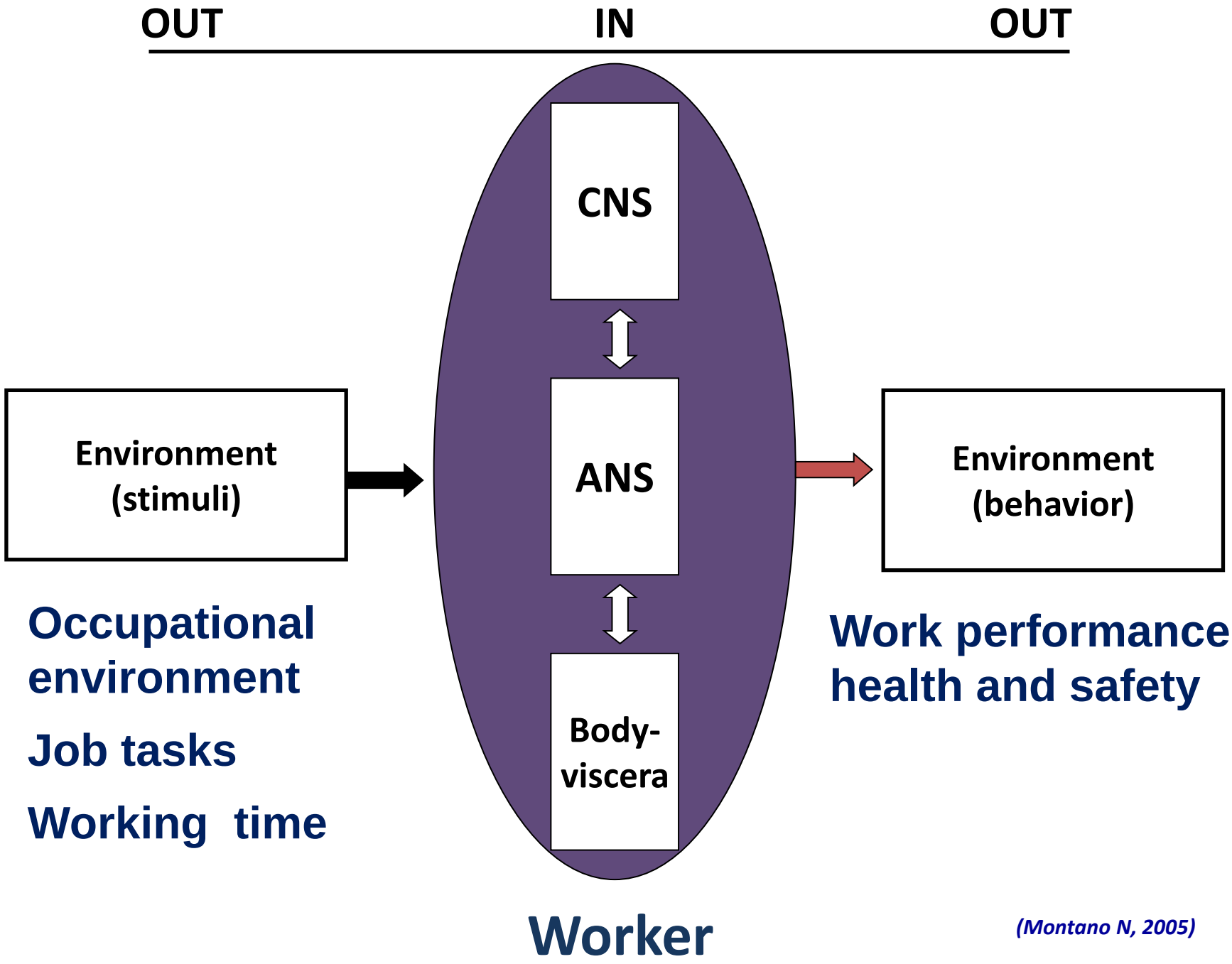
HUMANITAS
RESEARCH HOSPITAL
HUMANITAS
UNIVERSITY

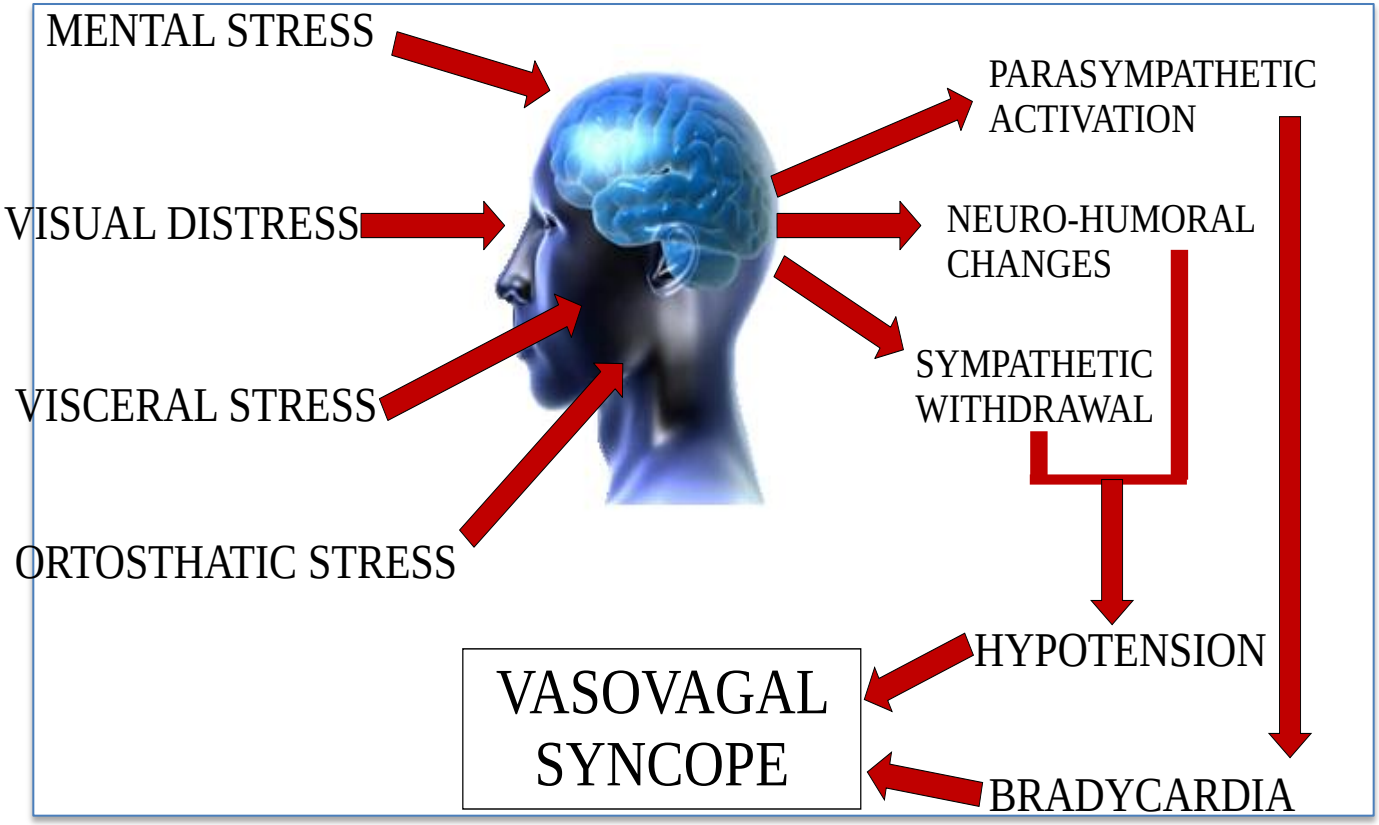
Individual Cardiovascular Autonomic Profile and "Precise Medicine" from the Clinical Laboratory to the Working Place

Franca Barbic
Humanitas Research Hospital, Internal Medicine and Syncope Unit,
Department of Biomedical Sciences, Humanitas University, Rozzano. Italy

May 3th 2017


OUT
IN
OUT
CNS
ANS
Body-viscera
Environment (stimuli)
Environment (behavior)
Occupational environment
Job tasks
Working time
Work performances health and safety
Worker
(Montano N, 2005)

Initiating factors (central and peripheral) and autonomic systems involved in Reflex Syncope



R. Mosqueda-Garcia in «Vasovagal Syncope»; Ed P. Alboni, R. Furlan, Springer. 2015

In susceptible individuals different stimuli potentiallly present in the work environment or during specific job task might promote reflex syncope.

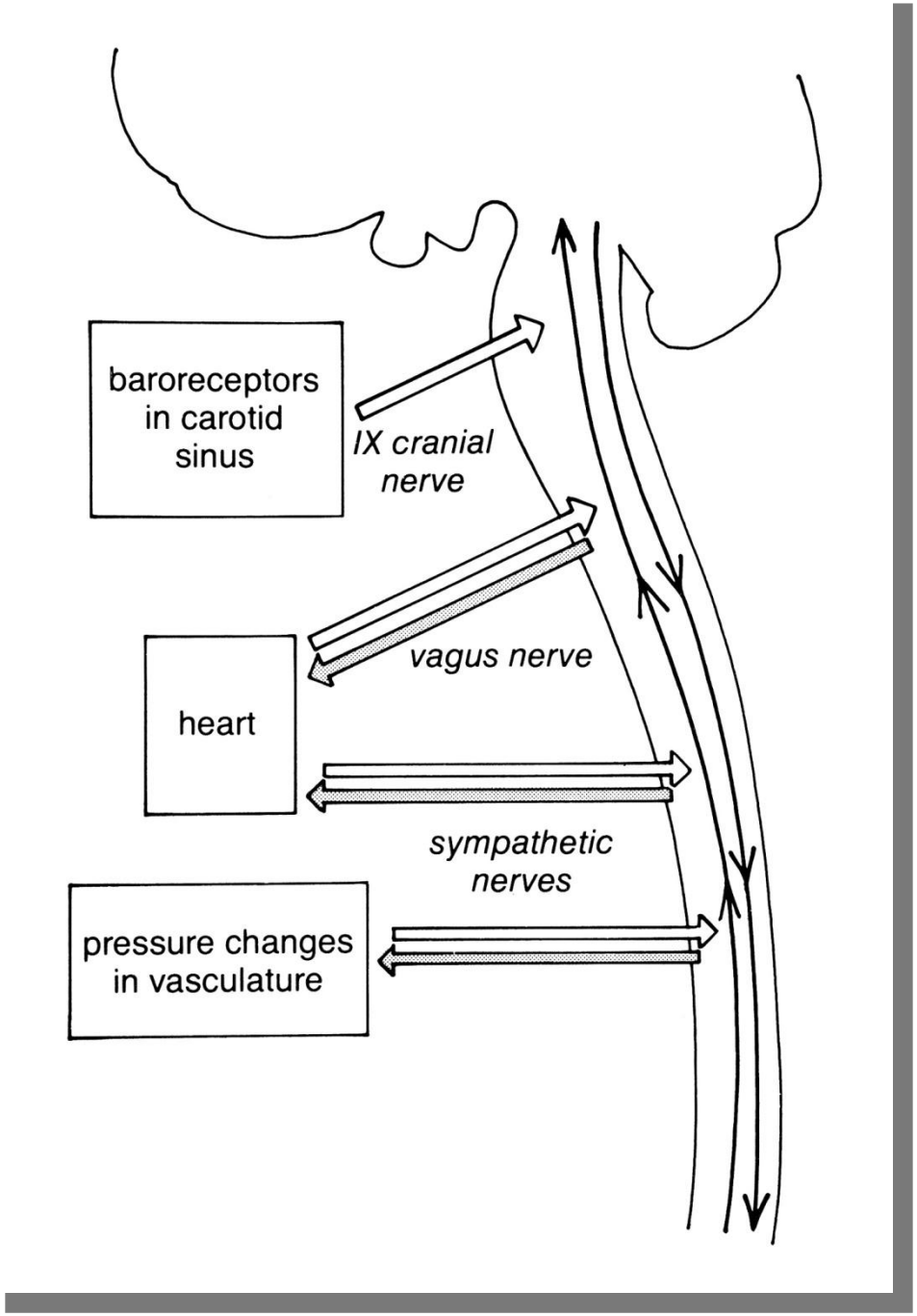
A New Initiative on Precision Medicine Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D. N Engl J Med 2015;

“Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

President Barack Obama, State of the Union Address, January 20, 2015

Precise Medicine and Work Environment

According to the National Research Council, based on genetic, environmental, and lifestyle factors, precision medicine focuses on identifying which approache will be effective for each patient.


baroreceptors in carotid sinus
IX cranial nerve
vagus nerve
heart
sympathetic nerves
pressure changes in vasculature

Cardiovascular Autonomic Profile Assessment

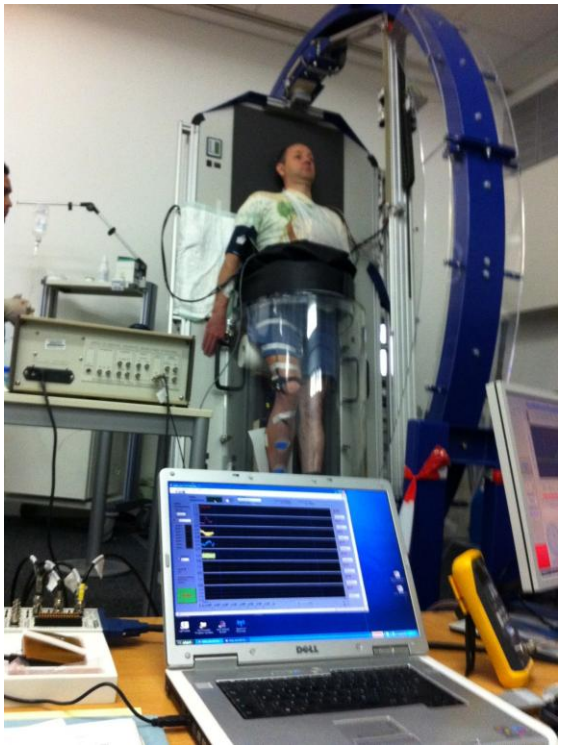
In Clinical Laboratory: experimental standardized protocols

Clinical Laboratory

HUMANITAS RESEARCH HOSPITAL

European Space Agency
Kholn – Germany
Clinical Laboratory

esa
European Space Agency



80 head-up Tilt-test
Lower body negative pressure
Microneurography

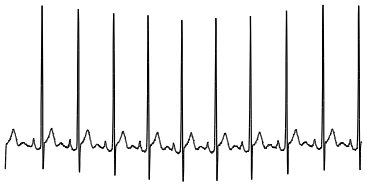
Standard protocol:

- 5-10 minutes in supine position, baseline
- Sinus Arrhythmia (relationships resp/HR)
- Valsalva Maneuver (relationships BP/HR)
- Supine plasma caths (epinephrine, norepinephrine)
- Head- up **Tilt** 60 -75 for 20 minutes (BP and HR)
- Orthostatic plasma caths (epi and norepinephrine)

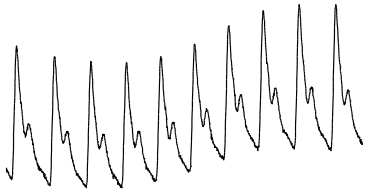
- Specific additional provocative test (hyperventilation, cough, mental arithmetic, noise exposure, inhalation of polluted air or other occupational pollutants)

Variables continuously recorded to assess cardiovascular autonomic profile in clinical laboratory

ECG



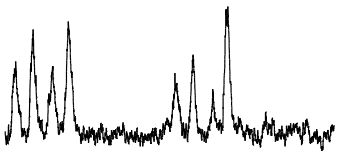
BP



Total Peripheral Resistances (TPR), and Cardiac Output (CO)

RESP

MSNA



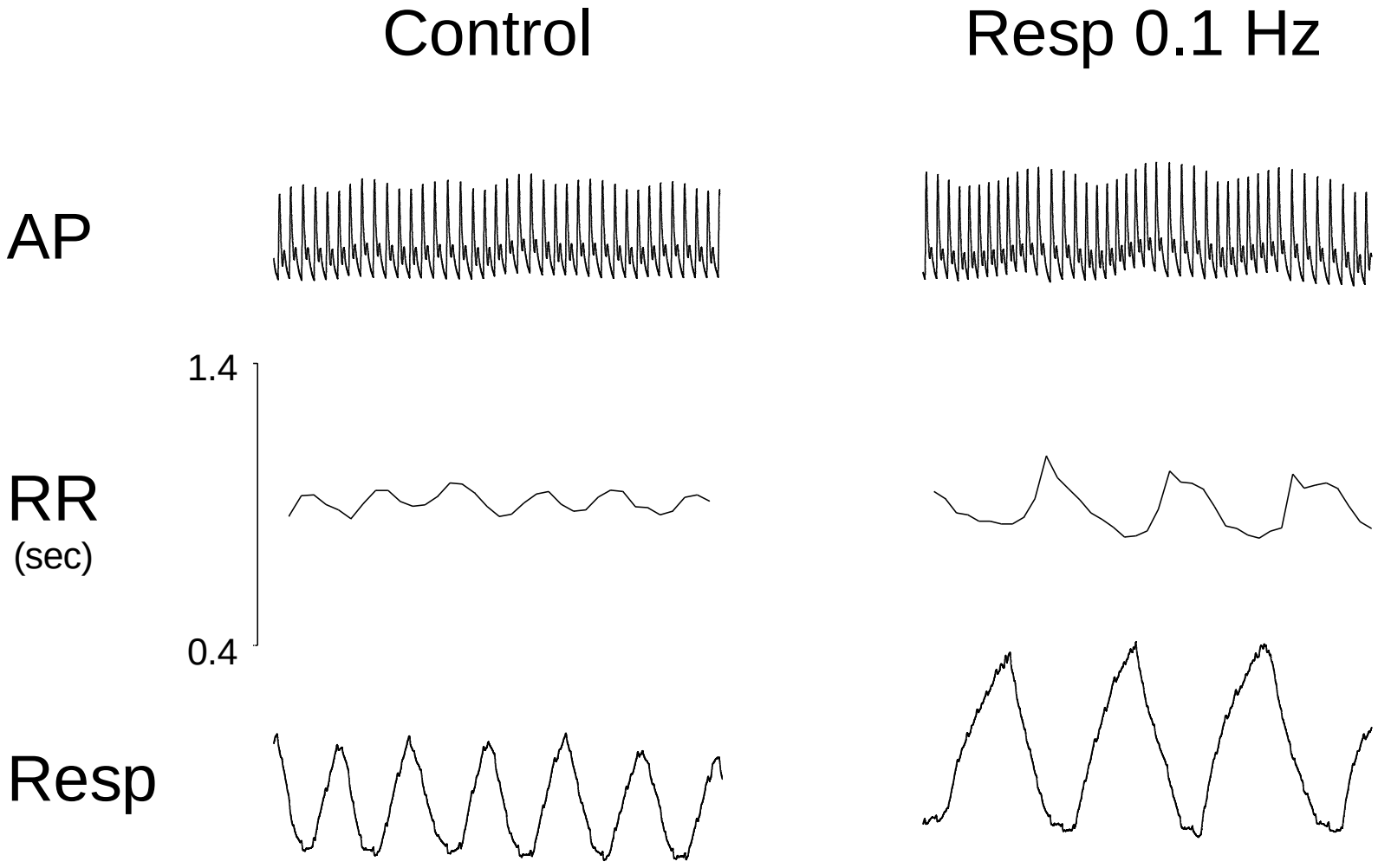
Muscle Sympathetic Nerve Activity, MSNA (burst/min or burst/100 beats)

Multiunit postganglionic sympathetic nerve discharge recording from peroneal nerve by microneurography technique

$ETCO_2$

SINUS ARRHYTHMIA

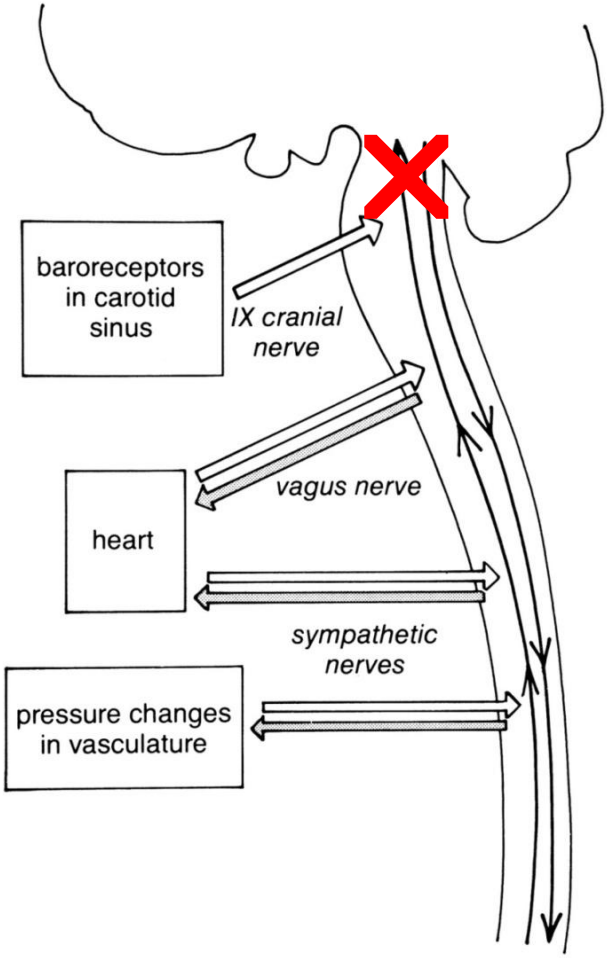
Test the reflex change of HR induced by changes in respiratory rate.



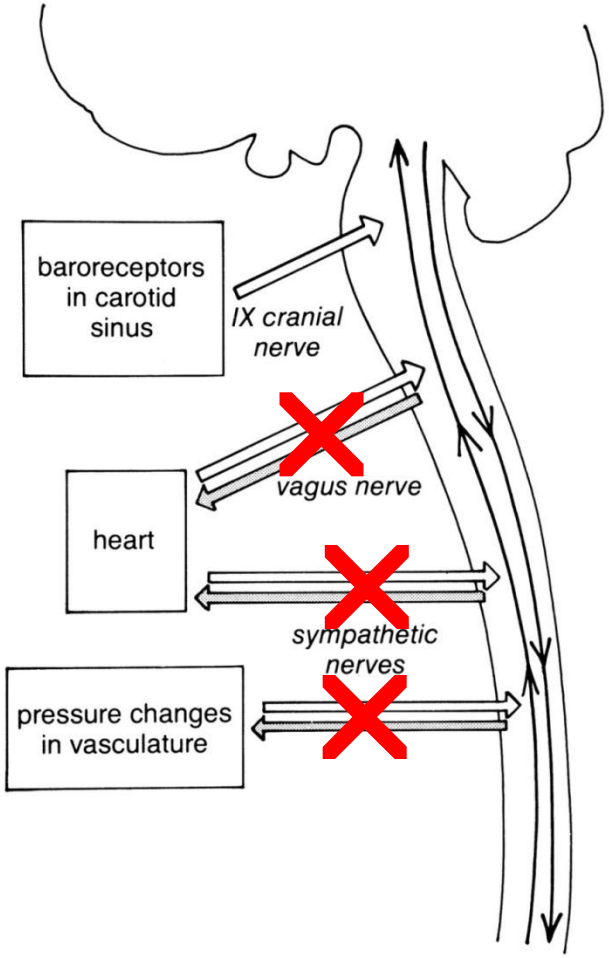
SA (HR max - min): **26** (v.n.>8)

