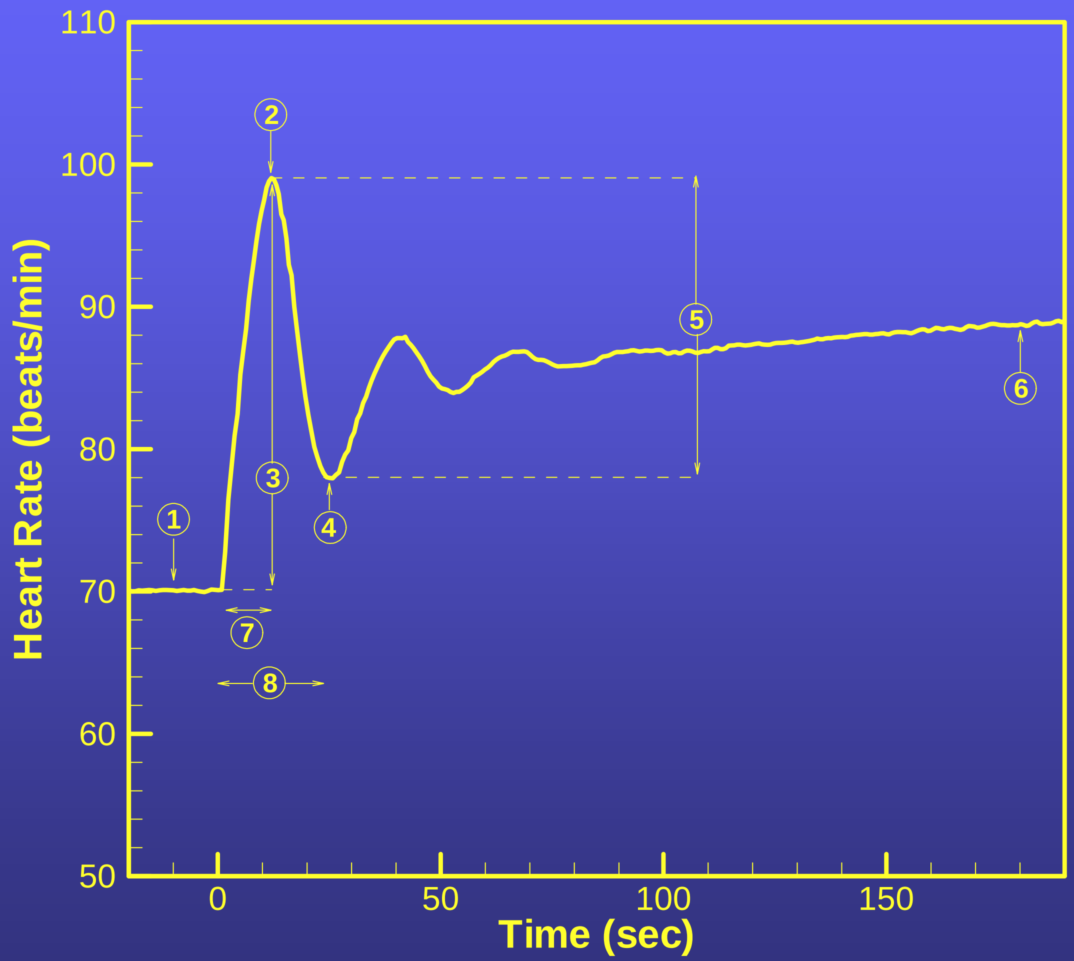
Transient Response to Tilt:



Features taken from: Rossberg et al. Europ. J. Physiol., **50**, 291, 1983.

