

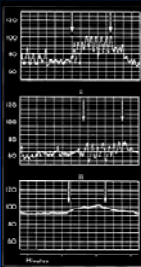
HRV in Diabetes and Other Disorders

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Beth Israel Deaconess Medical Center
Harvard Medical School



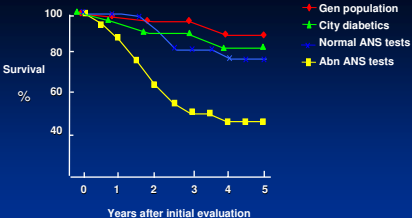
Control



Propranolol

Atropine

Wheeler and Watkins Br. Med. J. 4: 584-586; 1973



The natural history of diabetic autonomic neuropathy
Ewing et al. Q.J. Med 1980;45:95-108.

Neuropathy prevalence

- Clinical criteria for diagnosis
- 4,400 subjects - 1948 - 1973
- Newly diagnosed diabetics - 7.5%
- After 25 years ~ 50%

Pirart J, Diabetes Care 1978; 1: 168-188

Neuropathy prevalence

Rochester Diabetic Neuropathy Study

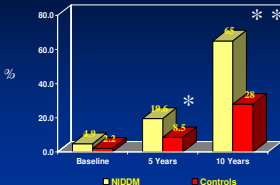
- Clinical DM - 1.3% of population
- Type 1 - 26.8% Type 2 - 73.2%
- Diabetic neuropathy in 66%
- Non-DM neurological disease - 10%

Dyck et al, Neurology 1993; 43: 817-824

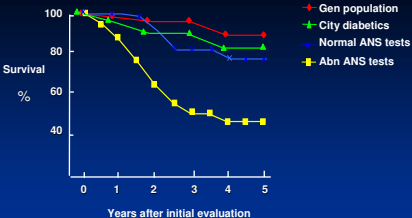
Autonomic neuropathy prevalence

- Rochester Diabetic Neuropathy cohort
- Symptoms more common in type 1 patients
- More severe in type 2 patients
- Prevalence of autonomic test abnormalities - 54% in type 1 and 73% in type 2 diabetes
- Abnormalities moderate to severe in 14%

Prevalence of abnormal R-R variation Kuopio study



E:I ratio < 1.10



The natural history of diabetic autonomic neuropathy
Ewing et al. Q.J. Med 1980;45:95-108.

Mortality of autonomic neuropathy

Author	Follow-up (years)	Mortality with AN (%)	Mortality without AN (%)
Ewing et al., 1980	5	56	15
Navarro et al., 1990	7	40	14
Sampson et al., 1990	10	27	12
O'Brien et al., 1991	5	27	6
Rathman et al., 1993	8	23	3

Possible factors:

- Silent ischaemia
- Sympathetic-parasympathetic nervous system imbalance
- Impaired baroreflex sensitivity
- QT interval prolongation
- Myocardial ischaemia - autonomic interactions
- Distal sympathetic denervation with islands of proximal hyperinnervation

Sudden cardiac death

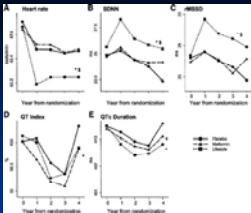
- 21 cases of sudden death over 15 year follow up
- In a multivariate analysis, predictors included EKG changes, nephropathy, QTc interval, autonomic scores, HDL cholesterol
- Adjusting for nephropathy autonomic scores no longer a significant predictor
- Possible ANS acts as a transient risk factor conducive to the final event

Autonomic neuropathy and nephropathy

- Steno study prospective assessment – 10.1 years
 - 197 type 1 diabetic patients with diabetic nephropathy
 - 191 patients with long-standing type 1 diabetes and normoalbuminuria
 - Heart rate variability with deep breathing
 - Endpoint – fatal and non-fatal cardiovascular disease
- Hazard ratios in a patient with nephropathy and an abnormal HRV
 - For reaching the primary end point 6.4 (95% CI 1.5-26.3, $P = 0.01$)
 - For dying 3.3 (95% CI 1.0-10.7; $P = 0.04$)
- HRV is an independent risk factor predicting cardiovascular morbidity and mortality in type 1 diabetic patients with nephropathy

Risk factors for cardiac autonomic neuropathy in type 1 Diabetes

- Age
- HbA1c
- Feeling faint on standing
- Hypertension
- Distal neuropathy
- Other microvascular complications (nephropathy and retinopathy)



The association among autonomic nervous system function, incident diabetes, and intervention arm in the diabetes prevention program.