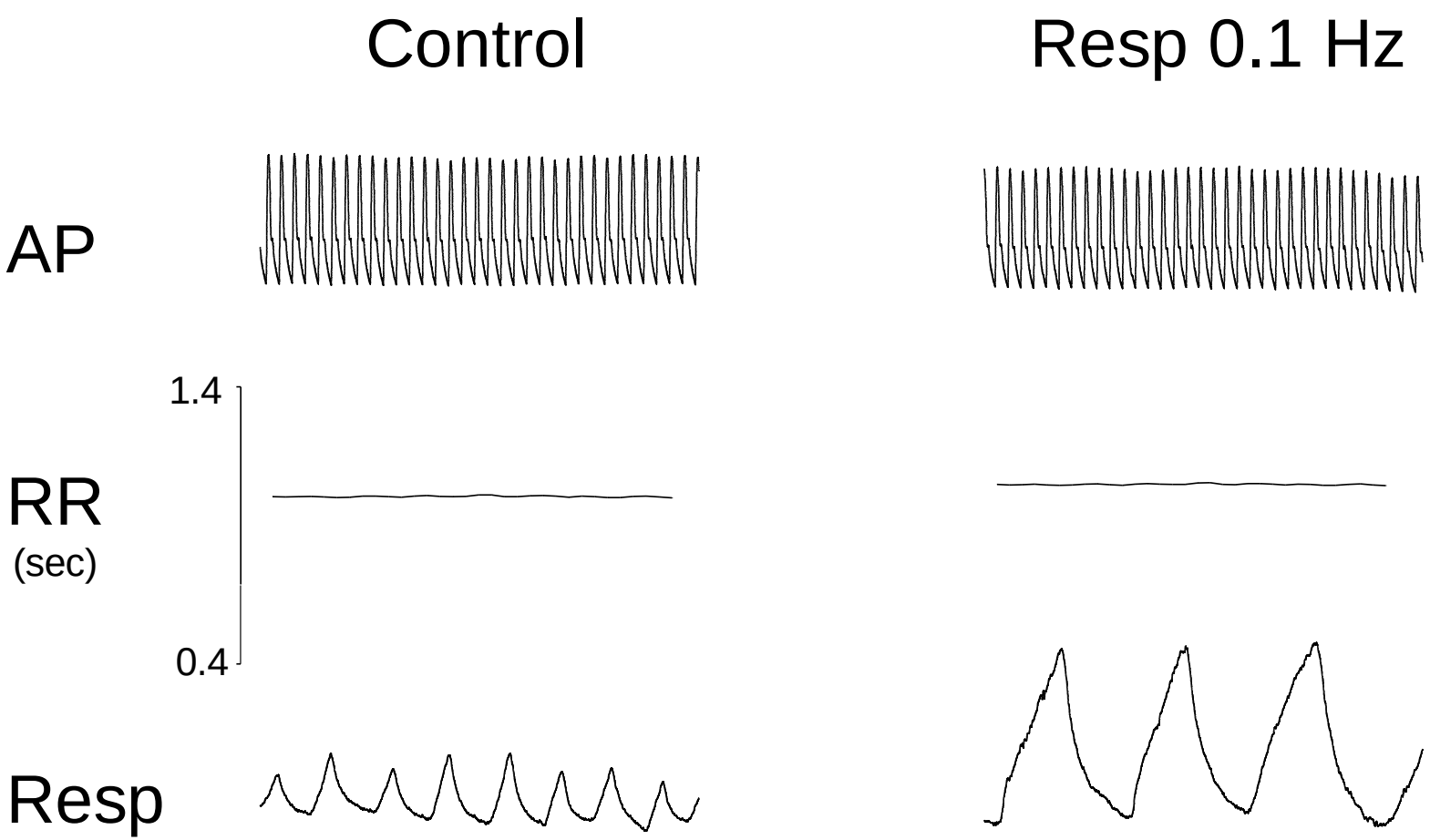
SA (ratio): **1.44** (v.n.>1.2)

PARKINSON'S DISEASE
Central dysautonomia



PURE AUTONOMIC FAILURE
Peripheral dysautonomia



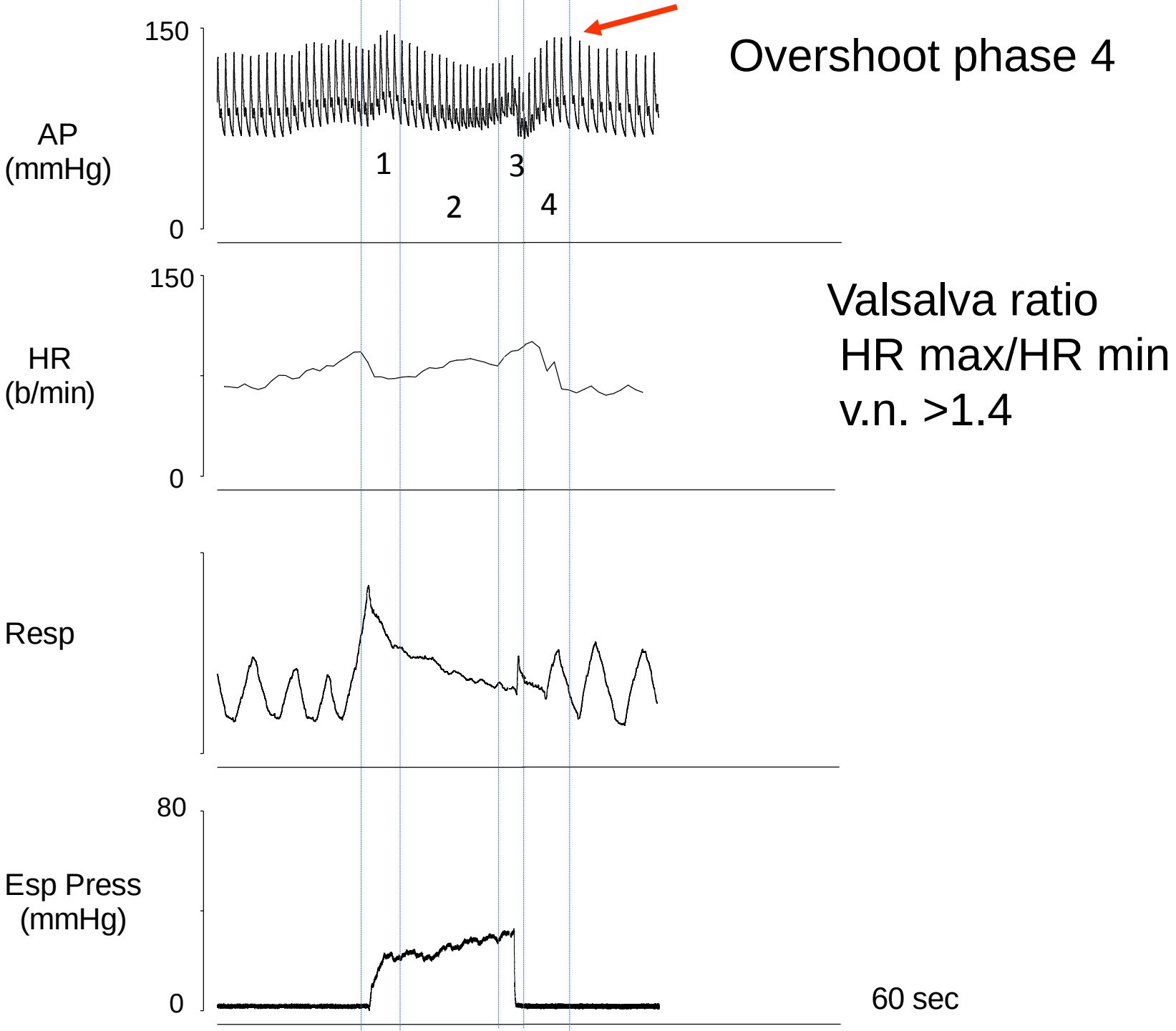


SA (HR max - min): **0.6** (v.n.>8)

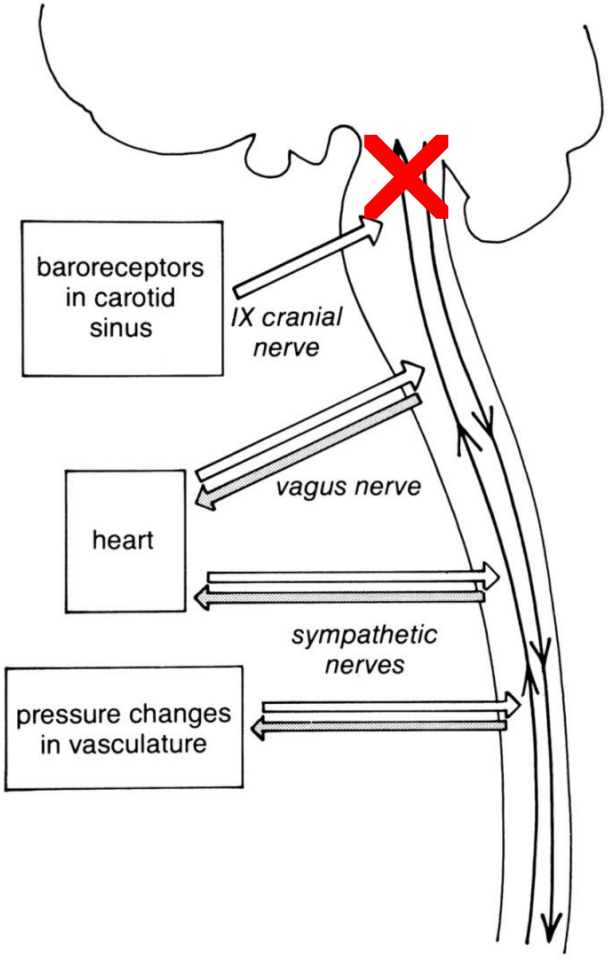
SA (ratio): **1.01** (v.n.>1.2)

VALSALVA MANEUVER

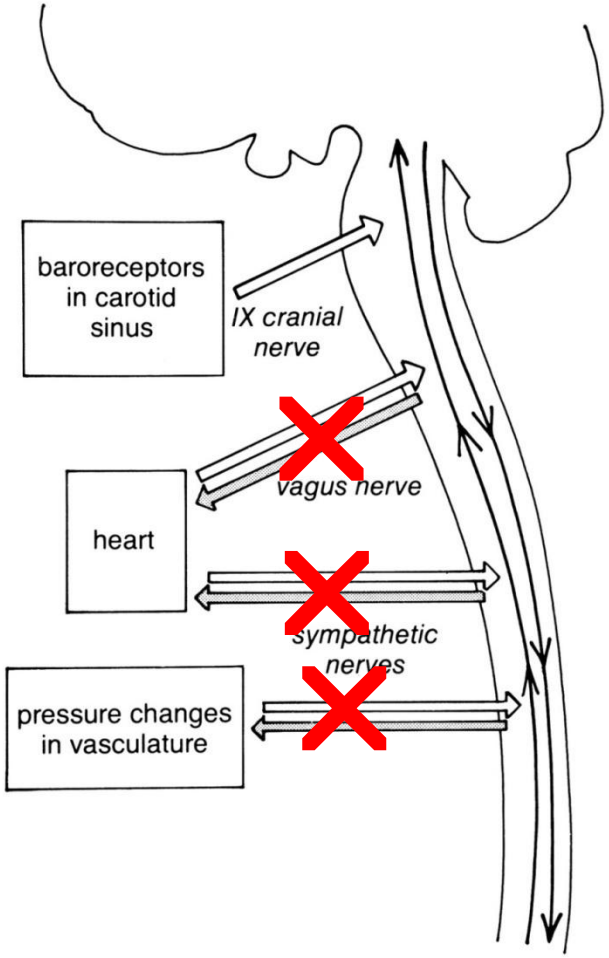
Test the reflex changes of HR in response to changes in systemic blood pressure (baroreceptors activity, cardiac and vascular autonomic control)

