Integrating Basic Science and Clinical Research in a Goal Directed Approach to Biomedical Problems:

An Example From Spaceflight Research

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Statement of the Problem

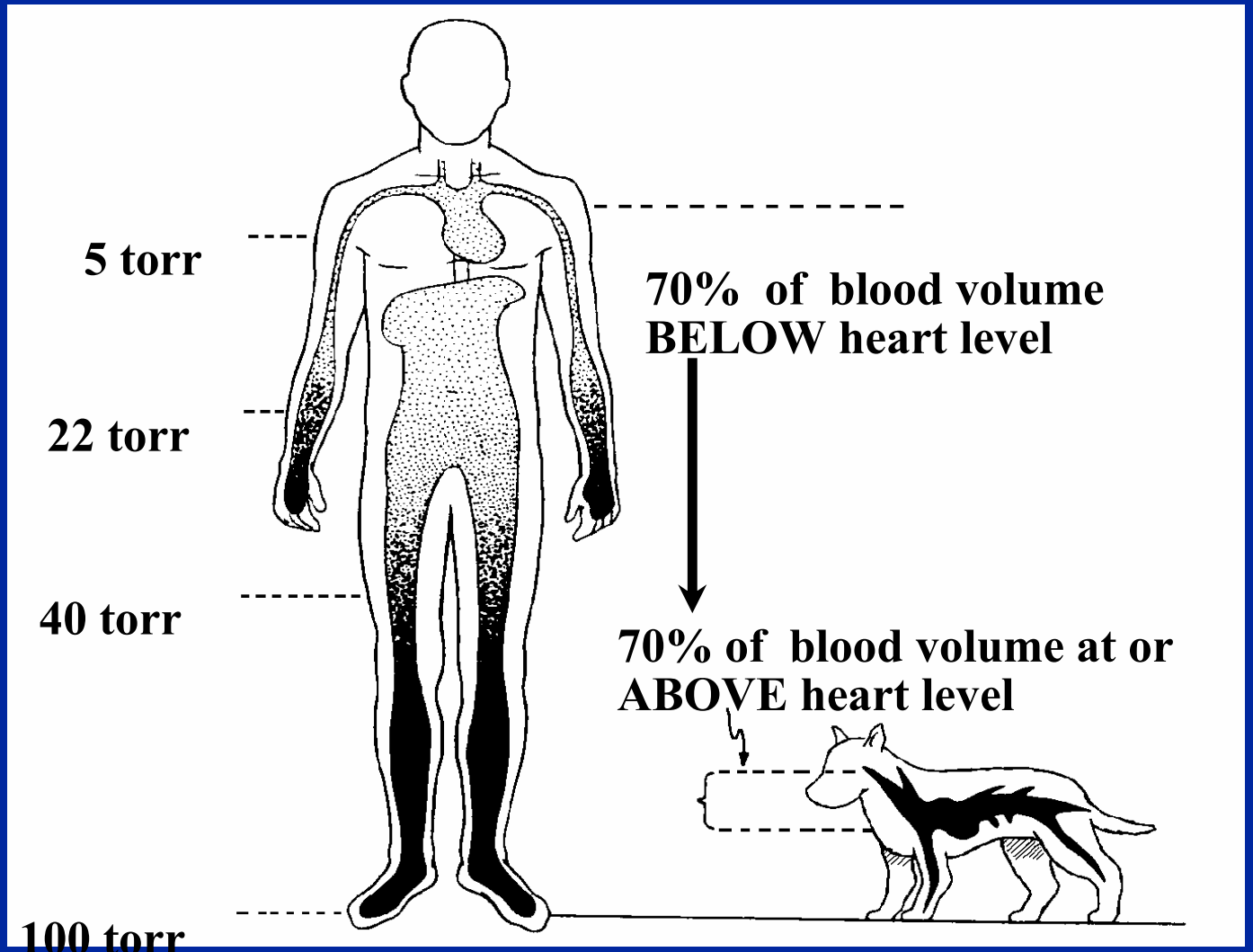
Orthostatic hypotension (the inability to maintain standing blood pressure), has been experienced by returning astronauts since the Mercury Program. About 20% of Shuttle astronauts and 83% of Space Station astronauts are unable to complete 10 minutes of unassisted standing without presyncope or syncope. This presents a risk to both crew and vehicle.

In the early years of manned spaceflight, it was ASSUMED that the loss of circulating blood volume caused by spaceflight was the primary cause of postflight orthostatic hypotension:

AND

That restoration of blood volume would correct postflight orthostatic hypotension.

Why does spaceflight cause loss of blood volume?



Loring B. Rowell, 1986

In 1993, a flight rule was imposed that required astronauts to consume salt tablets and water prior to landing (fluid load).

This fluid load was implemented without an understanding of the integrated mechanisms of the fluid loss or of the orthostatic hypotension.

The efficacy of the fluid load was not determined because the method proposed to the astronauts for measurement of blood volume required injection of a radioactive tracer. This method was unacceptable to them.

A new, acceptable, technique was developed (using carbon monoxide to tag red blood cells) to measure plasma volume.

It was subsequently discovered that the salt tablets and water did NOT restore blood volume (still a 9% loss) OR prevent post-flight orthostatic hypotension. Other volume restoring countermeasures were pursued.

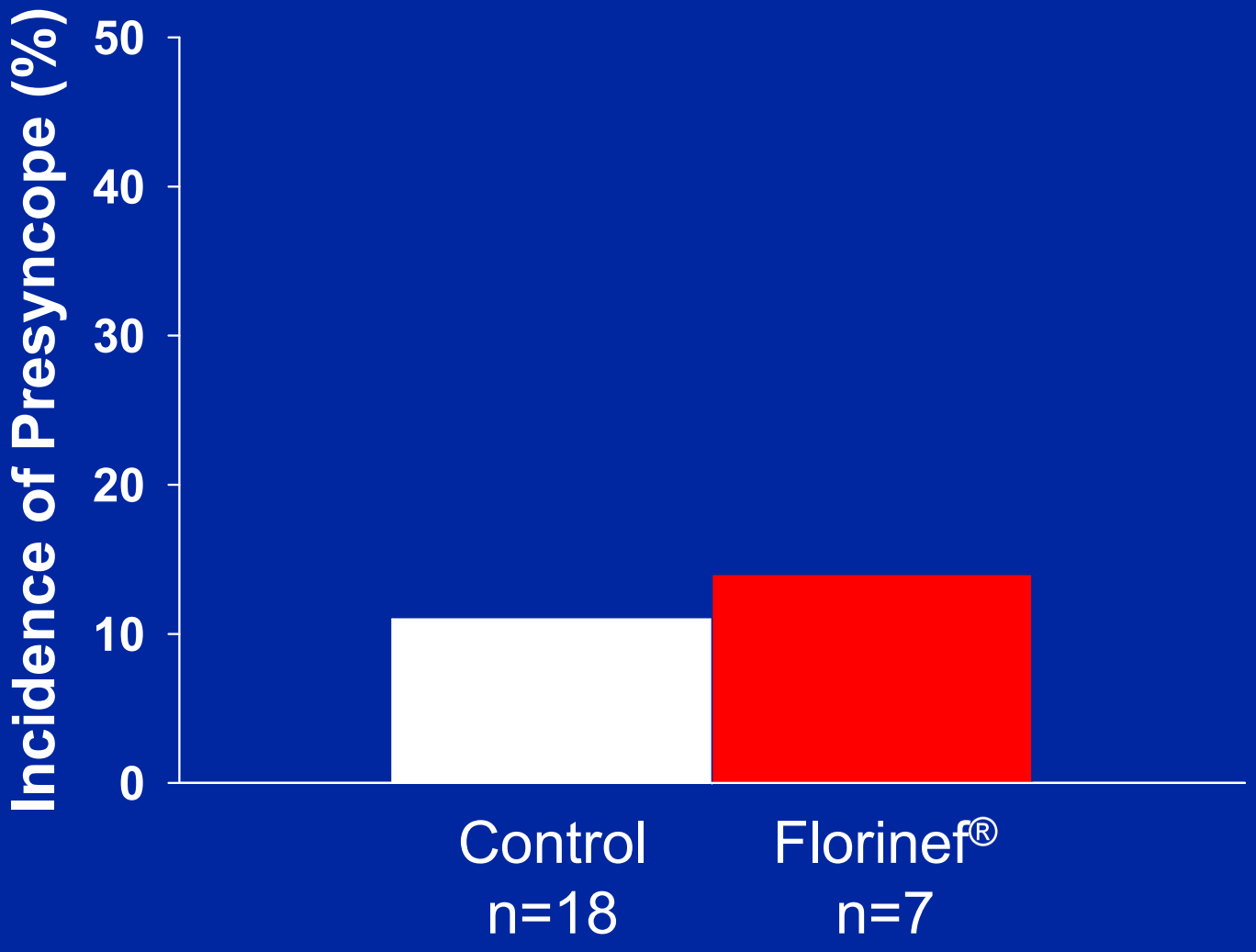
Florinef® Trials

Florinef®, a mineralocorticoid, was ingested prior to landing.

Florinef® DID prevent loss of blood volume, but DID NOT correct post-flight orthostatic hypotension.

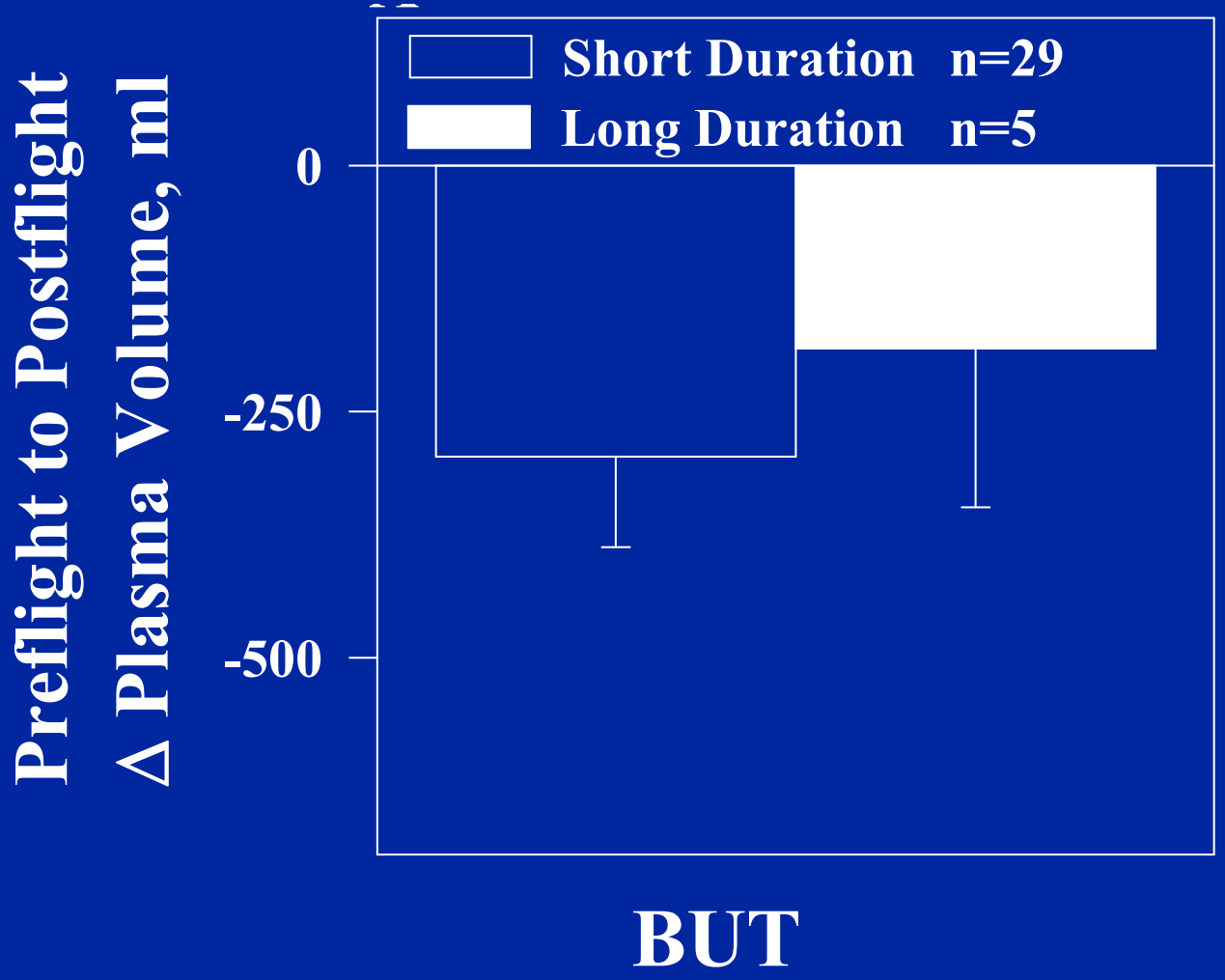
In addition, the crew complained of unacceptable side effects including headaches and pain behind the eyes.