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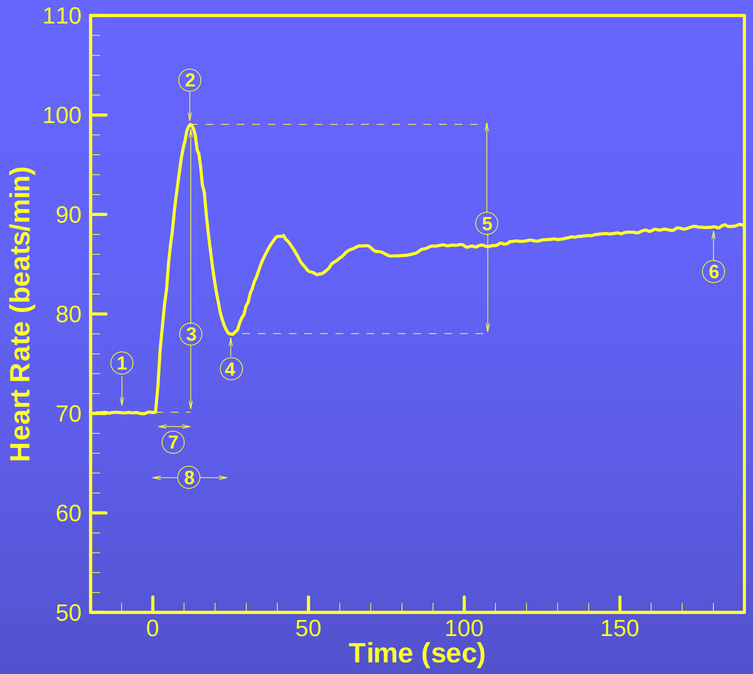


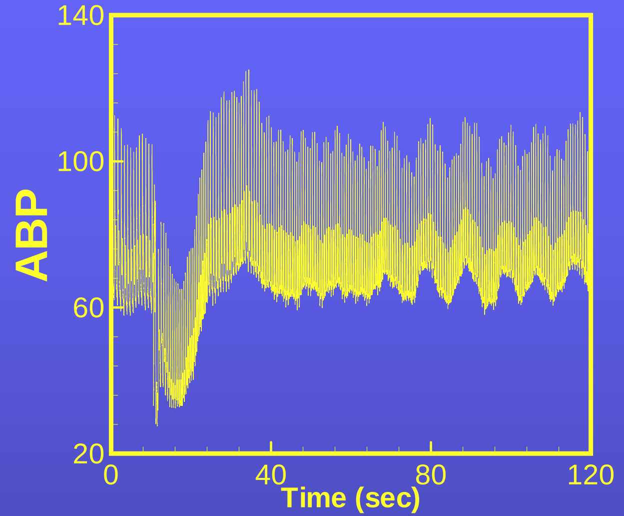
Men (N=20)

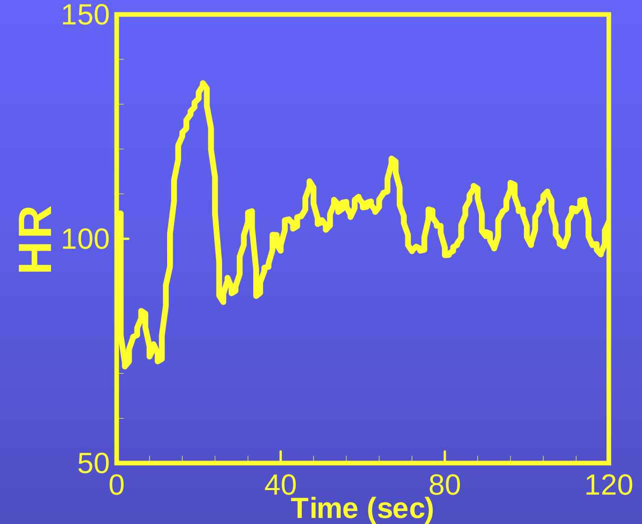
		Experiment	Simulation
1	bpm	59.2 ± 14.6	70.1
2	bpm	92.2 ± 12.1	99.1
3	bpm	29.5 ± 8.4	29.0
4	bpm	75.7 ± 12.9	78.0
5	bpm	17.0 ± 9.5	21.1
6	bpm	89.1 ± 13.1	88.7
7	s	7.9 ± 3.9	11.7
8	s	15.6 ± 5.0	24.9

Data taken from: Rossberg et al. Europ. J. Physiol., **50**, 291, 1983.