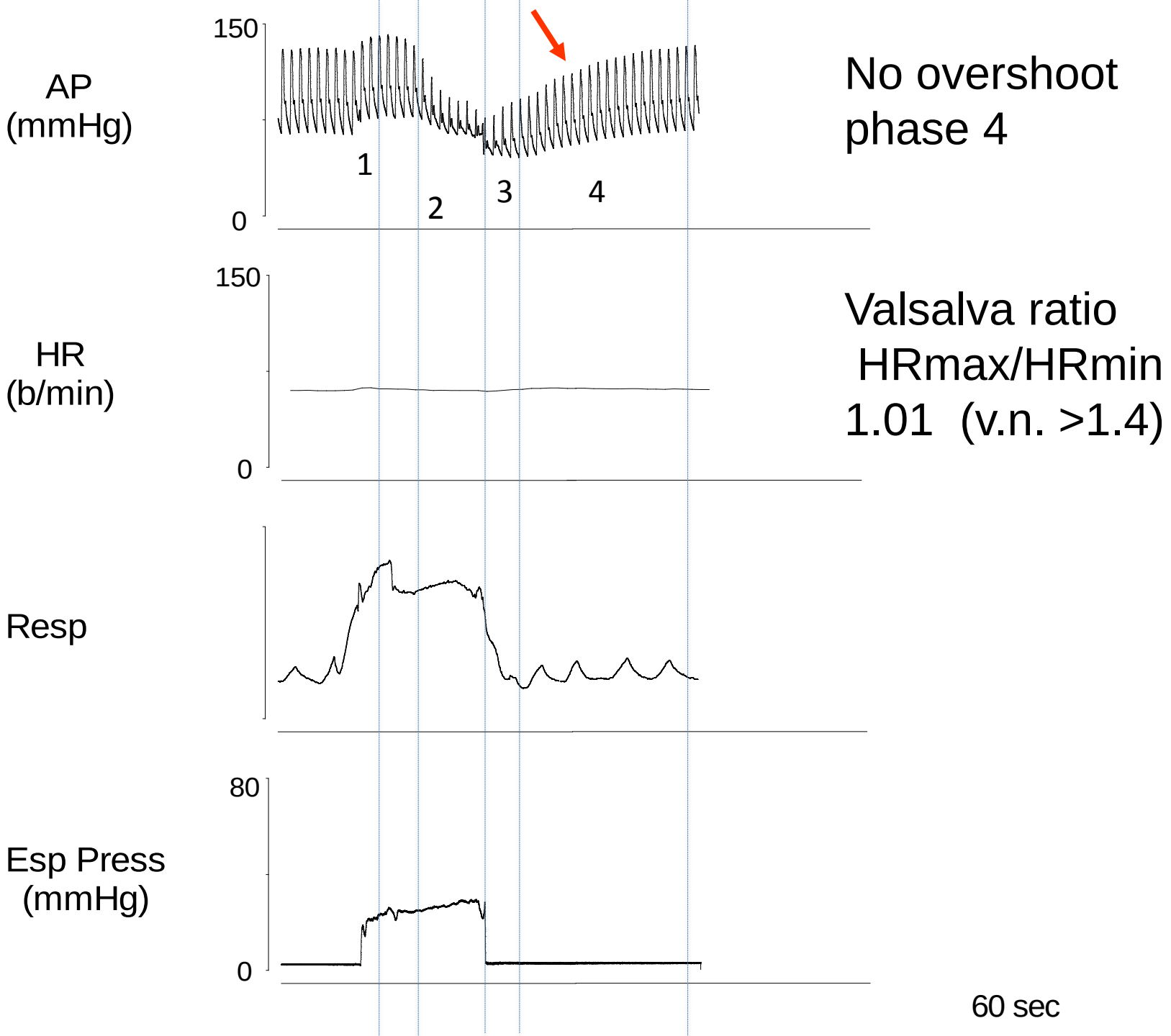

150
AP
(mmHg)
0
1
2
3
4
Overshoot phase 4
150
HR
(b/min)
0
Valsalva ratio
HR max/HR min
v.n. >1.4
Resp
80
Esp Press
(mmHg)
0
60 sec

PARKINSON'S DISEASE
Central dysautonomia



PURE AUTONOMIC FAILURE
Peripheral dysautonomia



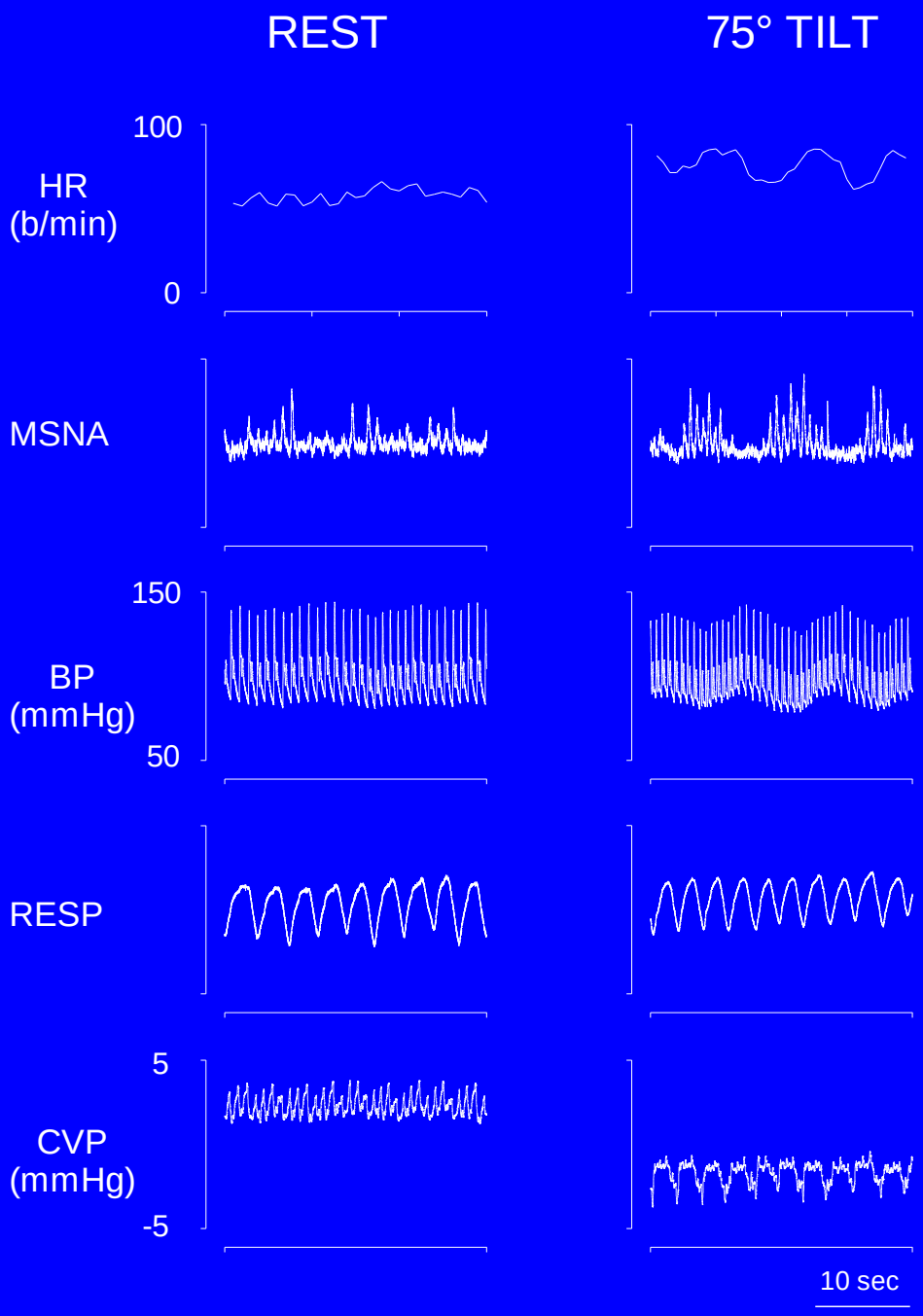


No overshoot
phase 4

Valsalva ratio
HRmax/HRmin
1.01 (v.n. >1.4)

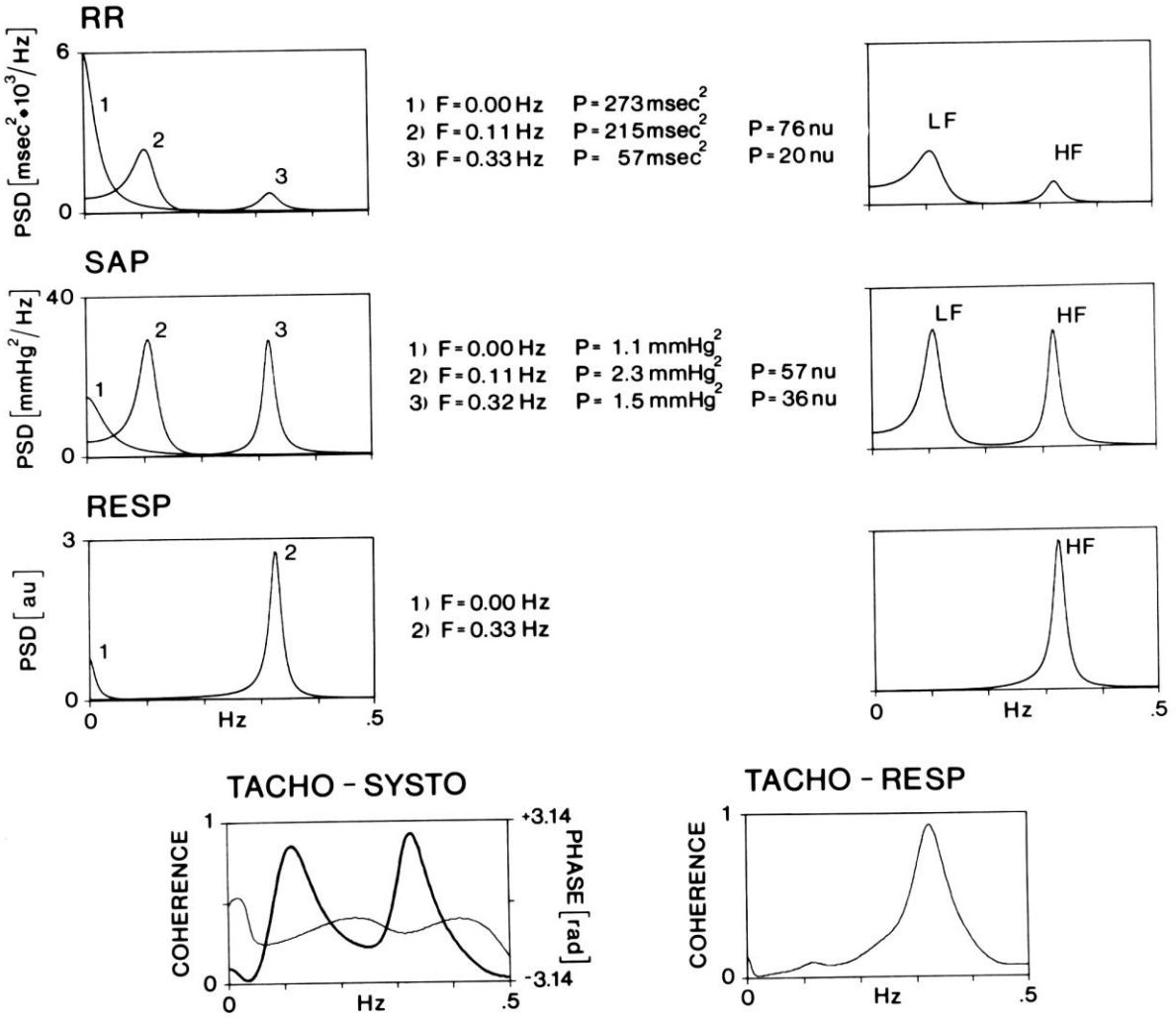
TILT TEST

- Gravitational stimulus
- Increase of cardiovascular sympathetic tone and vagal cardiac withdrawal



Furlan et al, Circulation 2000; 101: 886

Spectral analysis of R-R, BP, Resp variability provides indices od cardiovascular autonomic control