Florinef® does not correct post-spaceflight orthostatic hypotension

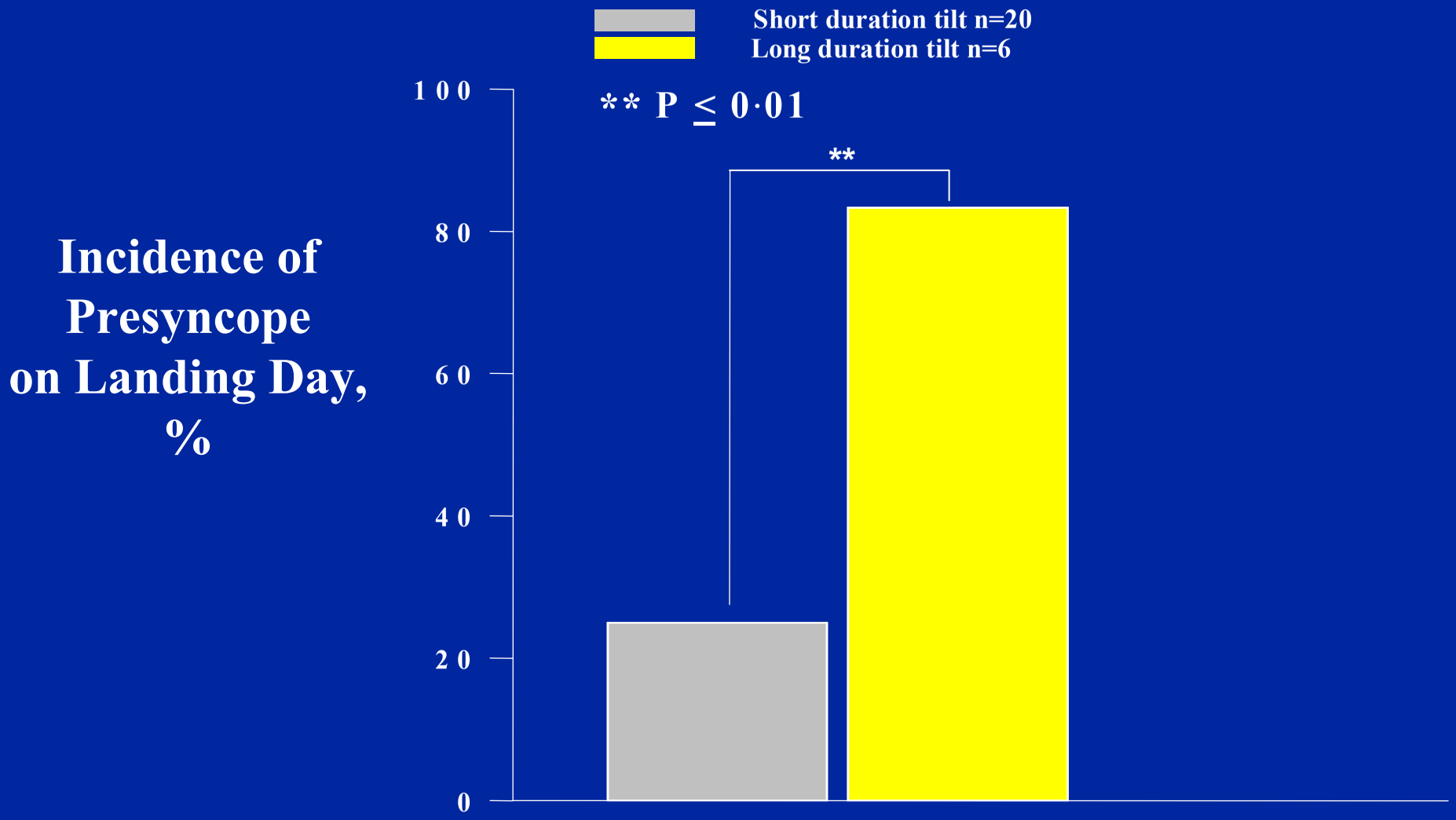


It has since been determined that loss of blood volume is NOT the definitive cause of postflight orthostatic hypotension.

Plasma volume losses are similar after short and long-duration spaceflight



Incidence of presyncope is greater after long-duration spaceflight



Loss of plasma volume is not different between astronauts who DO and astronauts who DO NOT suffer from postflight orthostatic hypotension.

	Preflight Plasma Vol, l/m^2	Landing day PlasmaVol, l/m2	% Spaceflight-Induced Loss
Presyncopal Men (*n*=6)	1.67 ± 0.1	1.55 ± 0.12*	7.1 ± 0.03
Non-Presyncopal (*n*=24) Men	1.73 ± 0.0	1.60 ± 0.05 **	7.1 ± 0.03

Values are means ± SE; *p ≤ 0.05, **p ≤ 0.01, vs. preflight

A new, integrated approach was formulated, that included:

- **collaboration with clinicians who treat orthostatic hypotension;**
- **mechanistic studies in astronauts;**
- **supporting studies in bed rested subjects;**
- **follow-up mechanistic studies in animal models;**
- **mathematical modeling;**
- **selection of specifically targeted countermeasure;**
- **countermeasure trials in bed rest;**
- **countermeasure validation in astronauts;**
- **transfer to flight surgeons for implementation.**

What mechanisms contribute to maintenance of upright blood pressure?

↓Central Venous Pressure
↑Sympathetic Activity
↑Plasma Norepinephrine
↑Vasoconstriction

↓Central Venous Pressure
↑Sympathetic Activity
↑Plasma Norepinephrine
↑Vasoconstriction
↑Heart Rate
↓Arterial Pulse Pressure
↑PRA Angio. II - Aldost.

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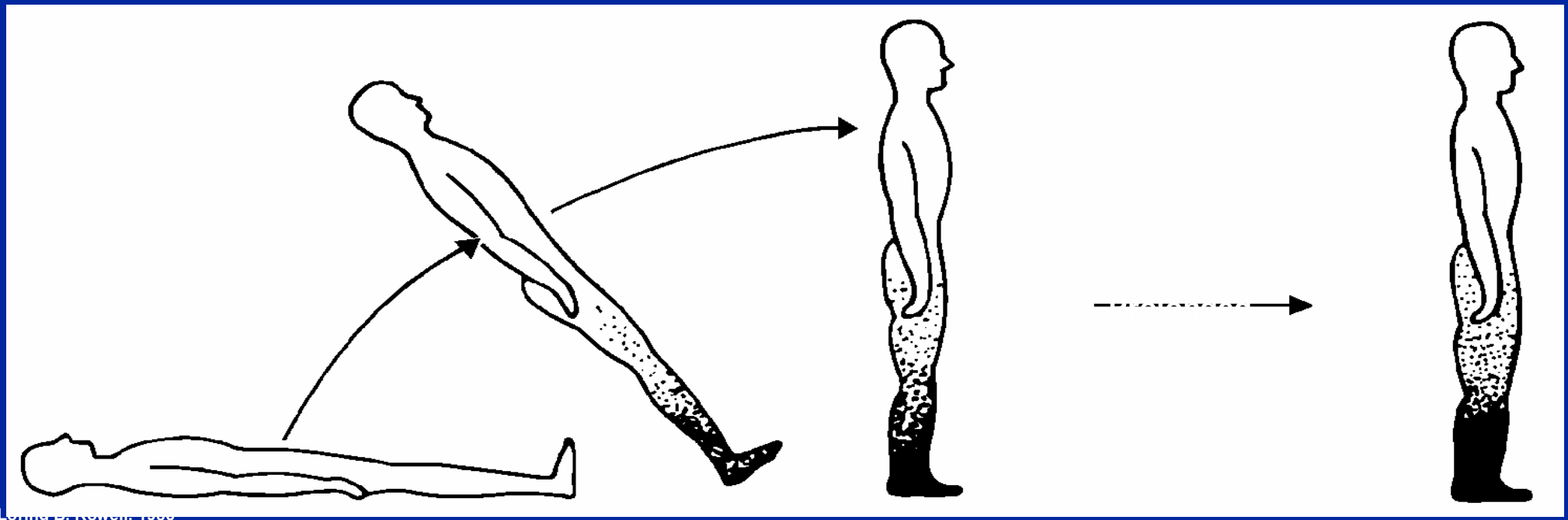
↑PRA Angio. II - Aldost.
↑Vasopressin