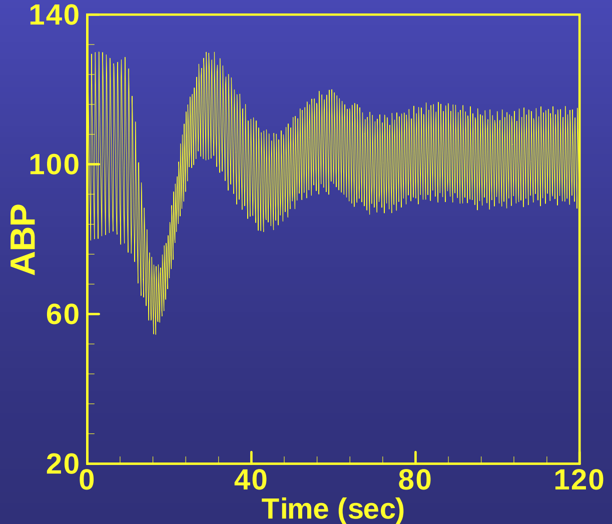
Stand-Test Simulation:

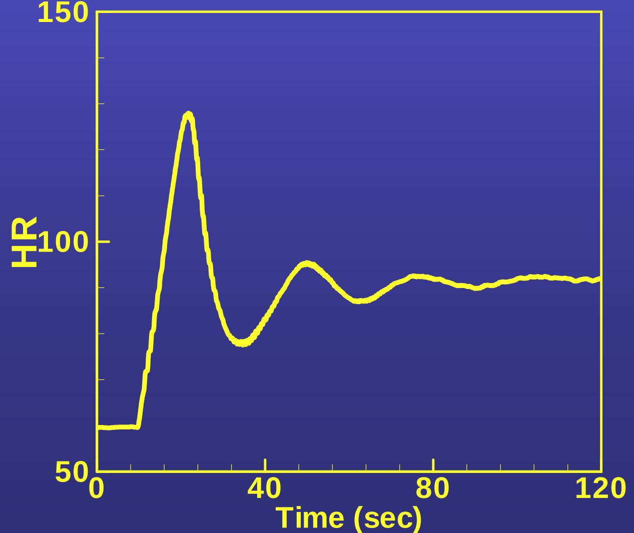
Pre-Spaceflight





Simulation





Testing of Hypotheses:

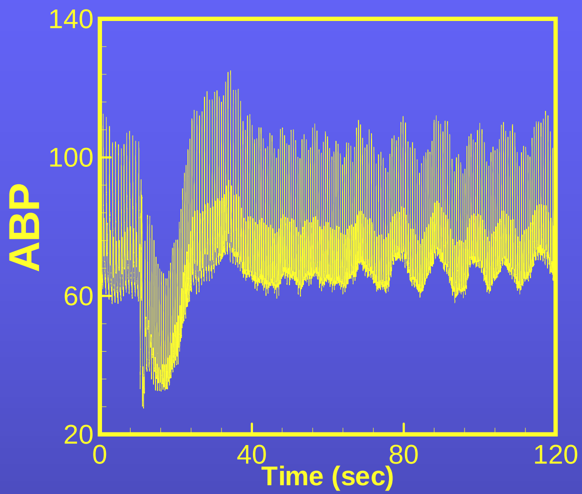
- Simulate response to orthostatic stress test for different sets of hemodynamic and/or control parameters

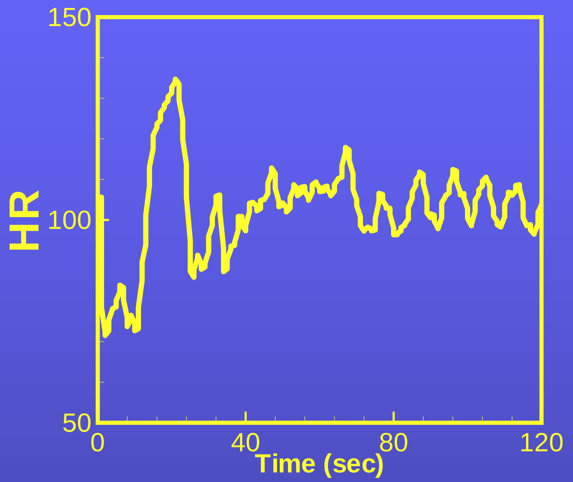
- Compare simulation to experimental observation based on some “measure”

- Repeat simulation with different sets of parameters until “best fit” is achieved