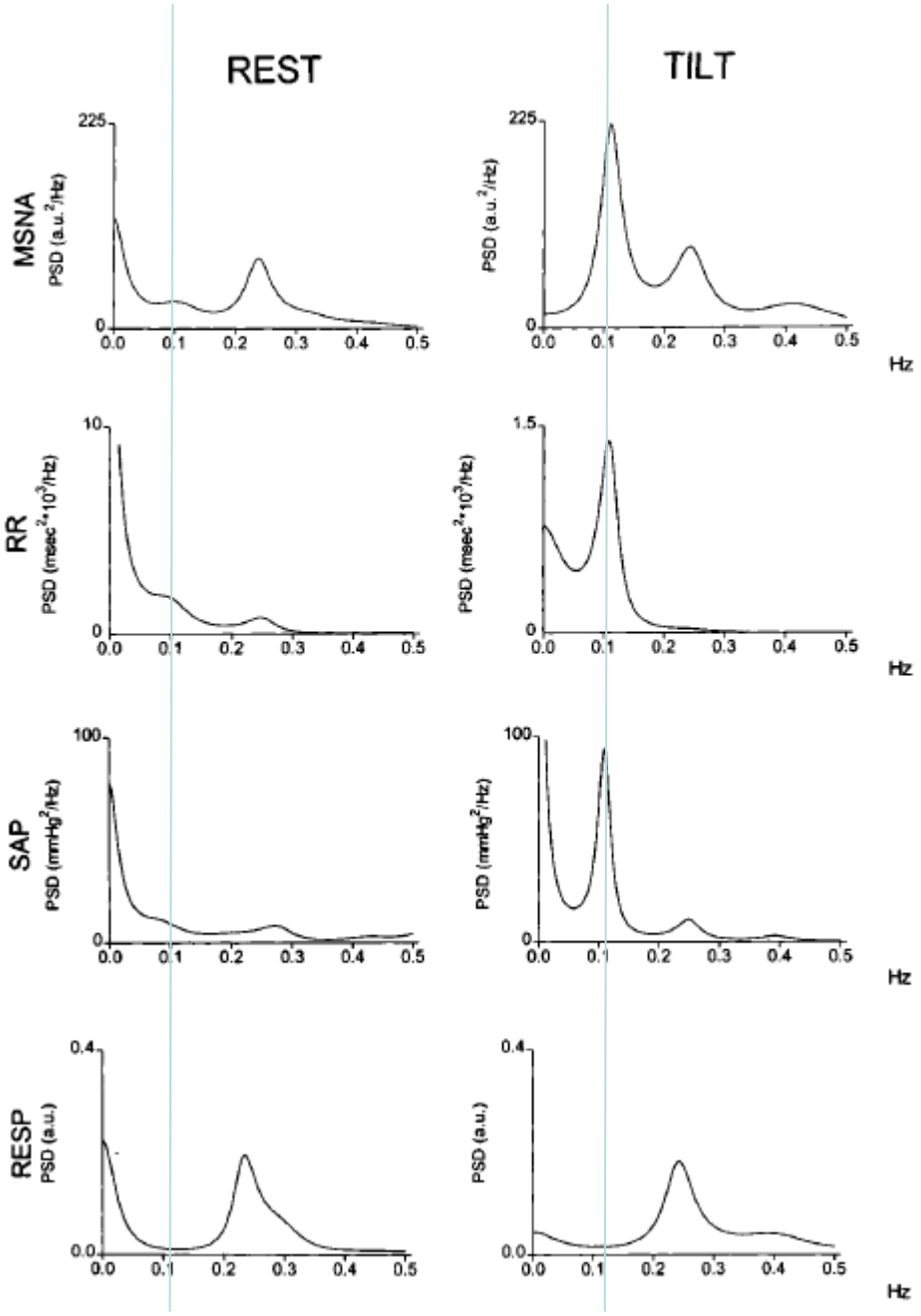


LF $_{RR}$ index on cardiac sympathetic modulation

HF $_{RR}$ index of cardiac vagal modulation

LF/HF index of instantaneous sympathovagal modulation to the heart

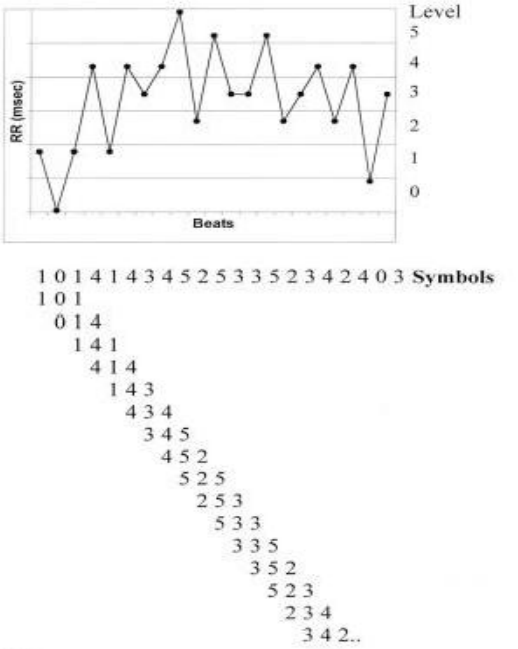
LF $_{SAP}$ index of simpathetic modulation to the vessels

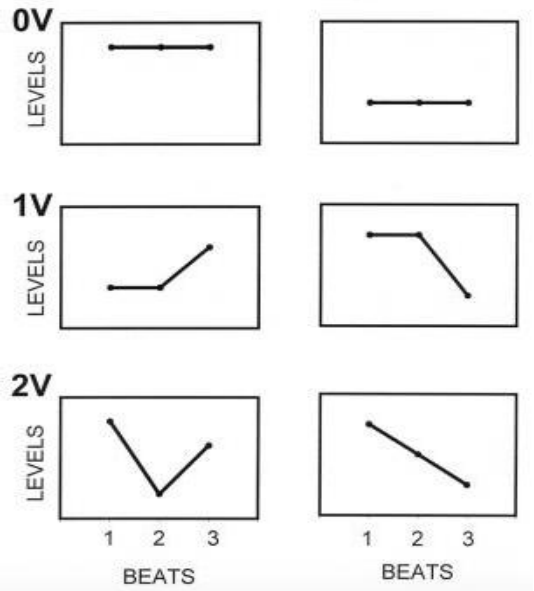


LF $_{MSNA}$ index of modulation at 0.1 Hz of sympathetic nerve discharge to the vessels strictly coupled with RR and SAP oscillations by the baroreceptor mechanisms

Furlan et al, Circulation 2000; 101: 886

Non linear analysis techniques of short-term R-R variability: **the symbolic analysis**





RR series (msec) is spread over 6 levels and each level is given a symbol number (0-5) (upper panel). Patterns of 3 length symbols are created (lower panel).

The symbolic indexes have the potential to detect *non-reciprocal changes* in sympathetic and parasympathetic or *reciprocal changes with different magnitudes*

0V (no change of levels) is an index of sympathetic modulation

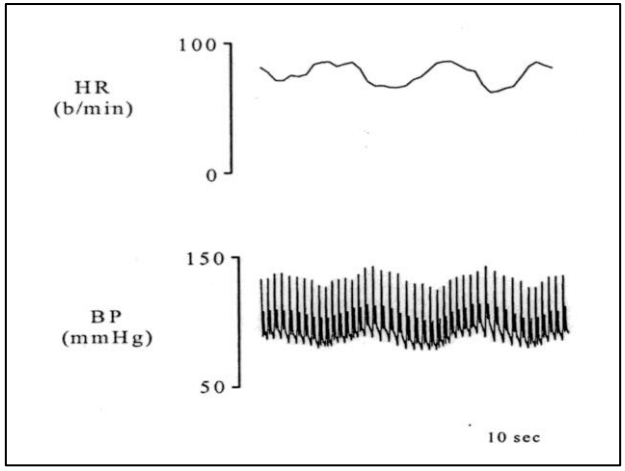
2V (2 changes of level in the pattern) is an index of **parasympathetic modulation, 2UV and 2LV.**

Porta A et al Chaos, 17, 015117 (2007)

Baroreflex sensitivity assessment

Cardiac: reflex changes of heart rate in response to change in blood pressure

1. in time domain: relationship between SAP and RR spontaneous +/- sequences



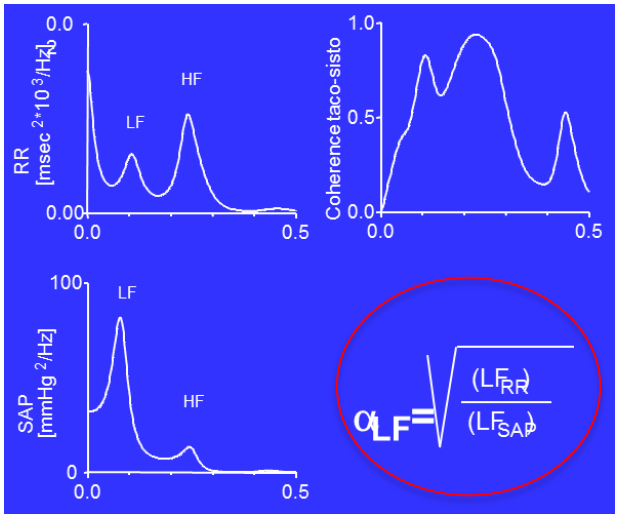
Negative sequence: systolic arterial pressure decrease HR increase (RR decrease)

Positive sequence: systolic arterial pressure increase HR decrease (RR increase)

BRS seq;
mmHg/msec

Bertinieri G. et all Am.J.Physiol. 1988;254:H377-83

2. in frequency domain: relationship between oscillatory component at 0,1 Hz of SAP and RR