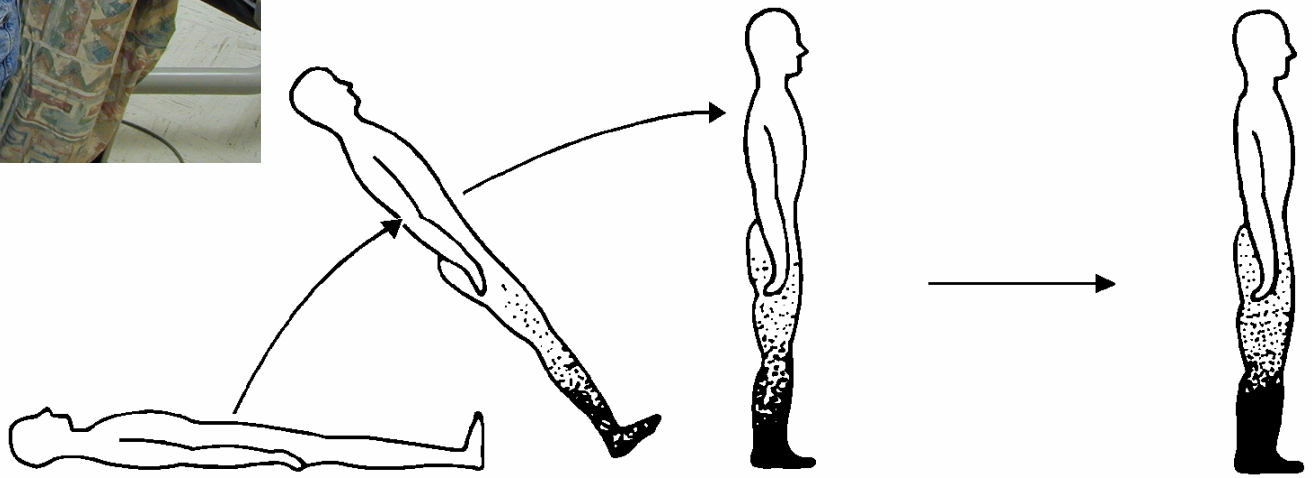


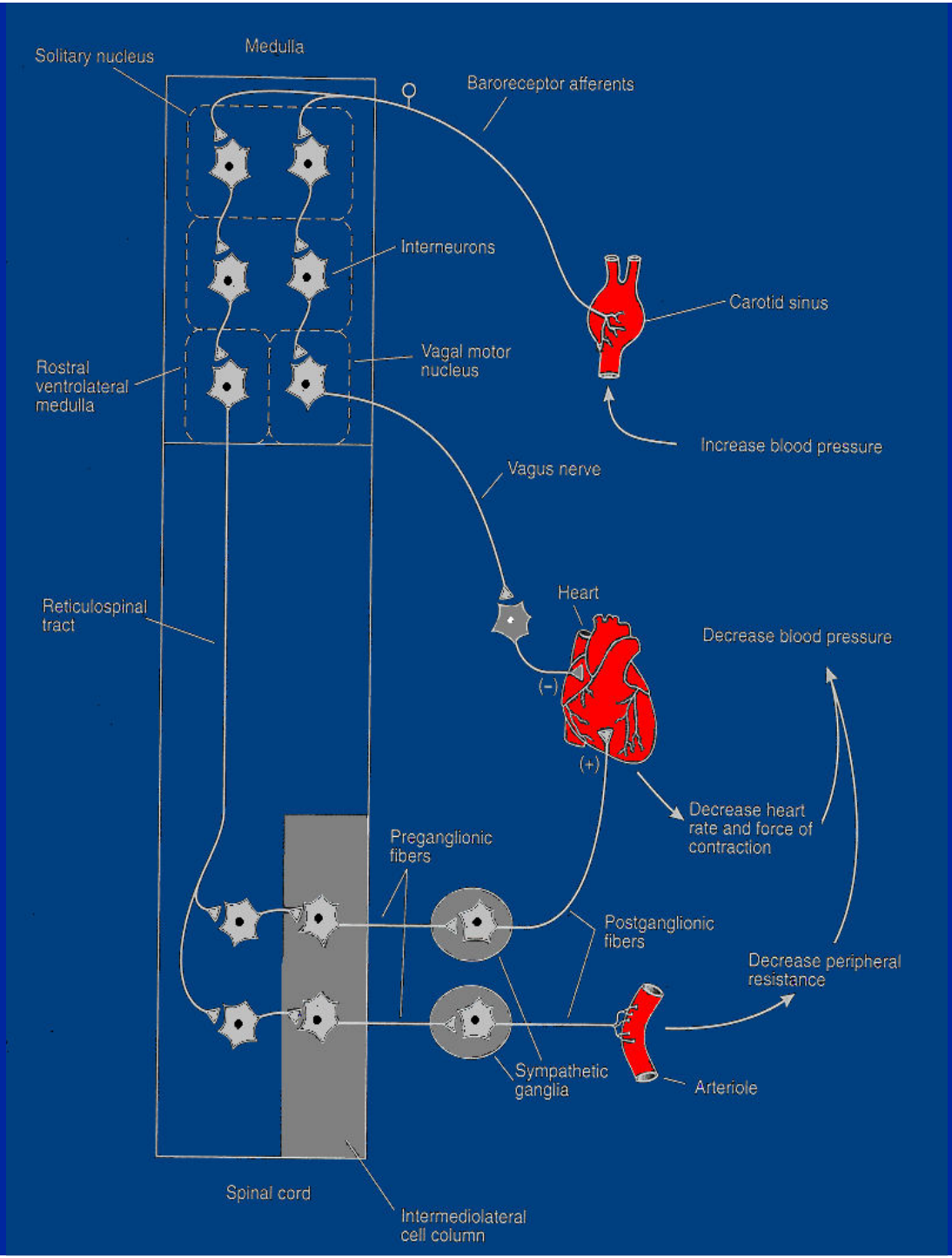
Loring B. Rowell, 1986

Tilt Table Test

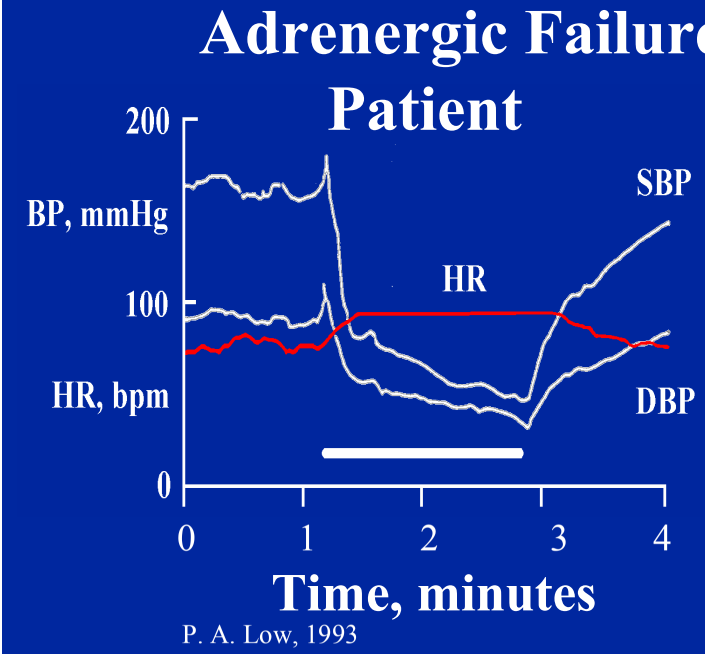
Measure of Orthostatic Tolerance

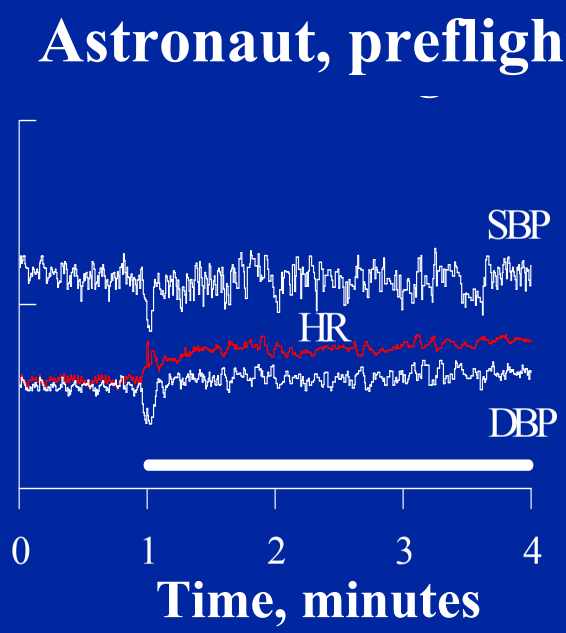
80° Tilt

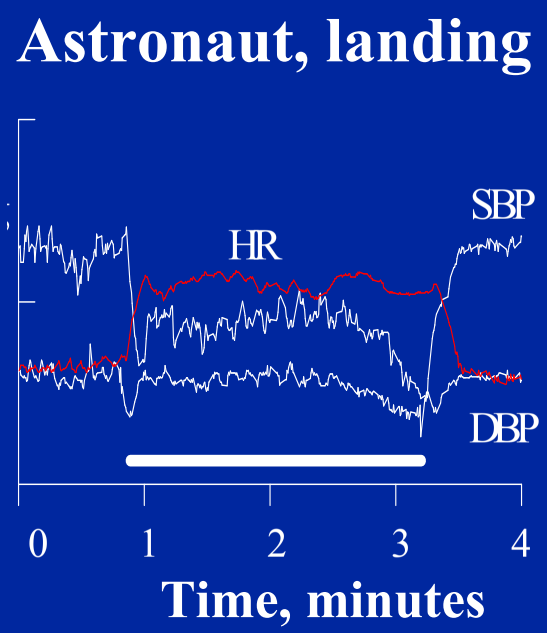



Solitary nucleus
Medulla
Baroreceptor afferents
Interneurons
Carotid sinus
Vagal motor nucleus
Rostral ventrolateral medulla
Increase blood pressure
Vagus nerve
Heart
Reticulospinal tract
Decrease blood pressure
(−)
(+)
Decrease heart rate and force of contraction
Preganglionic fibers
Postganglionic fibers
Decrease peripheral resistance
Sympathetic ganglia
Arteriole
Spinal cord
Intermediolateral cell column

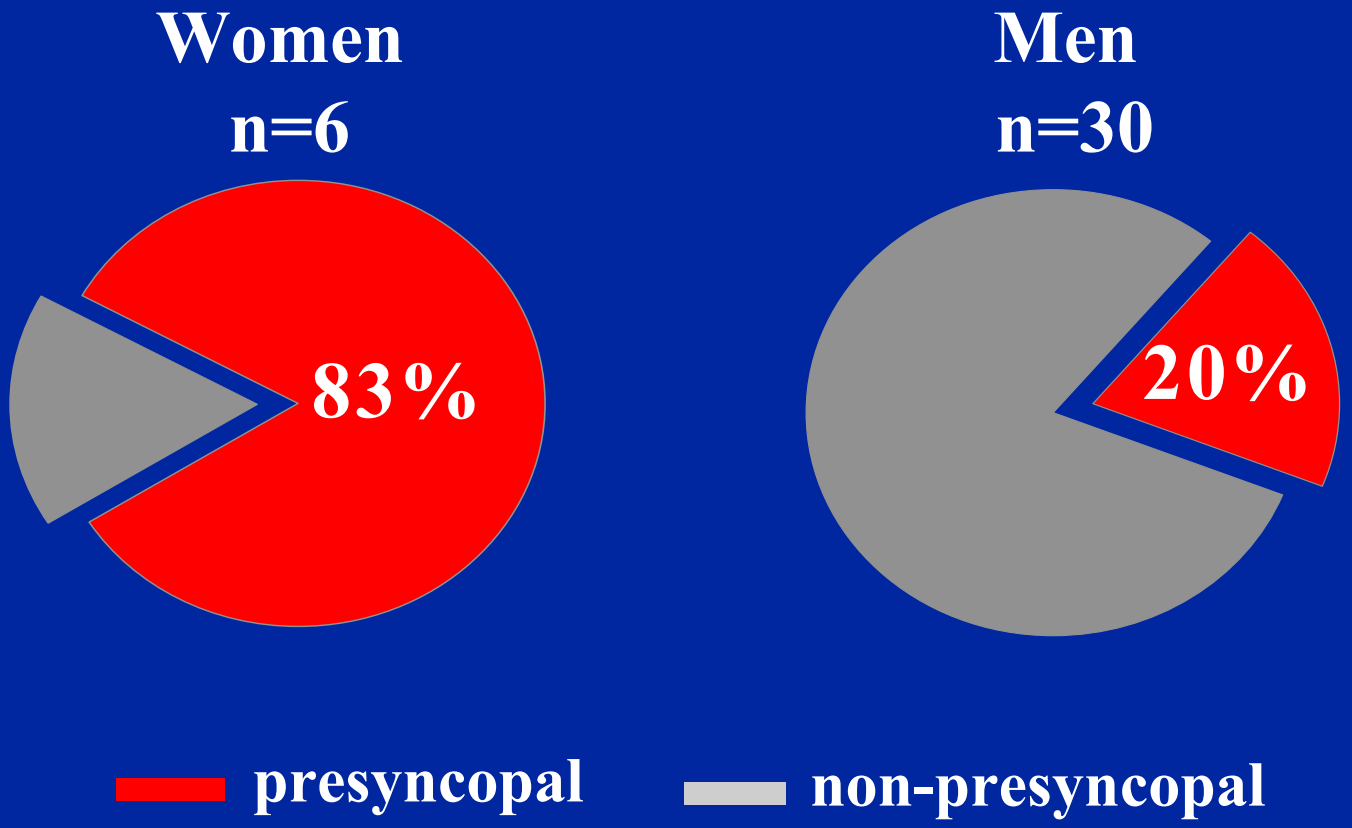
Cardiovascular responses to upright posture in a patient and an astronaut