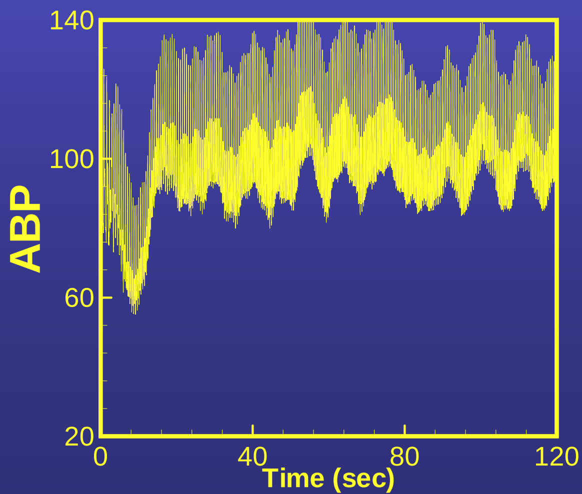
Astronaut Stand Tests:

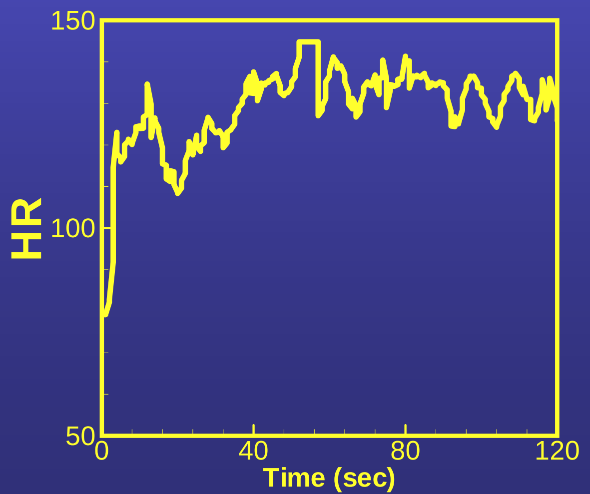
Pre-Spaceflight





Post-Spaceflight

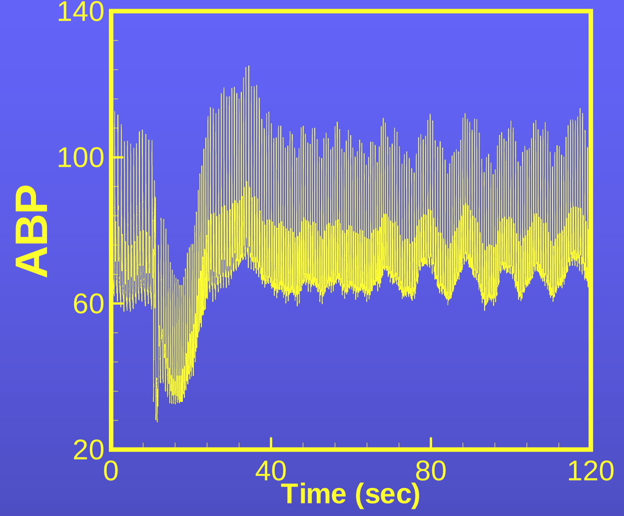


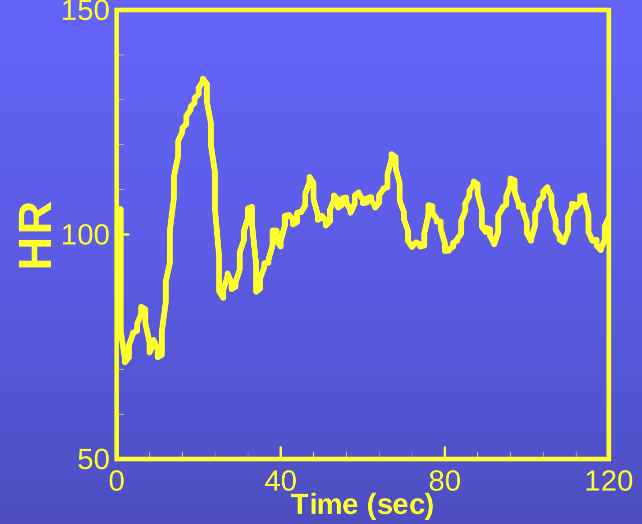


Source of data: J. Fritsch-Yelle, Johnson Space Center

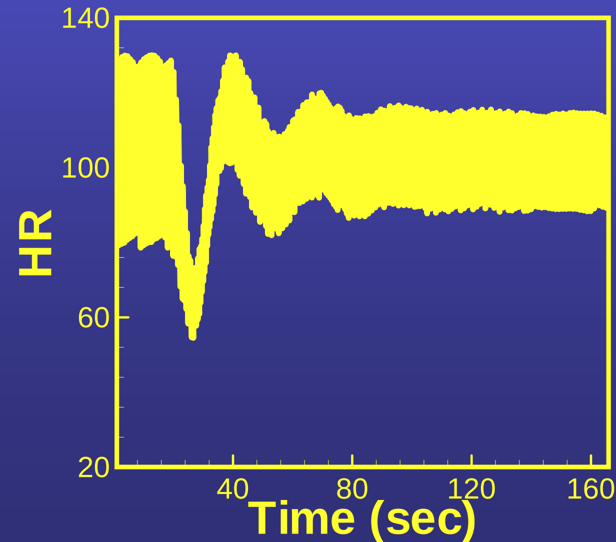
Stand-Test Simulation:

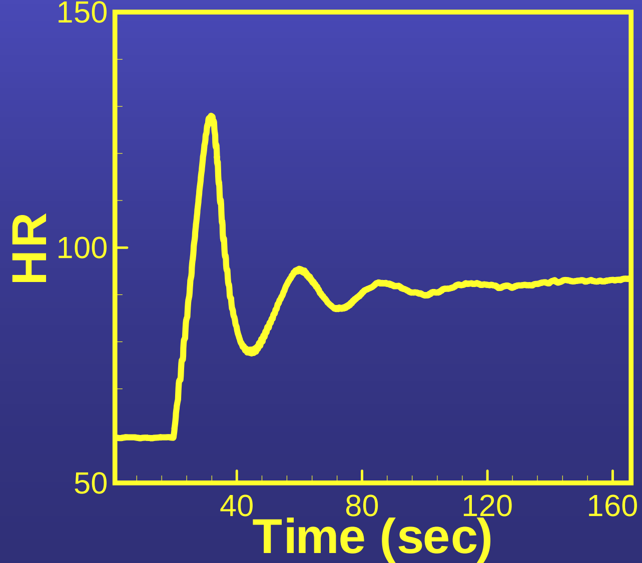
Pre-Spaceflight





Simulation





Cardiovascular Adaptation During Space Flight

Observations:

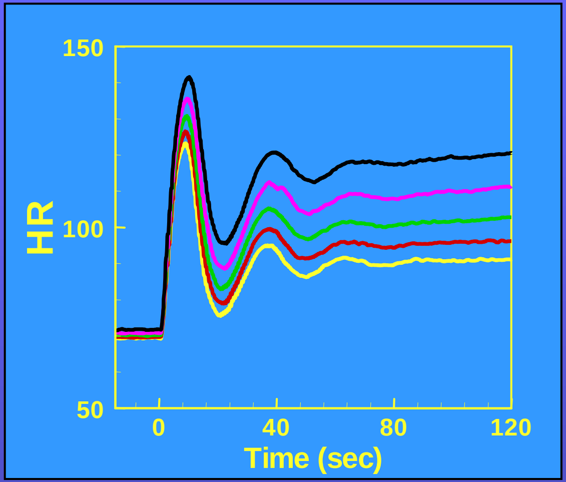
- Reduction in plasma volume by about 15%
- Reduction in baroreflex heart rate gain by 15%
- Increase in venous leg compliance by 26% - 45%

Hypothesis:

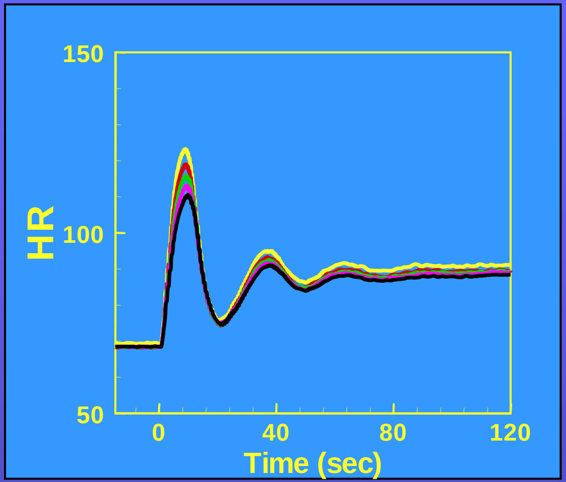
- Down-regulation of splanchnic venous receptors

Testing Hypotheses

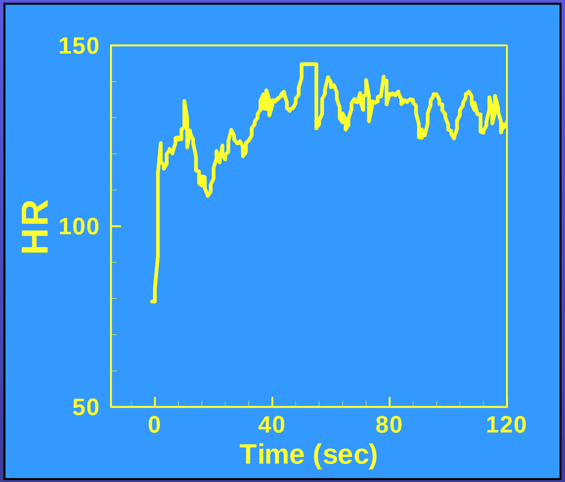
ΔTotal Blood Volume



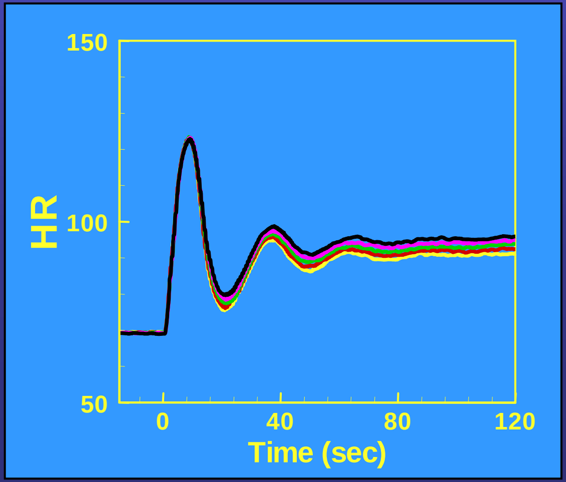
ΔHeart Rate Gain



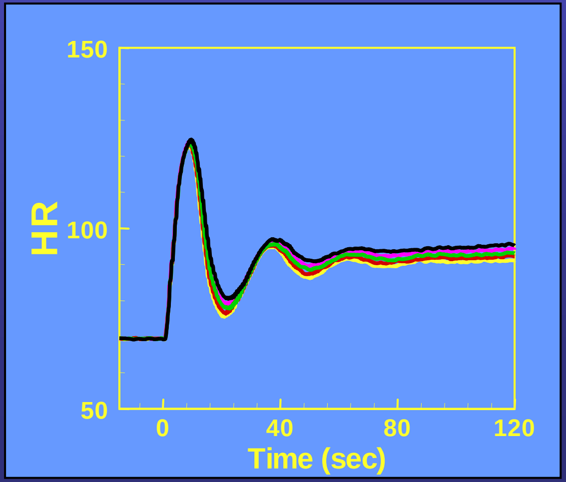
Post-Spaceflight



Δ Resistance Gain



ΔVenous Tone Gain



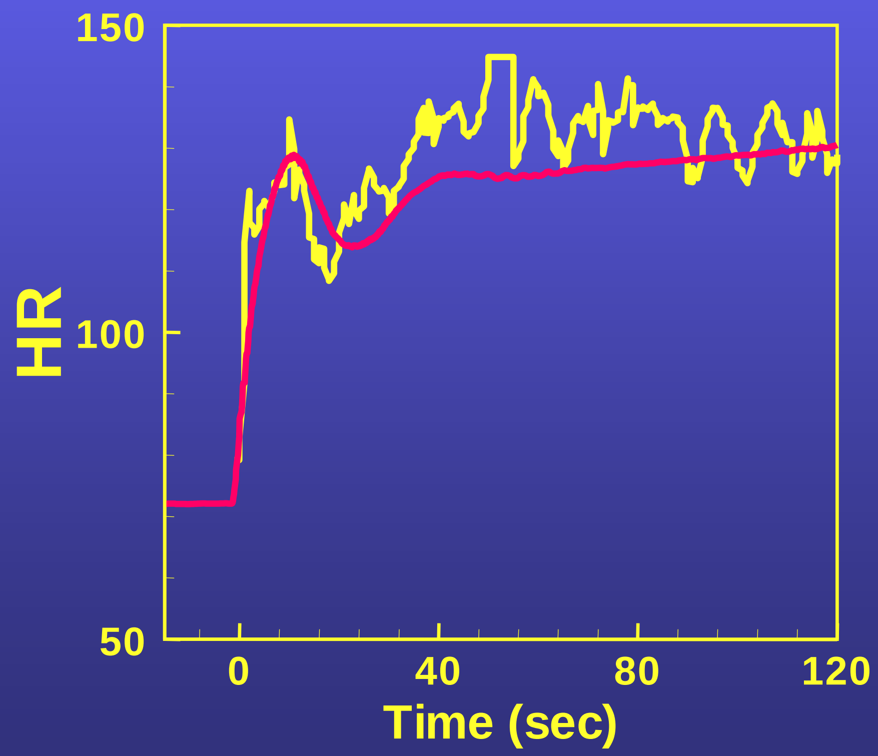
Source of data: J. Fritsch-Yelle, Johnson Space Center

Combining Hypotheses

Hypovolemia

↓ Venous Feedback

↓ Arteriolar Feedback