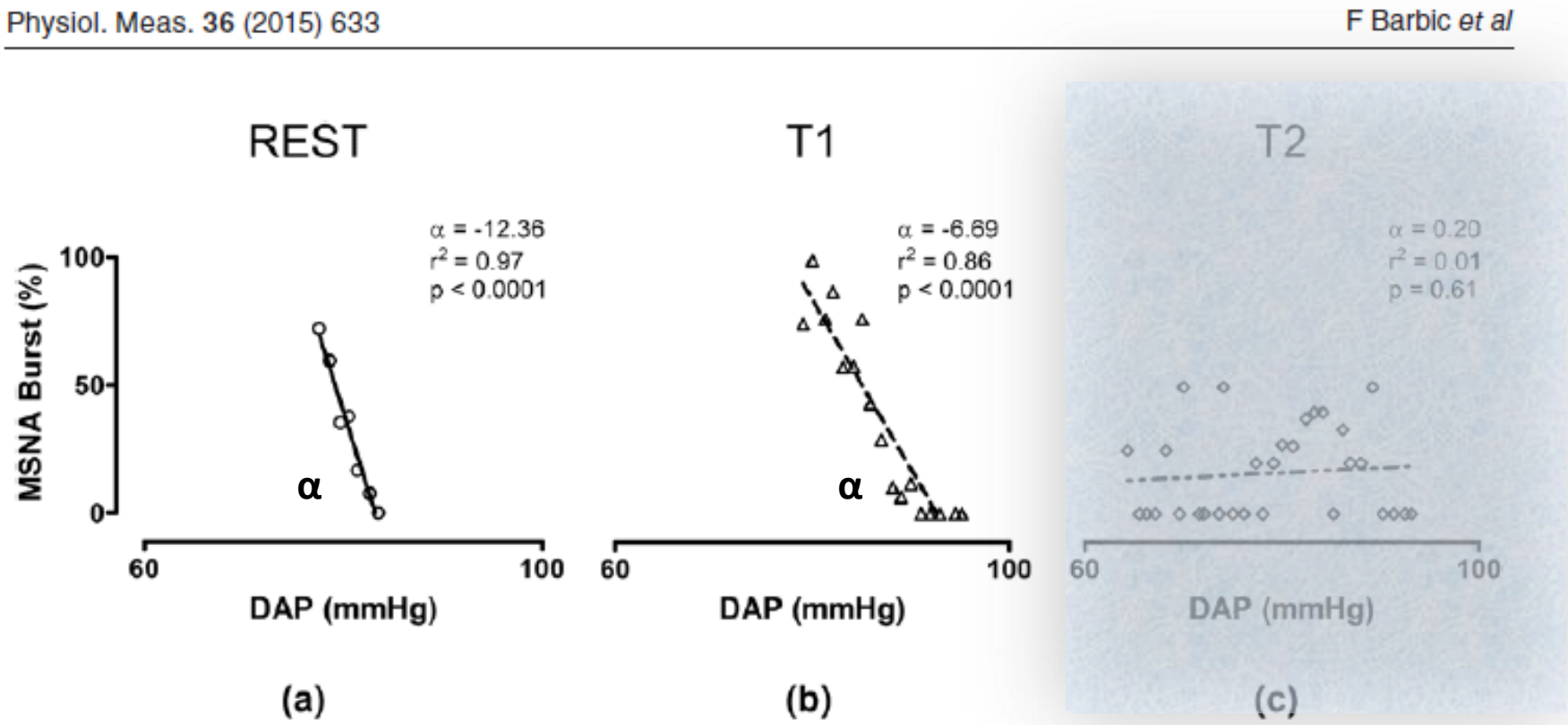


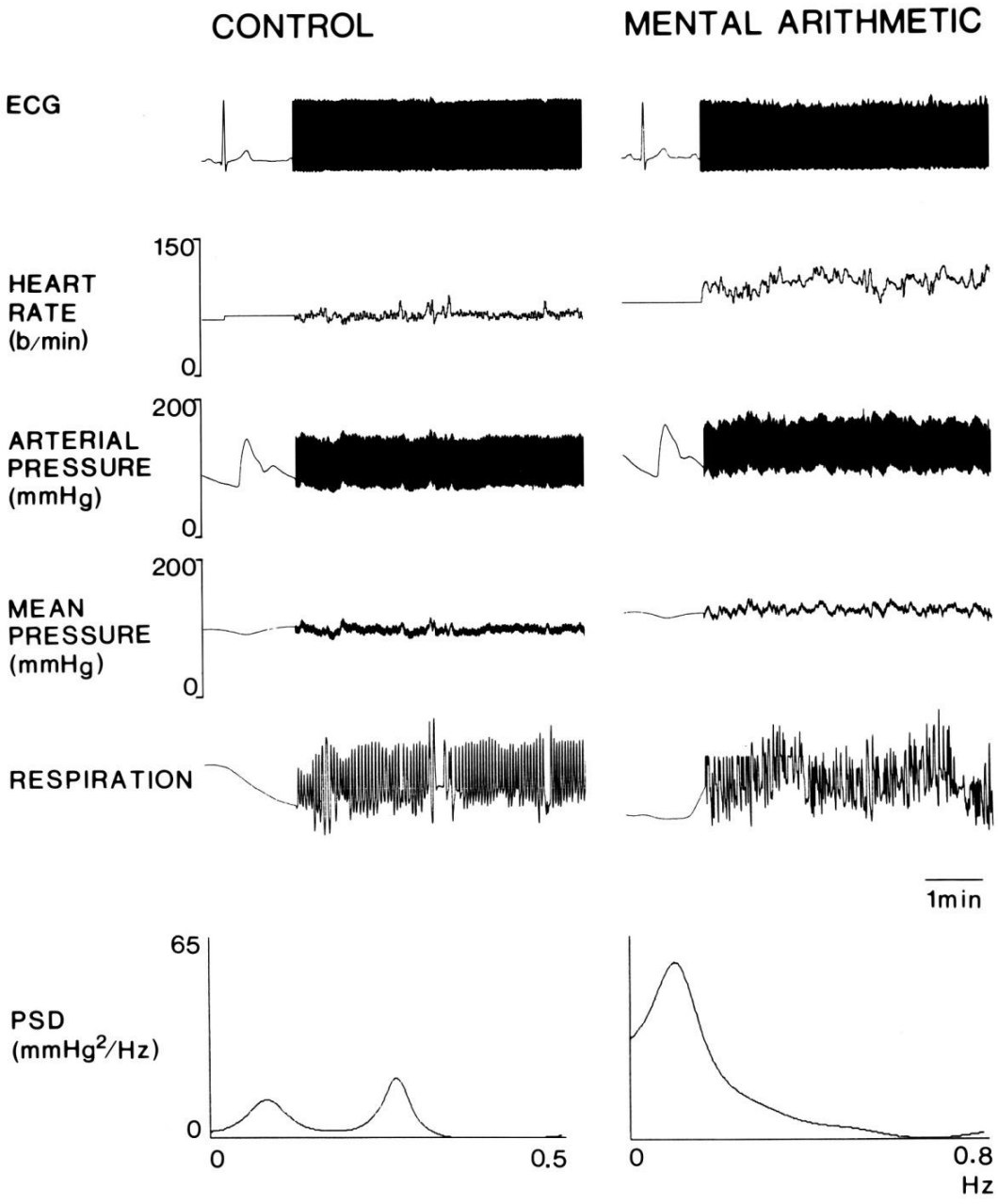
αLF
mmHg/msec

Pagani M et al Am.J.Physiol. 1988;254:H377-83

Vascular sympathetic baroreflex sensitivity (svBRS)

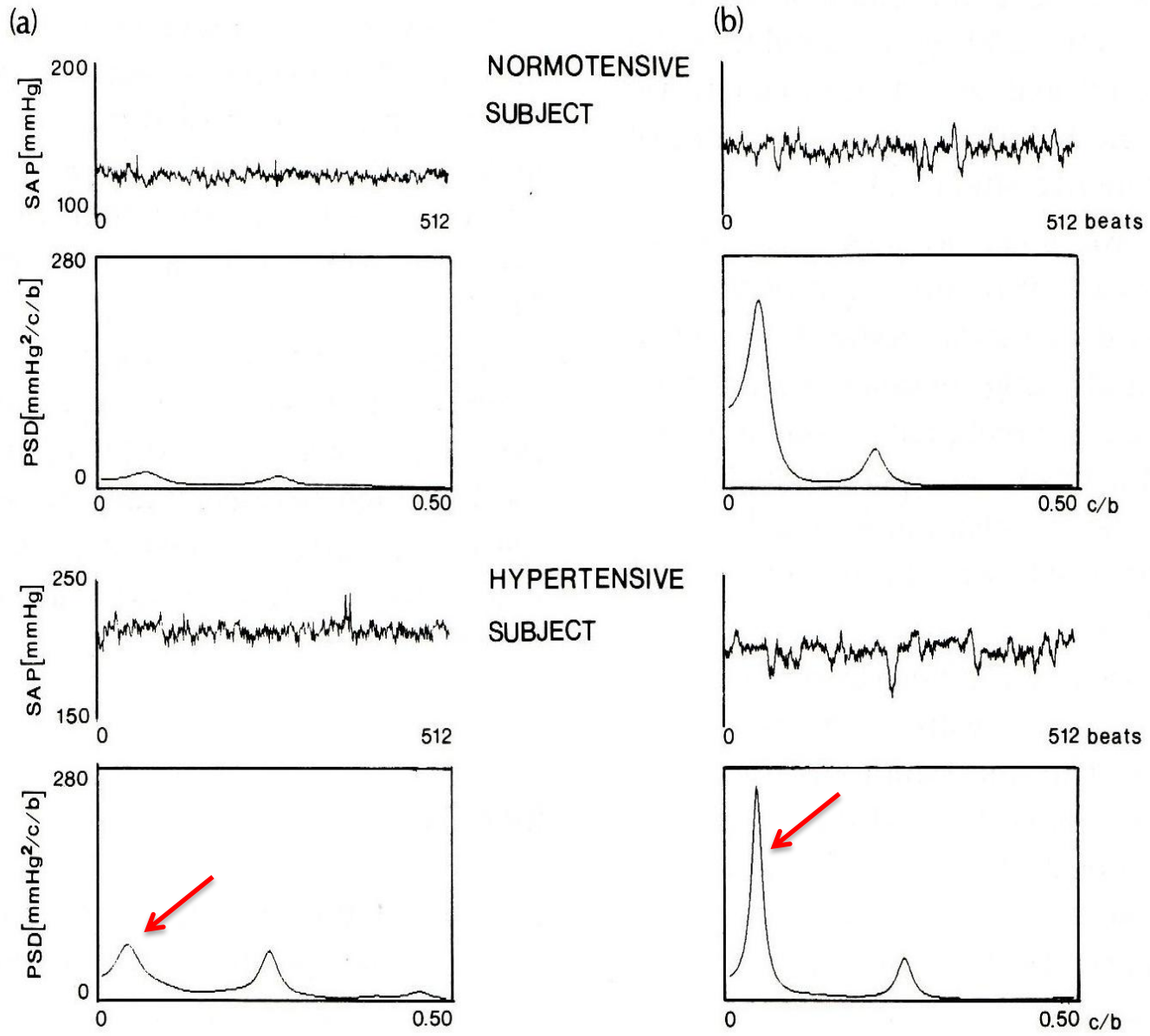
svBRS: α is the linear regression slope between MSNA bursts (%) and DAP




CONTROL
MENTAL ARITHMETIC
ECG
HEART RATE (b/min)
150
0
ARTERIAL PRESSURE (mmHg)
200
0
MEAN PRESSURE (mmHg)
200
0
RESPIRATION
1min
PSD (mmHg²/Hz)
65
0
0
0.5
0
0.8
Hz

Rest

Tilt



Furlan R. et al. J. Hypert. 1991.9:S60-61

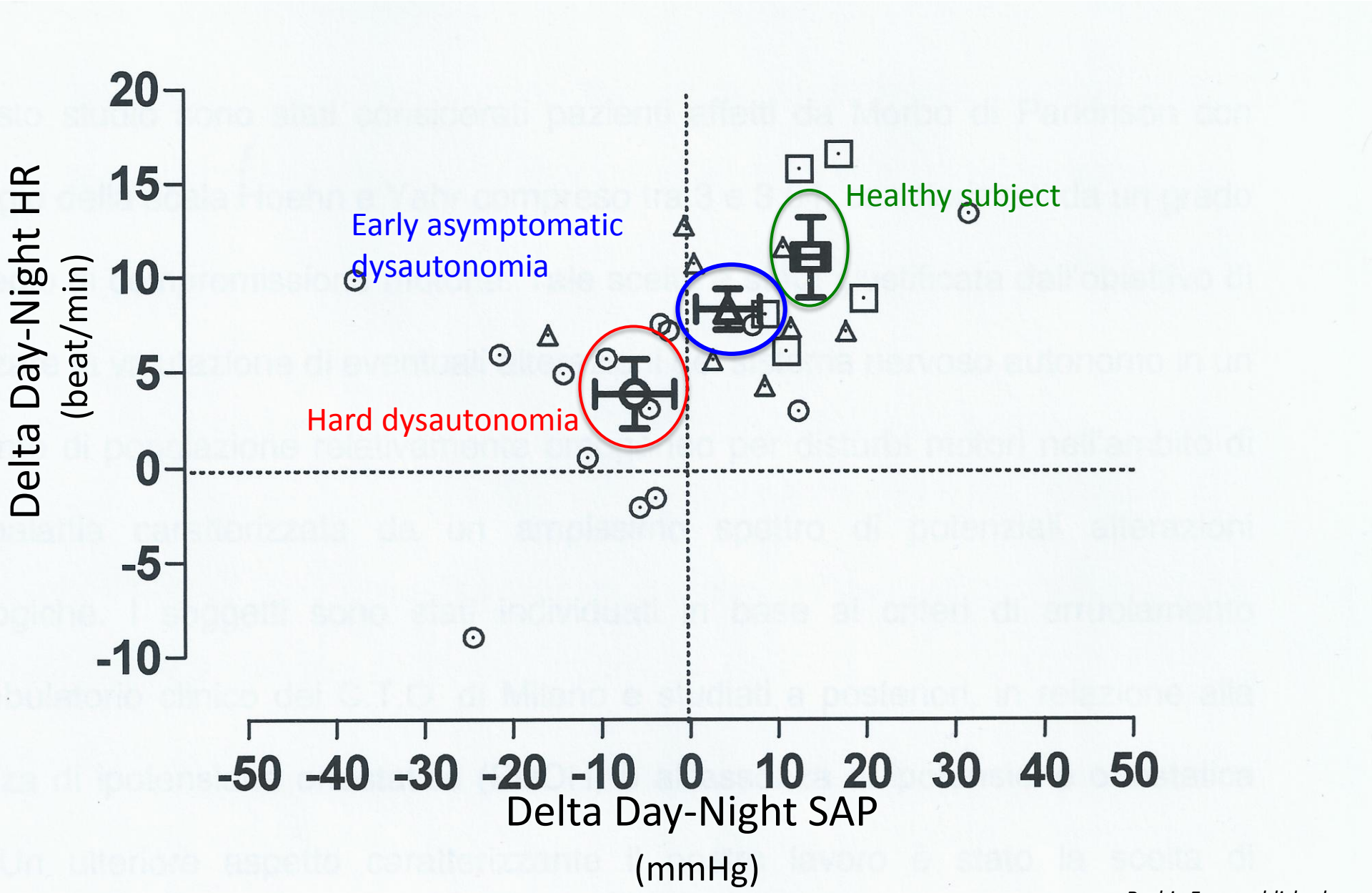
Cardiovascular autonomic response to environmental stimula

During working in occupational environment (24-hours or more)