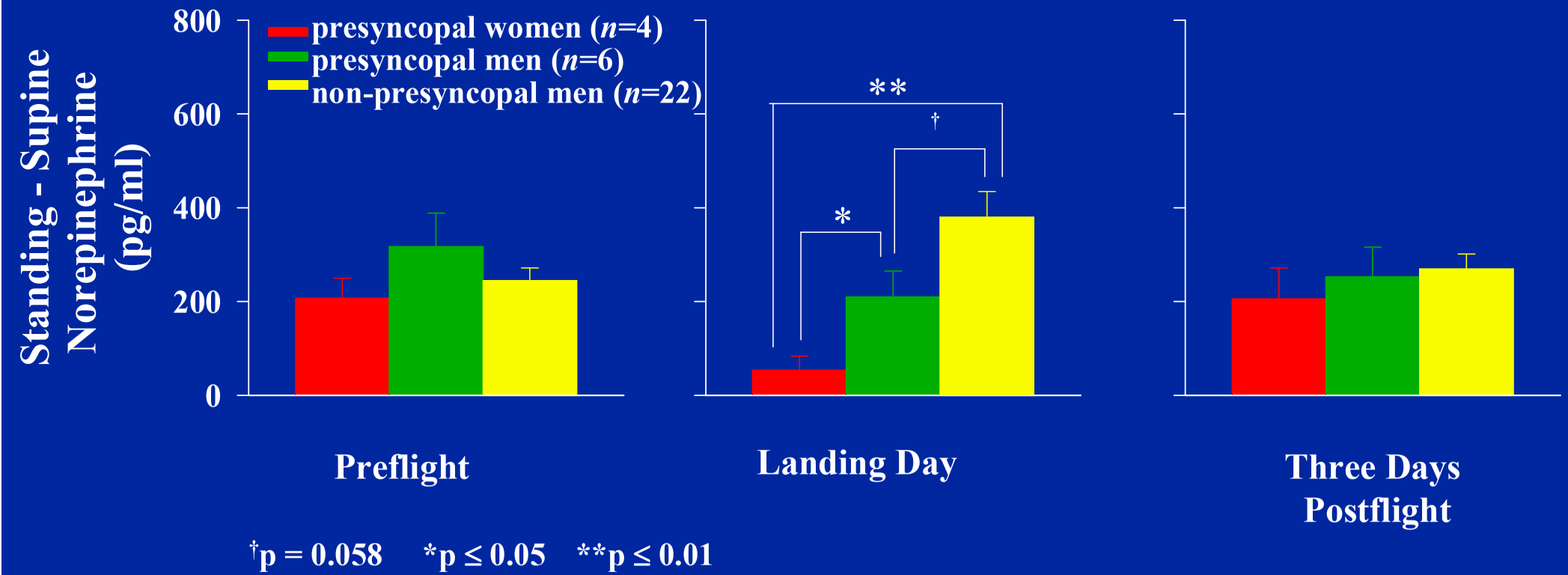




Incidence of presyncope is greater in female astronauts

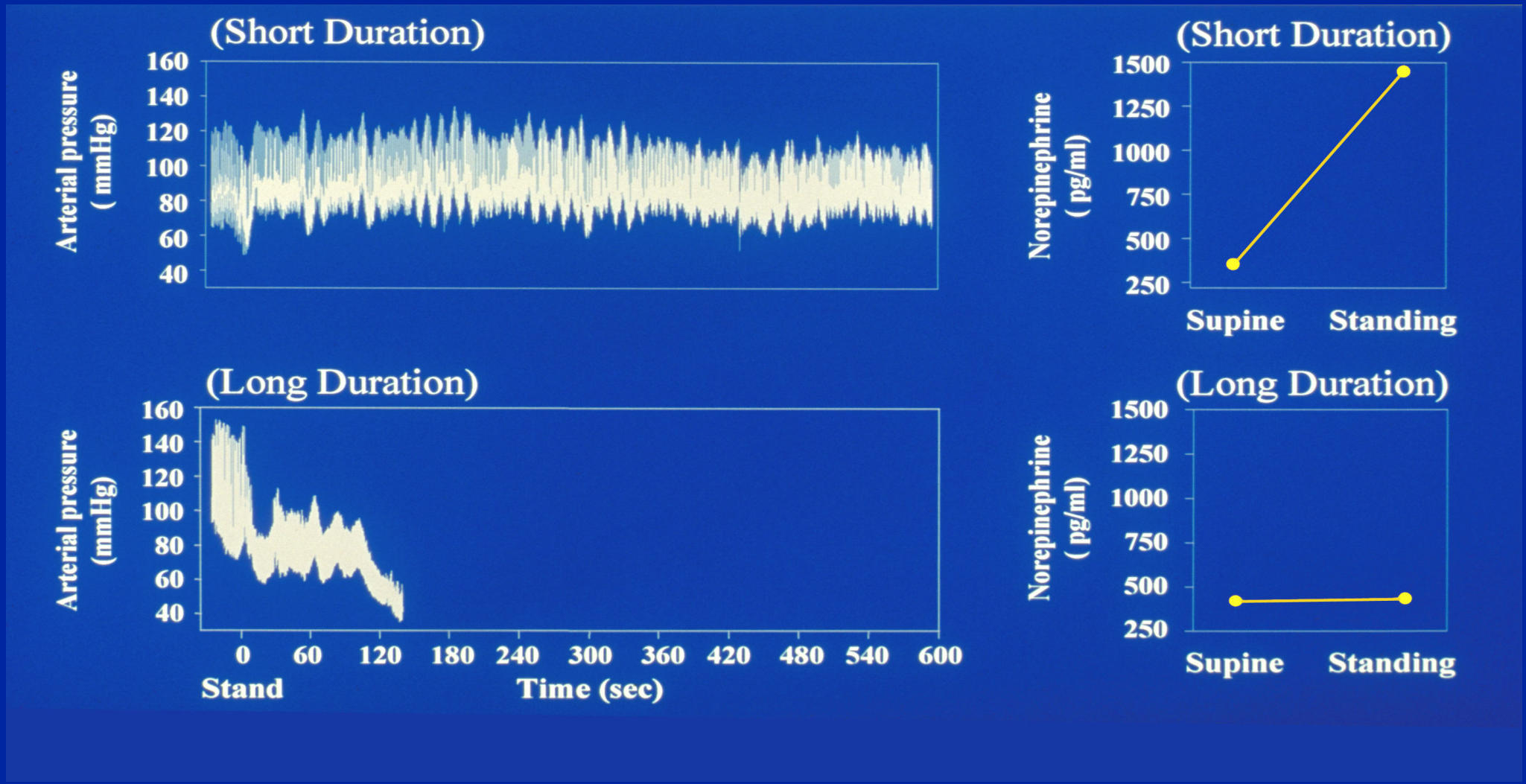


Norepinephrine responses to standing after Shuttle flights



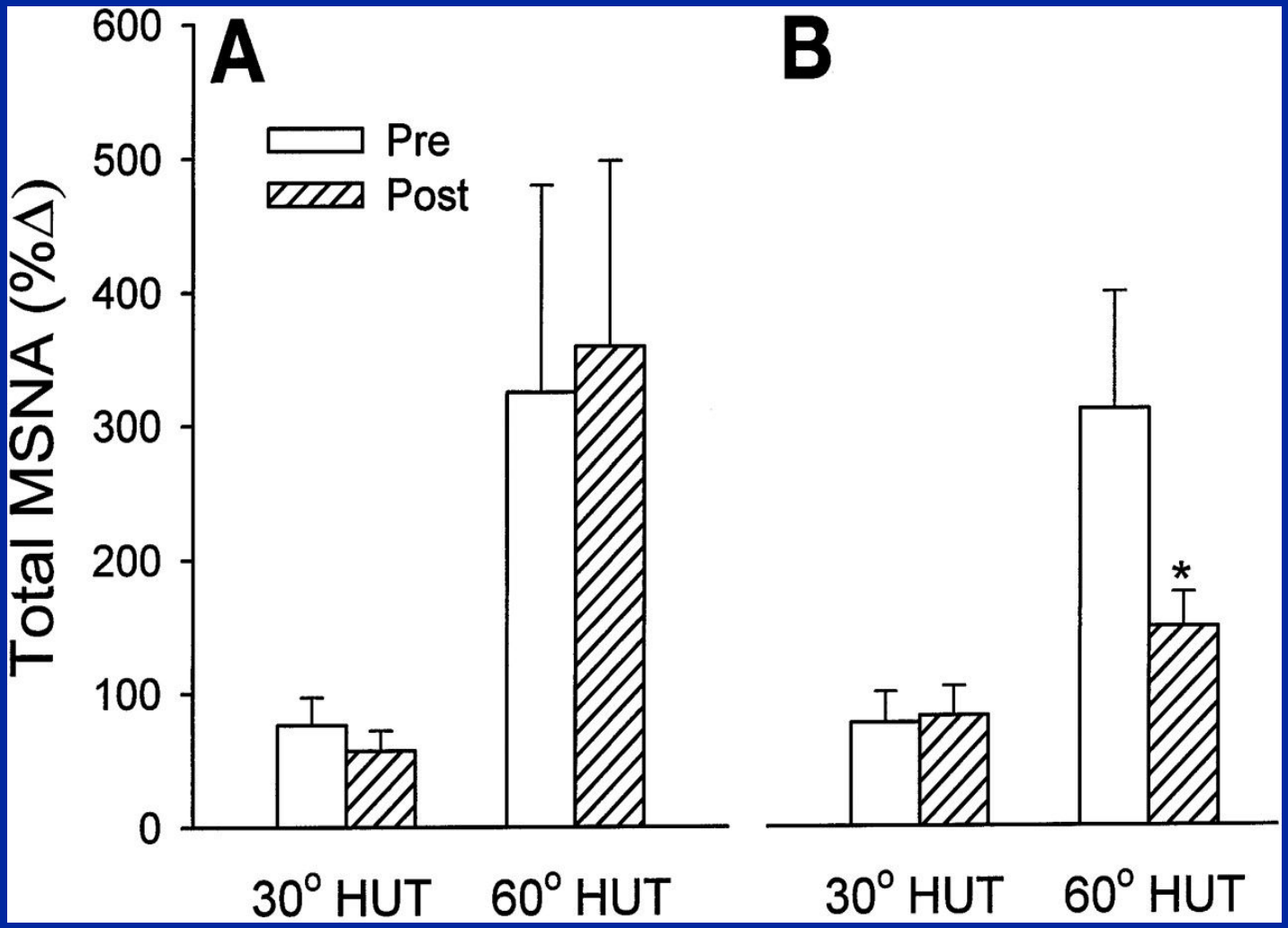
†p = 0.058 *p ≤ 0.05 **p ≤ 0.01

Responses to standing after a short (top) and a long (bottom) flight in the same astronaut