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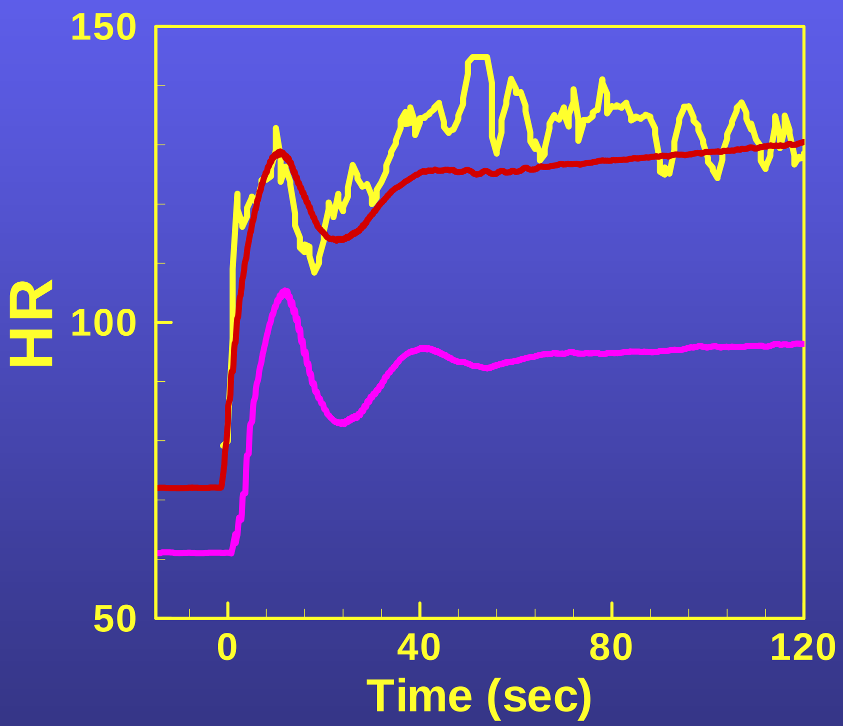
Simulation of Midodrine



Source of data: J. Fritsch-Yelle, Johnson Space Center

Conclusions:

- Even after 30+ years of research, OI is still poorly understood.

- Current efforts rely on ground-based analogs such as bedrest.

- Computational models can:
  - help interpret experimental observations
  - test hypotheses
  - simulate the effects of countermeasures.

→ Computational Models will save the world!