ECG recording 7-21 days

ECG recording blue tooth transmission system

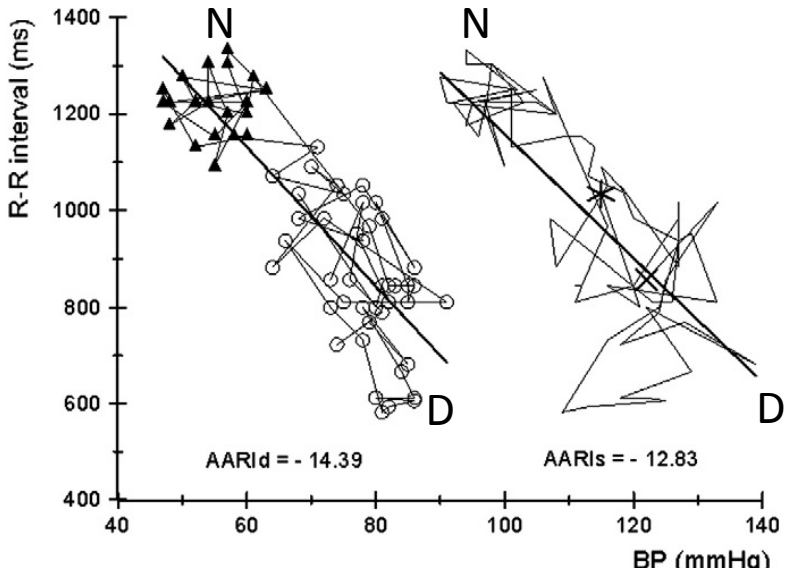
Combined ECG and BP



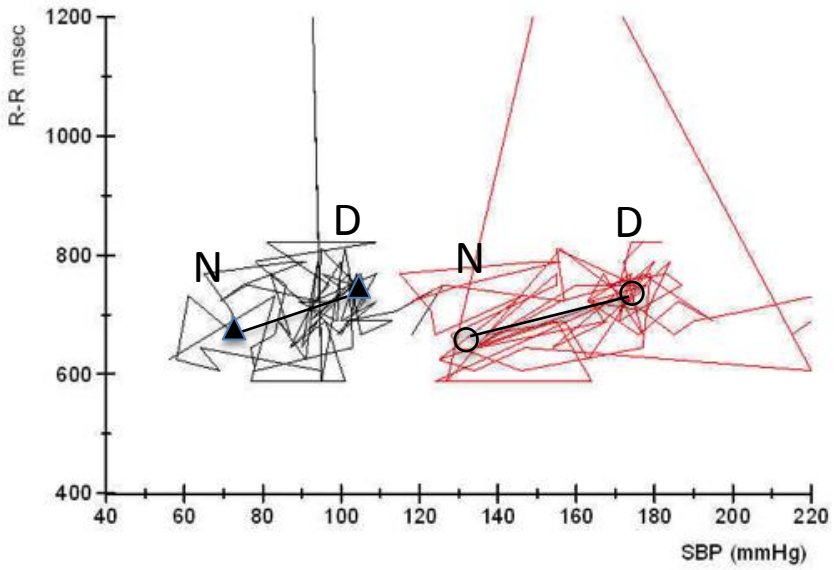
Barbic F., unpublished

Autonomic space: 24 h sympatho-vagal balance

Healthy subject

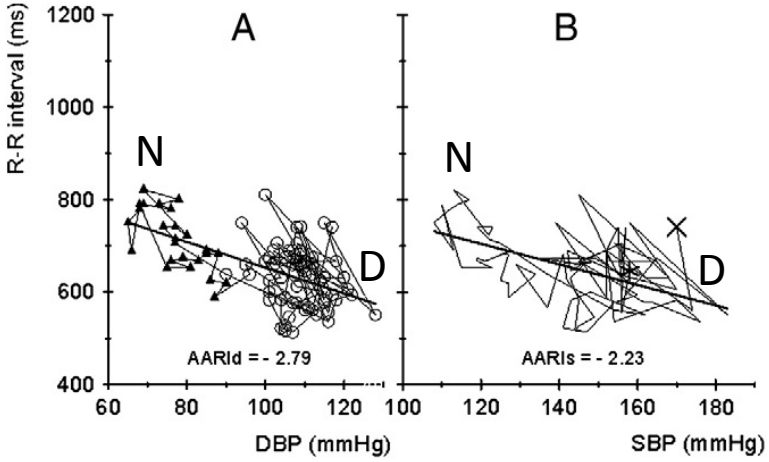


Dysautonomic subject



Barbic F., unpublished

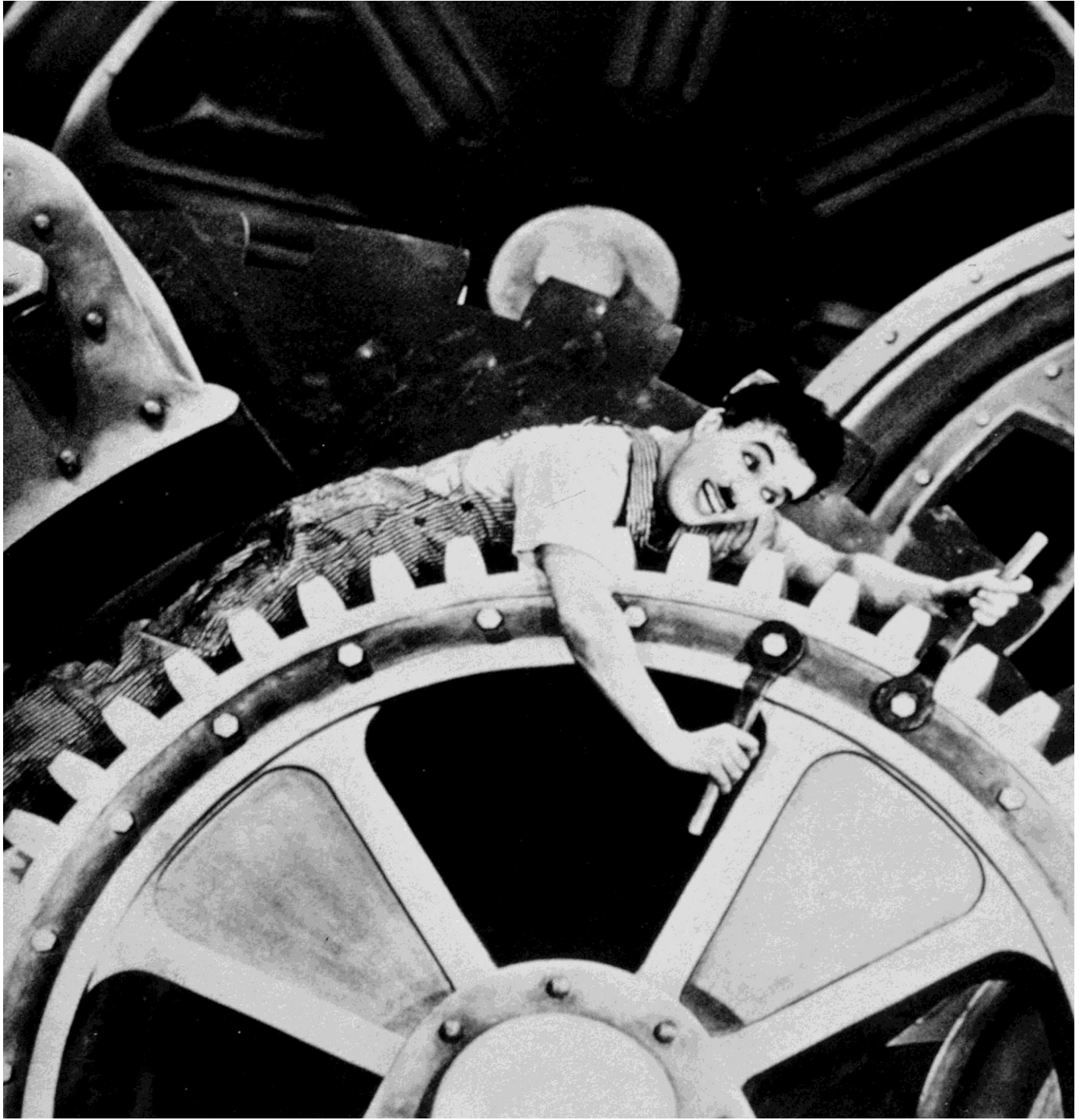
Hypertensive subject

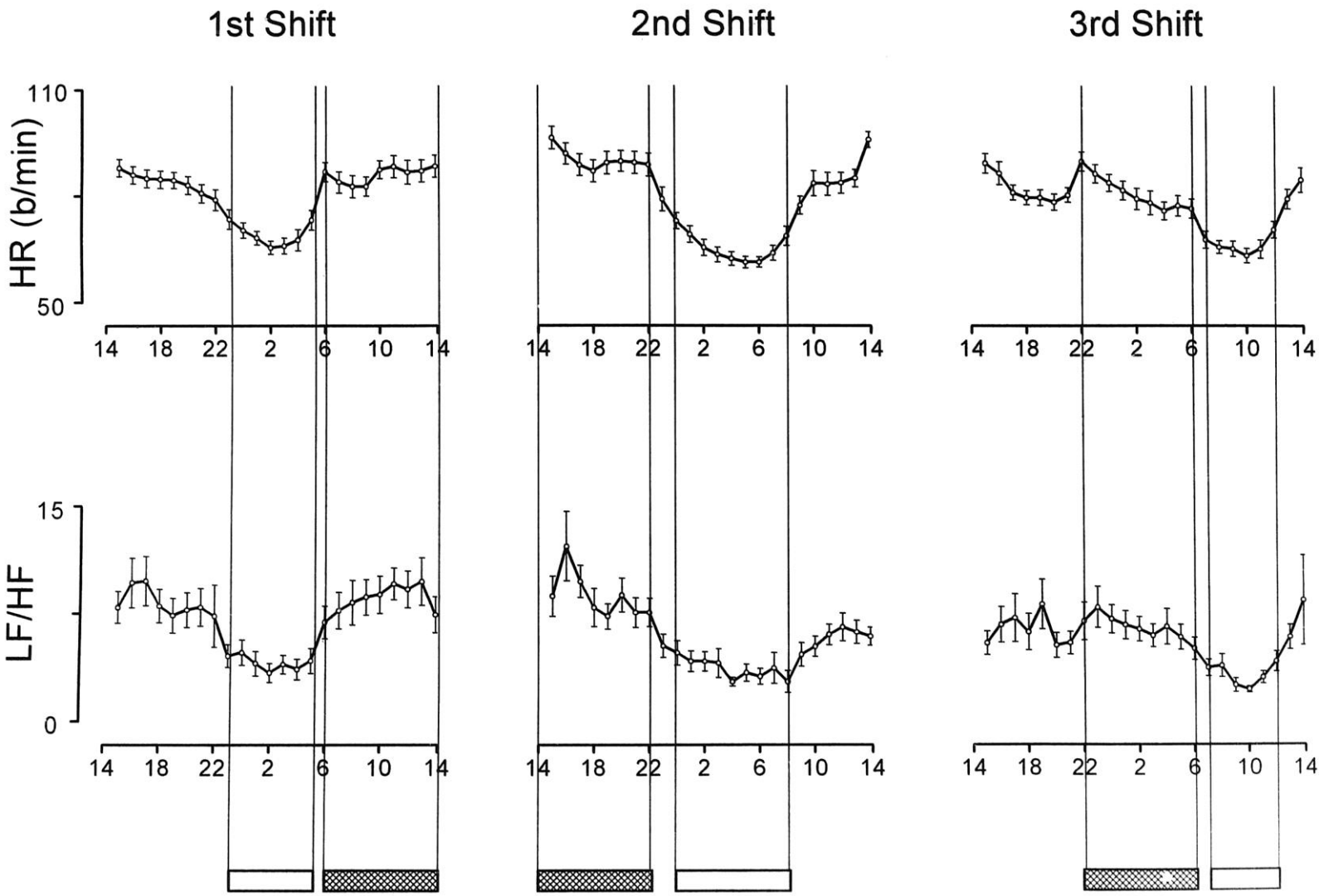


AARIs RR/SAP

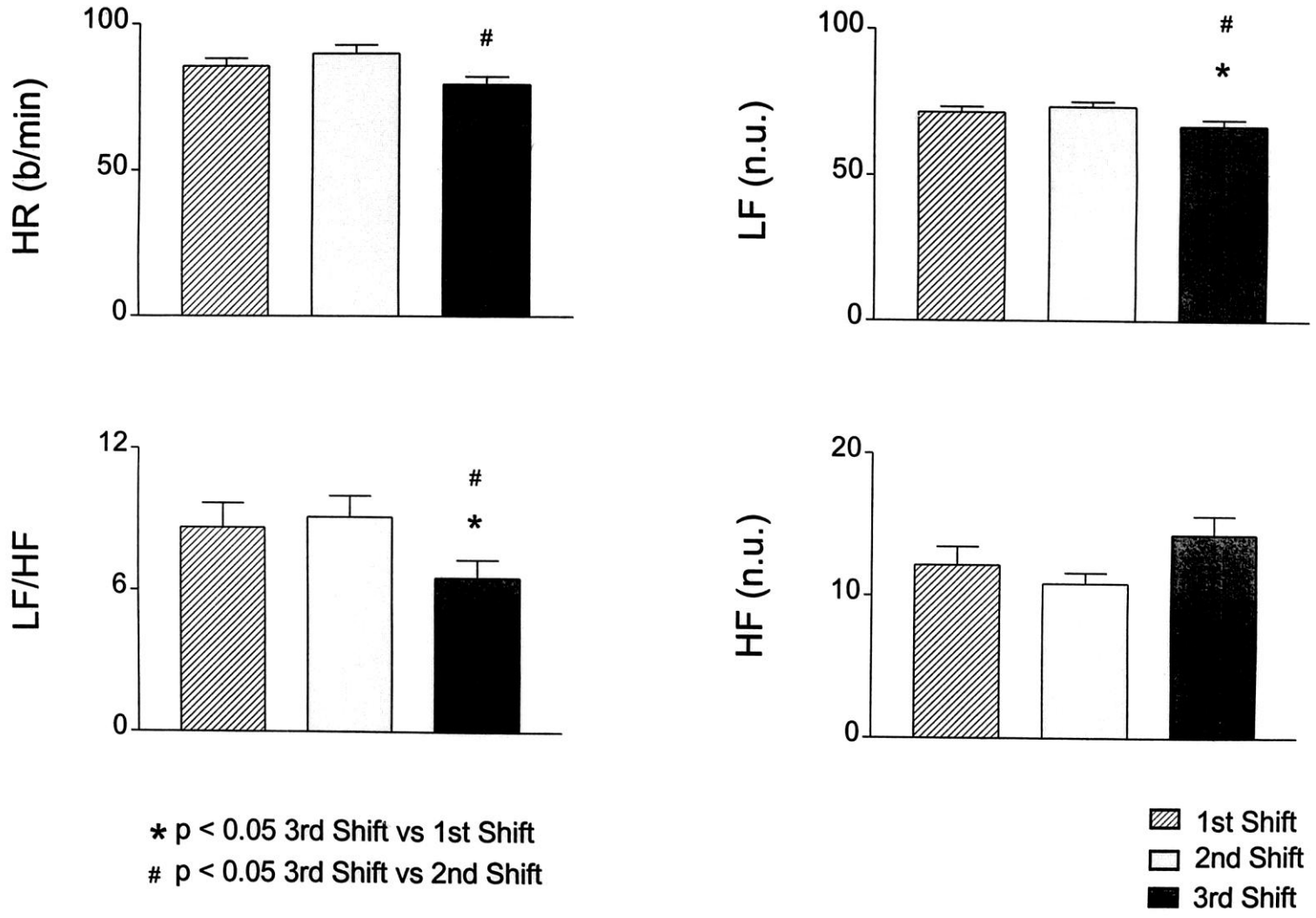
AARId RR/DAP

G. Recordati / Autonomic Neuroscience: Basic and Clinical 161 (2011) 103–109

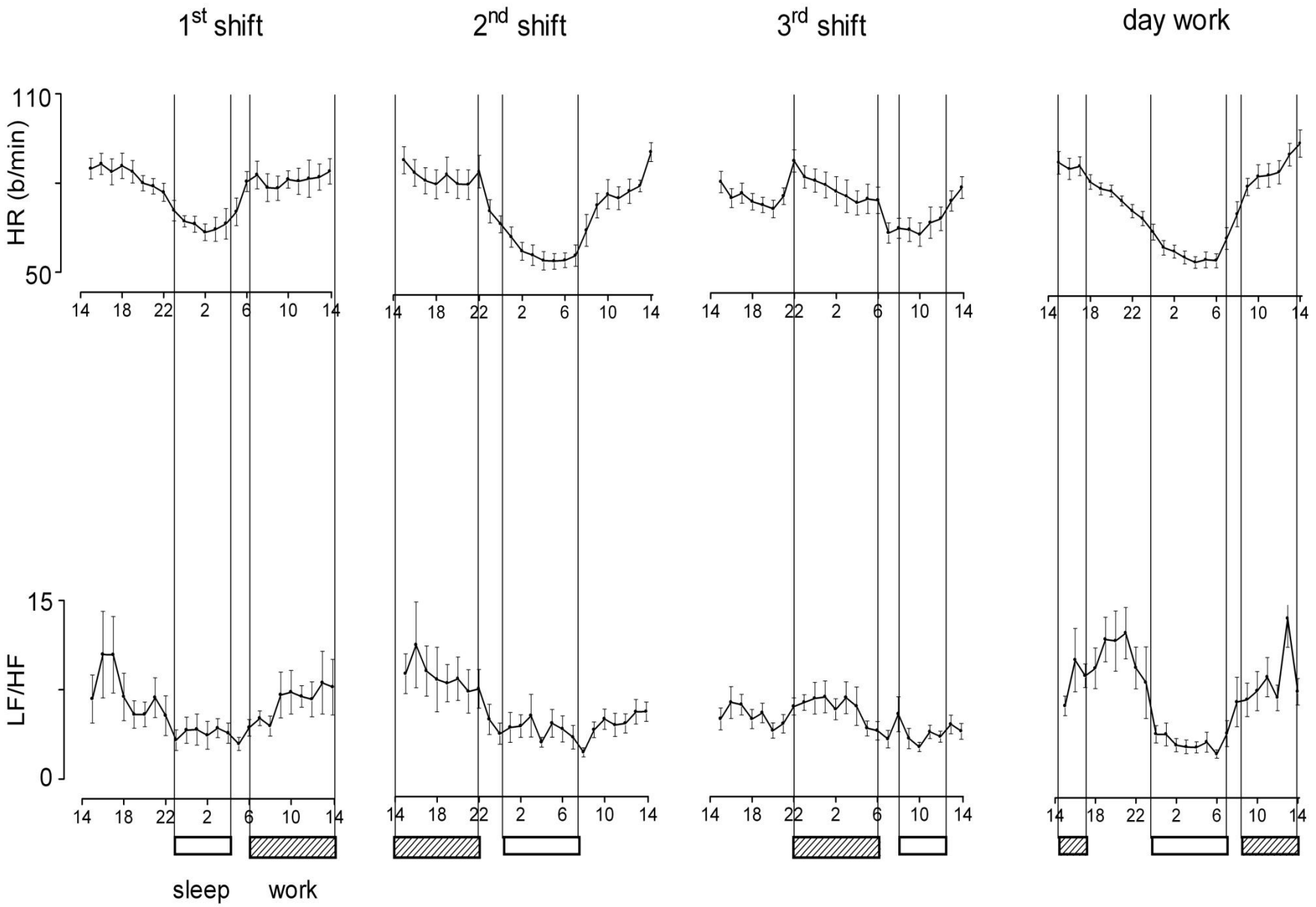




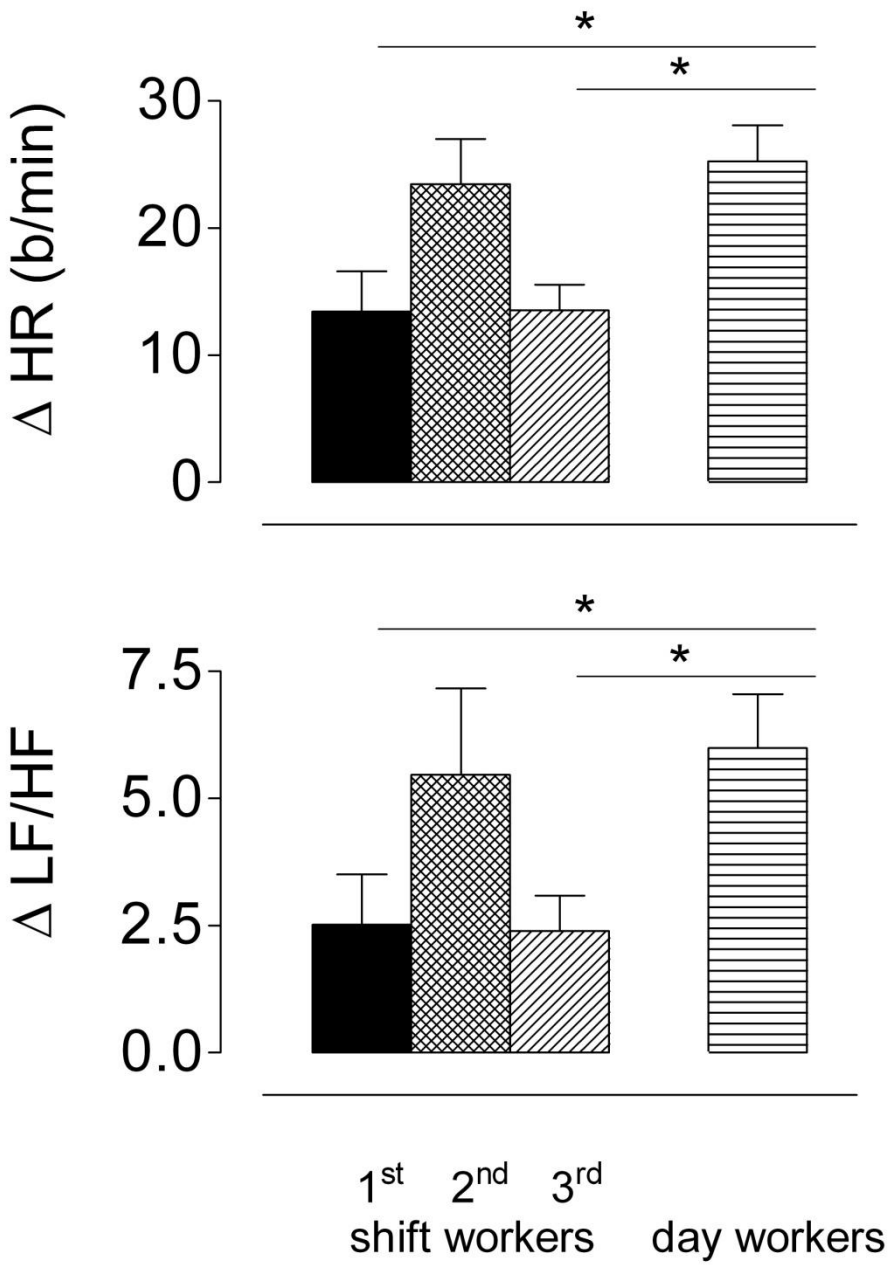
Furlan R., Barbic F., et al, Circulation 2000; 102: 1912



Furlan R., Barbic F., et al, Circulation 2000; 102: 1912



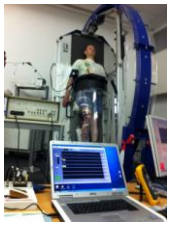
Barbic F. et al Ergonomia, 2007 Vol 29,199-204



Barbic F. et al Ergonomia, 2007 Vol 29,199-204

Conclusions 1

Clinical Laboratory



Cardiovascular and respiratory parameters (HR,BP, Resp, $EtCO_2$, SA ratio, Valsalva ratio, MSNA)