Supporting Ground-based Studies

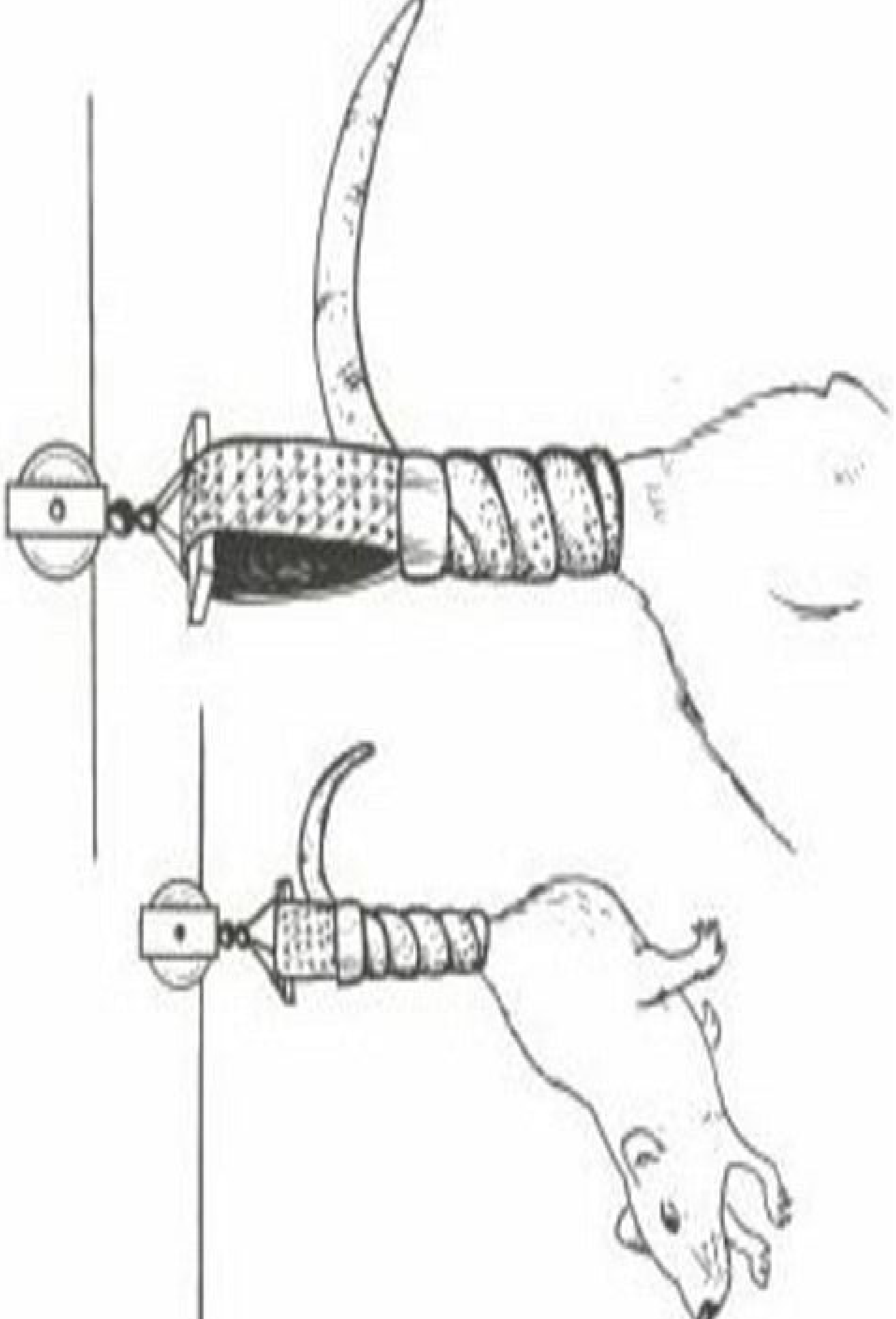
Sympathetic response to upright tilt in subjects without (left) and with (right) orthostatic hypotension after bed rest.



Shoemaker, J. K. et al. Am J Physiol Regul Integr Comp Physiol 277: R1084-R1090 1999

AJP - Regulatory, Integrativ
and Comparative Physiology

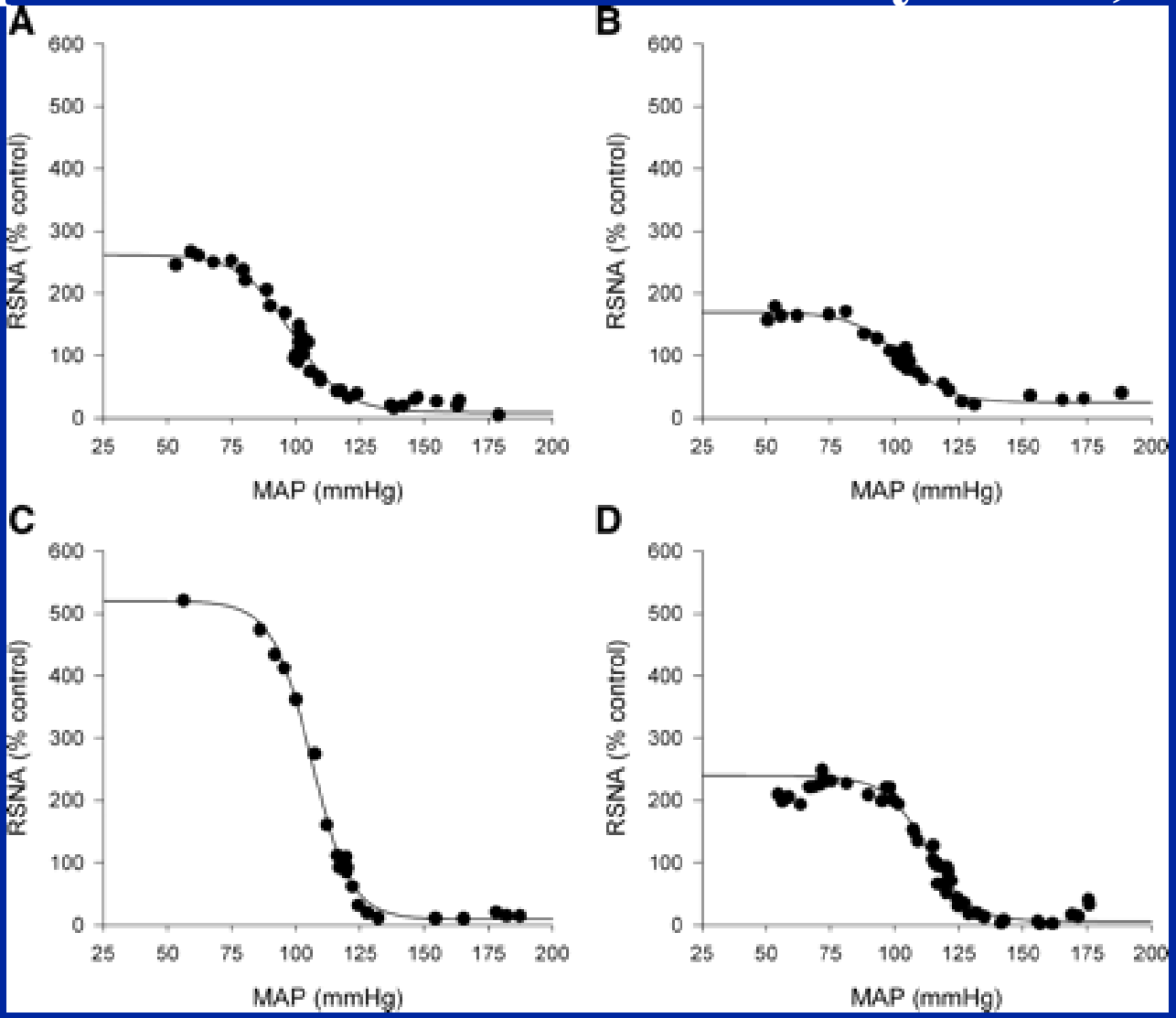
Computer model of mean arterial pressure responses to standing after 14 days in space



Attenuation of Sympathetic Responses After Hind-limb Suspension in Rats C.M. Foley et al., 2005

females

males

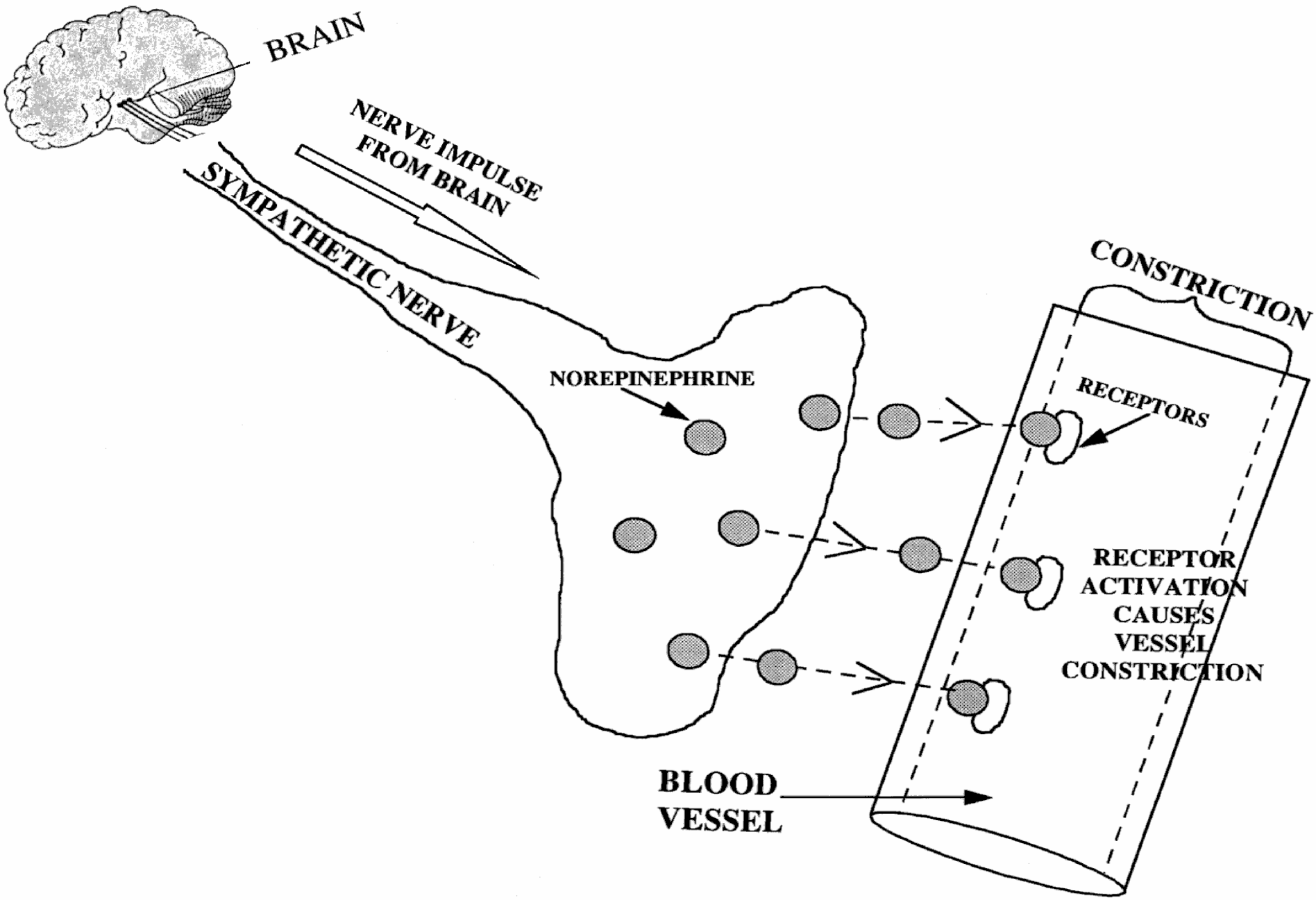


control suspended

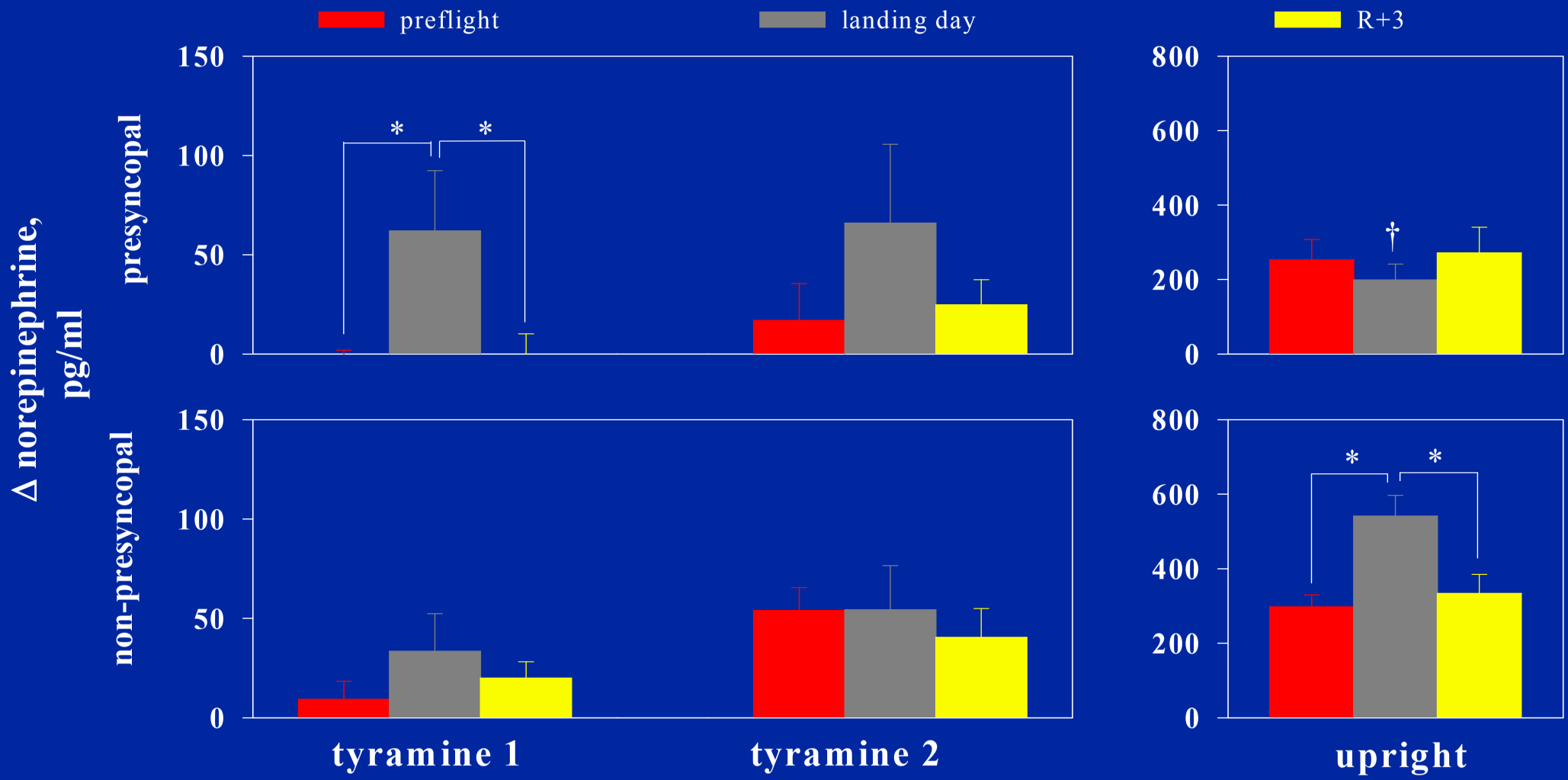
In order to develop a targeted and safe countermeasure, we needed to first know why the norepinephrine was not being released.

Was its synthesis disrupted during flight?

Was the neural signal for the release disrupted by flight?


BRAIN
NERVE IMPULSE FROM BRAIN
SYMPATHETIC NERVE
NOREPINEPHRINE
CONSTRICTION
RECEPTORS
RECEPTOR ACTIVATION CAUSES VESSEL CONSTRICTION
BLOOD VESSEL

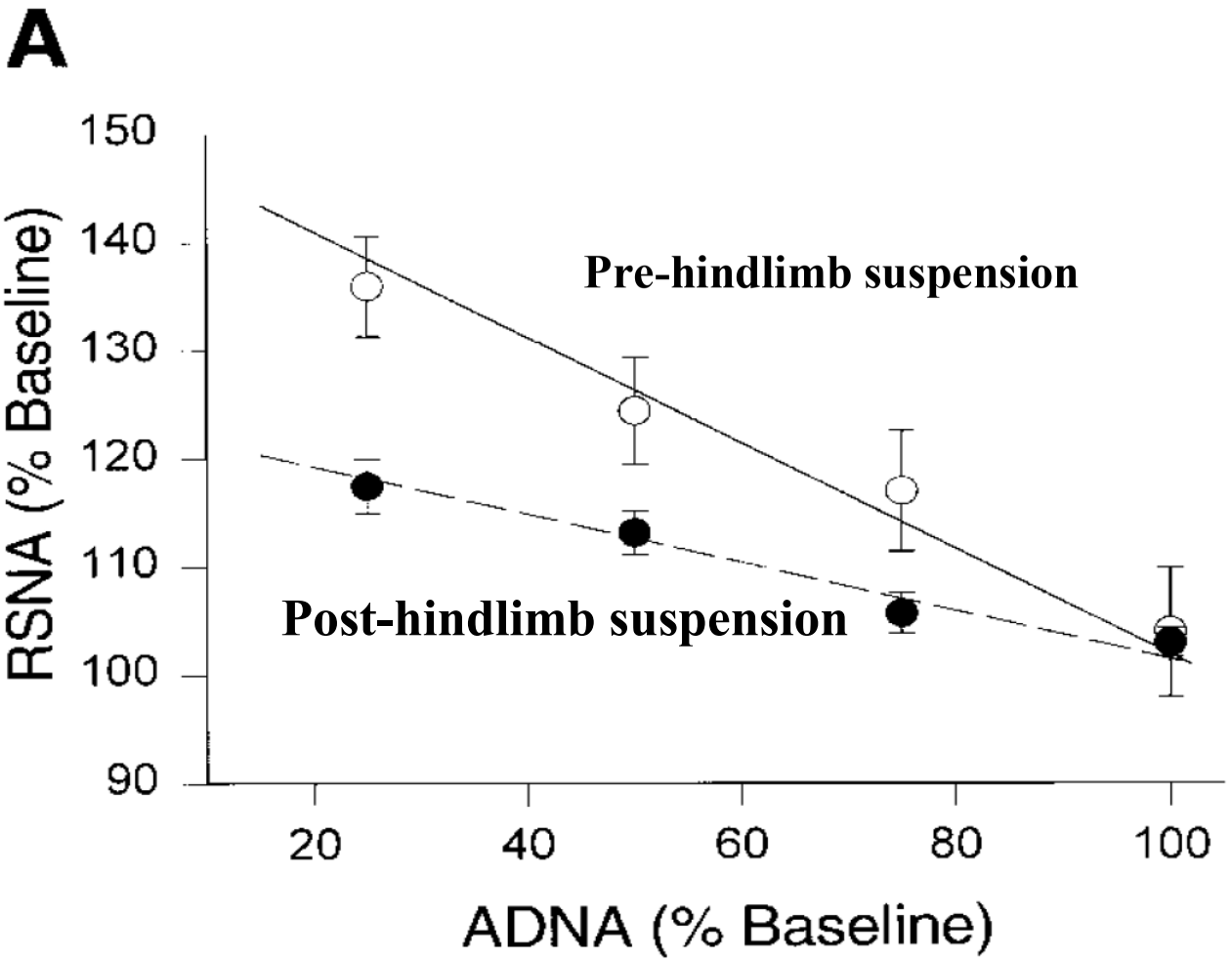
Norepinephrine responses to tyramine and tilt



In presyncopal subjects, stores of norepinephrine are adequate and can be released pharmacologically but are not appropriately released by sympathetic nerves.

This appears to be a central nervous system problem.

Attenuation of Sympathetic Responses to Afferent Input Following Hindlimb Suspension, Moffitt et al., 1998



Computer model of mean arterial pressure responses to standing with midodrine

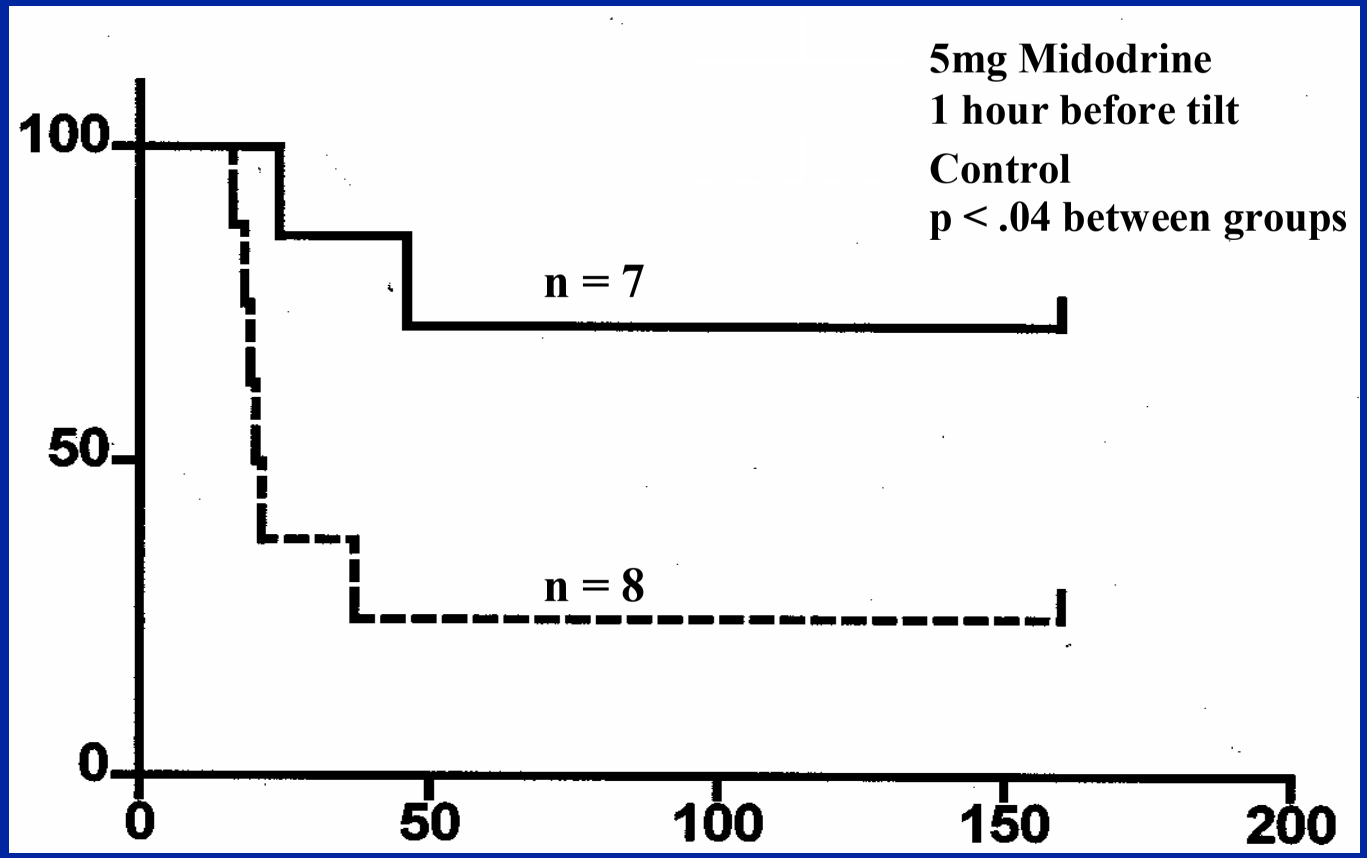
These studies suggested that a pharmacological substitute for the norepinephrine may be an effective countermeasure.