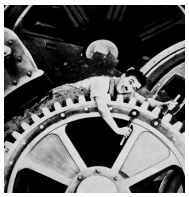
Spectral analysis of all parameters variabilities (RR-BP-RESP-MSNA) – reciprocal changes of sympathovagal balance

Cardiac (cBRS) and vascular sympathetic (svBRS) baroreflex sensitivity analysis

Non linear analysis of RR variability (symbolic analysis) - non reciprocal changes of cardiac sympathetic and vagal modulation

Conclusions 2

Working Place



In the working place, the long-term ECG recording provides indices of cardiac autonomic control in time and frequency domain by linear and non-linear (i.e symbolic analysis) of RR variability **over 24 hours and more**

The additional ambulatory BP monitoring (ABPM) may furnish indeces of cardiovascular autonomic profile over 24 hours

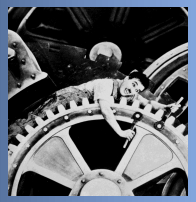
1. Autonomic Space (Berntson et al ; Recordati et al)
Ambulatory Autonomic Reciprocity index **AARI** msec/mmHg

2. Delta day-night HR/ Delta day-night SAP or DAP

Daily activity over 24 hours

Working activity

CV Autonomic Space during job tasks



CV Autonomic profile Clin Lab