The candidate pharmacological countermeasure recommended by our clinical collaborators was midodrine because:

- **it is an α-adrenergic agonist**
- **it does not cross the blood-brain barrier**
  - **(avoiding too much norepinephrine release)**
- **it is not cardiostimulatory**
- **its peak effect occurs at one hour, so it can be taken**
  - **at TIG (time of ignition of main engines to land)**
- **it is short acting**

A 14-day bed rest study was undertaken in collaboration with NSBRI (Richard Cohen at M.I.T.).

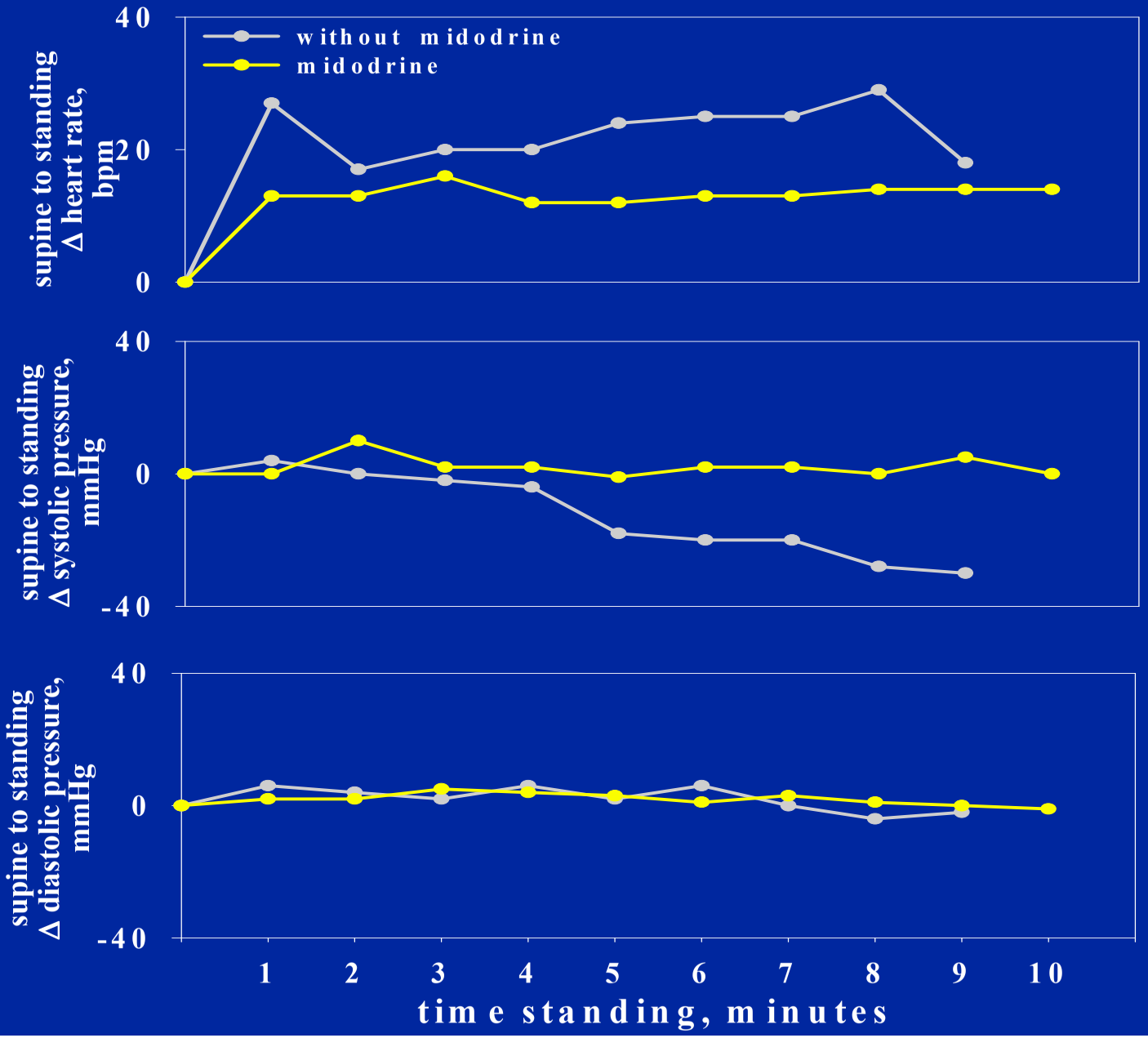
Kaplan-Meier Pre-Syncope Free Survival Following 14 Days Head-Down Bedrest



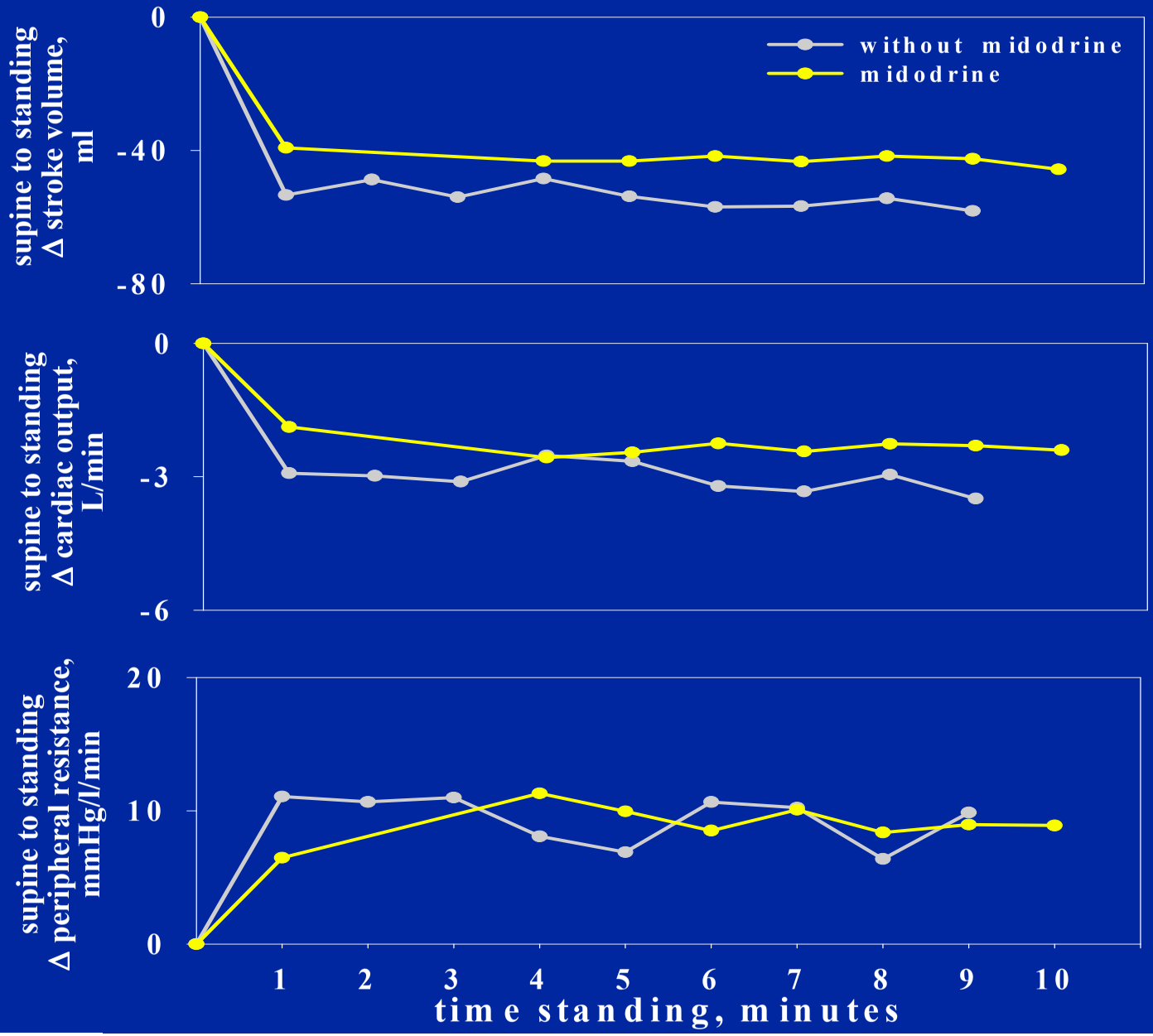
Given the positive results of the bed rest study, midodrine was approved for trial in astronauts after landing.

In order to be successful and "transparent" to the mission, midodrine must correct orthostatic hypotension in presyncopal astronauts, without causing hypertension in non-presyncopal astronauts. Initial trials were conducted on veteran astronauts, with known susceptibility.

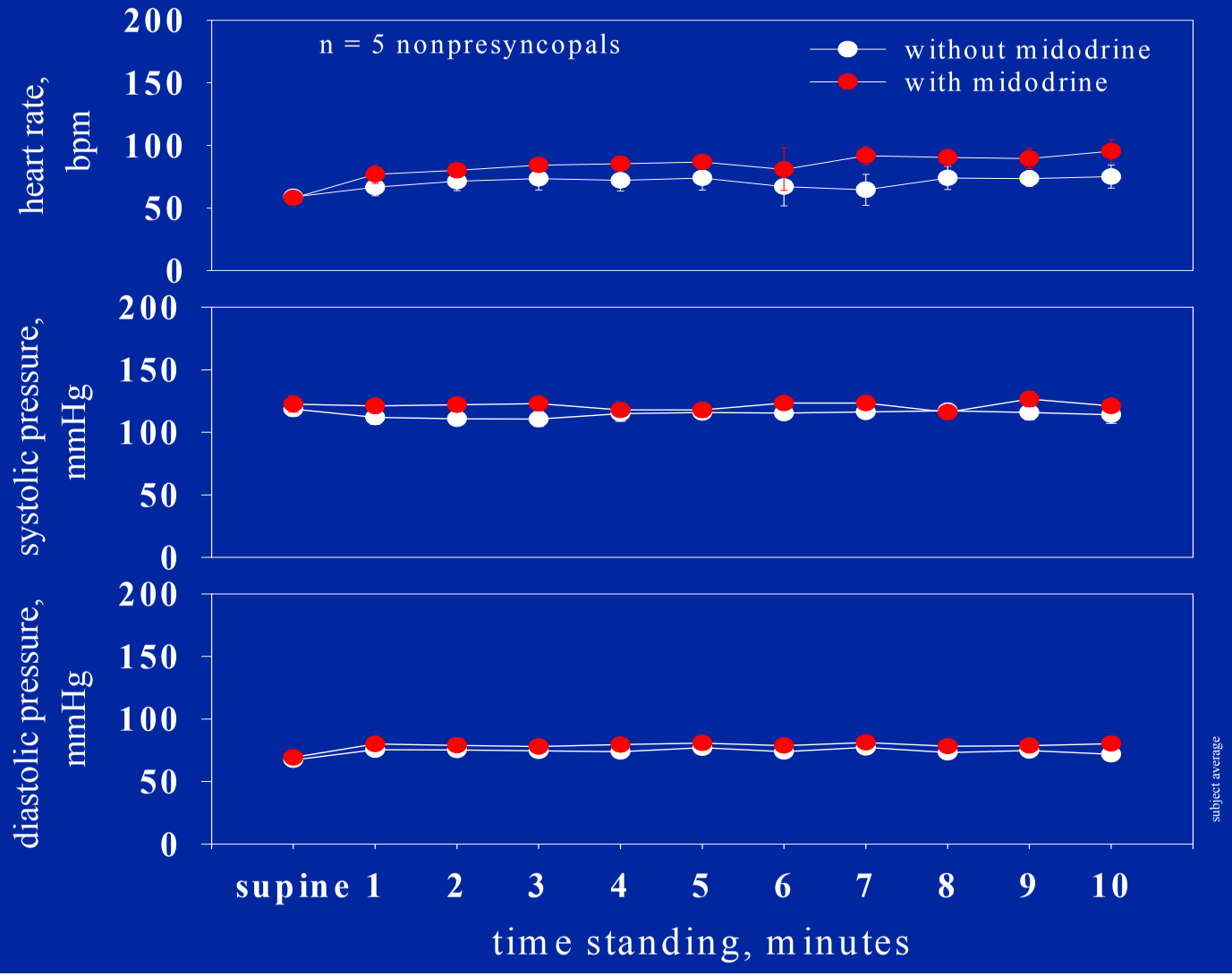
Postflight responses to upright tilt in a previously presyncopal female astronaut, one hour after midodrine



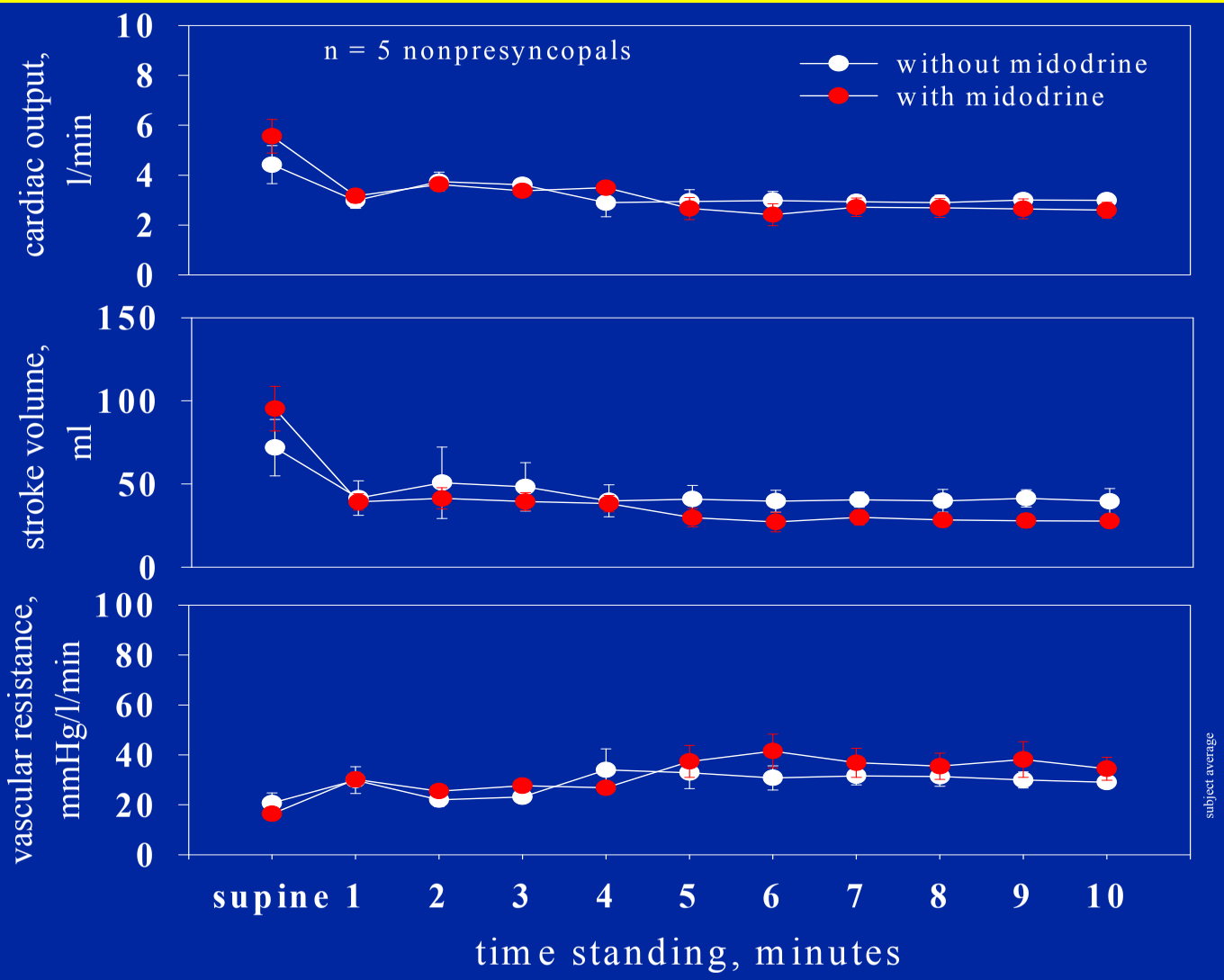
Postflight responses to upright tilt in a previously presyncopal female astronaut, one hour after midodrine



Postflight responses to tilt, with and without midodrine, in previously nonpresyncopal astronauts



Responses to tilt, with and without midodrine, in nonpresyncopal astronauts



Because of these promising results, trials of midodrine administration at TIG (time of ignition of main engines for return to Earth) have begun.

Many factors contribute to postflight orthostatic hypotension

The incidence and severity of postflight orthostatic hypotension has a complex, interrelated set of contributing factors, including:

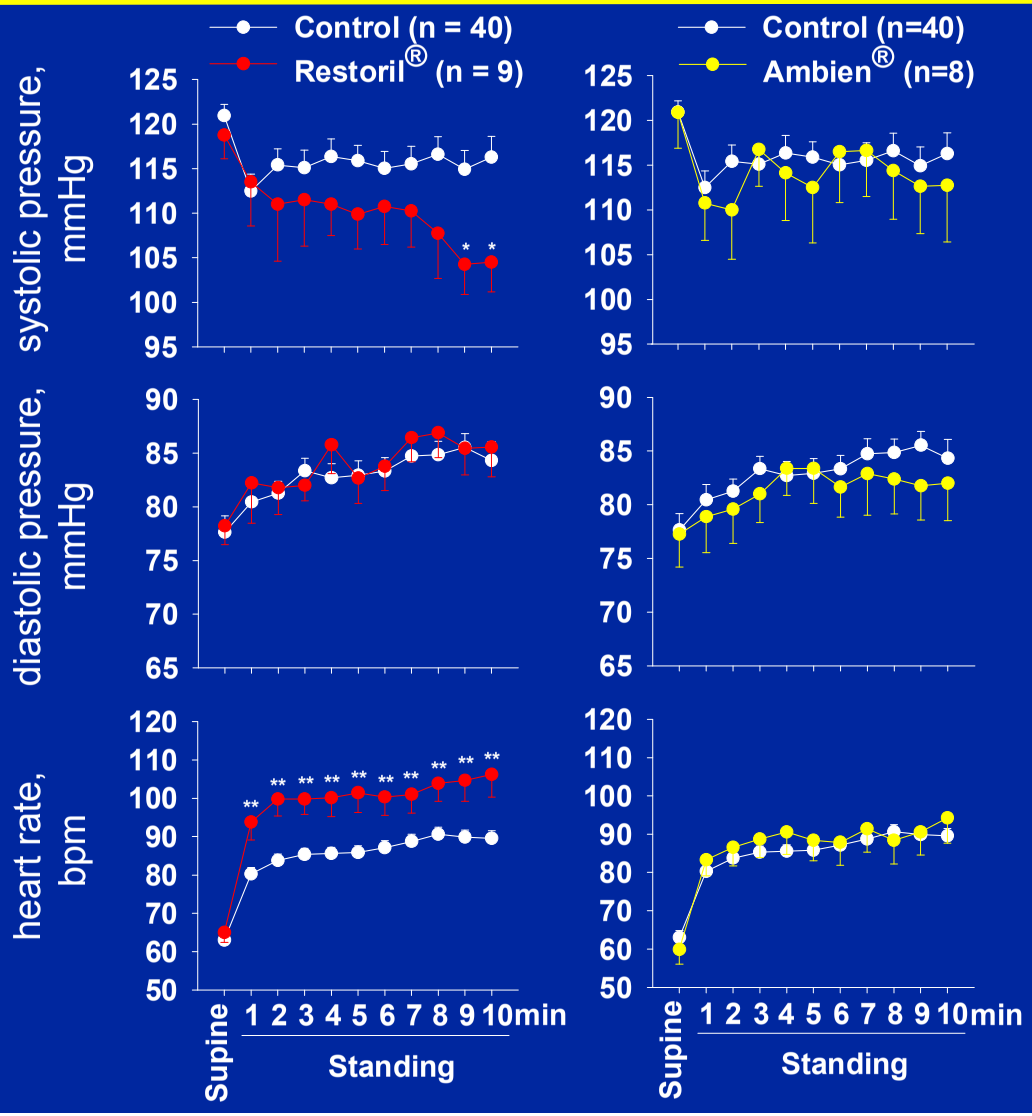
- Dehydration
- Loss of neural control of blood pressure
- Individual preflight characteristics
- Changes in blood vessel responses
- Duration of flight
- Gender
- Others

"Spinoffs"

Integrated approaches to clinical research create opportunities for new discoveries.

- Previously unreported interaction between promethazine and midodrine.
- Identification of subpopulations in normotensive subjects who may be predisposed to hypo- and hypertension.
- Importance of center of gravity of human bodies to fluid dynamics in bed rest and spaceflight.
- Tendency for temazepam to aggravate postflight orthostatic hypotension.
- Greater understanding of contributers to circulatory filling pressure.

53% of astronauts require sleeping medications during flight. Use of Restoril®, but not Ambien®, contributes to post-spaceflight orthostatic hypotension



Some Countermeasures Are Not Compatible

- Astronauts take promethazine for "space motion sickness".

- During a prospective study, we discovered a previously unreported interaction between midodrine and promethazine.

- The combination of midodrine and promethazine increased the incidence and severity of akathisia experienced with promethazine alone. Recent work has determined that the two drugs are metabolized by the same cytochrome P_{450} isozyme.

- This interaction was reported to the FDA and is in press in JAMA.

- It is now a flight rule that no crew member may take both midodrine and promethazine for landing.

Conclusion

Orthostatic hypotension following spaceflight is a real world problem that could limit our planned exploration of the Solar System. However, our approach to discover an appropriate solution is not uniquely suited to NASA. The methodology undertaken to solve this problem can be applied to any biomedical problem. This integrated approach requires the focused, directed collaboration of investigators with different skills and expertise.

Collaborating Institutions

University of Mississippi Medical Center
Johnson Space Center
Medical College of Virginia
University of California, San Diego
Vanderbilt University
Brigham and Women's Hospital
Massachusetts Institute of Technology
Harvard Medical School
Albany Medical School
University of Texas Health Science Center
Hermann Hospital
University of Texas Medical Branch at Galveston
Pennsylvania State University