Carnethon et al. Diabetes Care 2006

CARDIAC PARASYMPATHETIC FUNCTION

Heart rate variability in response
to:

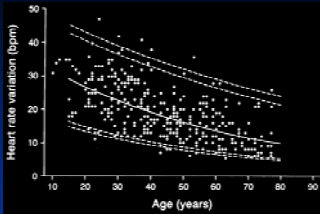
- Respiration
- Valsalva manoeuvre
- Postural change
- Apneic facial immersion

SINUS ARRHYTHMIA

- Stimulus: Deep respiration
- Six breaths per minute
- Afferent: Vagus, central, baroreceptors and local cardiac
- Efferent: Predominantly vagus
- Response: Inspiratory HR increase
Expiratory heart rate decrease
- Sensitive and specific measure

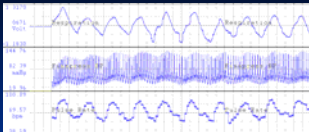
SINUS ARRHYTHMIA

- Respiratory frequency
- Respiratory amplitude
- Position
- Age
- Sympathetic activity
- Mean heart rate
- Hypocarbica
- Medications



Low et al. Muscle and Nerve, 1997

Respiration



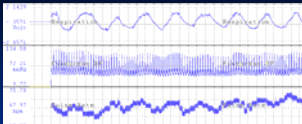
Finapres BP

Pulse Rate

HRV with deep respiration:

Ave Max	86.8
Ave Min	60.1
E:I	1.45
Max-Min	27
SD HR	9.26

Respiration



Finapres BP

Pulse Rate

HRV with deep respiration:

Ave Max 71.2

Ave Min 67.3

E:I 1.06

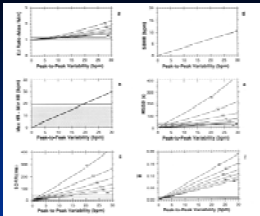
Max-Min 4

SD HR 1.71

Time domain statistical measures of HRV with respiration

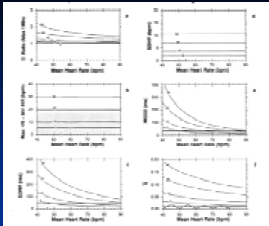
- Maximum minus minimum HR difference
- Maximum minus minimum RR interval difference
- Maximum / minimum HR
- Maximum / minimum RR interval
- Standard deviation (SD) of RR intervals
- SD of the HR
- Histogram displays of RR intervals
- Coefficient of variation of heart rate
- Coefficient of variation of RR intervals
- SDNN index
- SDANN index
- MSSD (Mean square successive difference)
- rMSSD (Root mean square successive difference)
- MSD (Mean successive difference)
- SDSD (SD of the successive differences in RR intervals)
- Histogram displays of RR interval differences
- Mean circular resultant

Simulation of the
effect of peak to
peak variability at
different mean
heart rates (40-90
bpm)



Assessing Heart Rate Variability: A computer simulated comparison of methodologies.
Harry J. Freeman R. *Muscle and Nerve* 1993;16:267-277.

Simulation of the
effect of mean
heart rate on peak
to peak variability
(0-30 bpm)



Assessing Heart Rate Variability: A computer simulated comparison of methodologies.
Harry J. Freeman R. Muscle and Nerve 1993;16:267-277.

CARDIAC PARASYMPATHETIC FUNCTION

Heart rate variability in response
to:

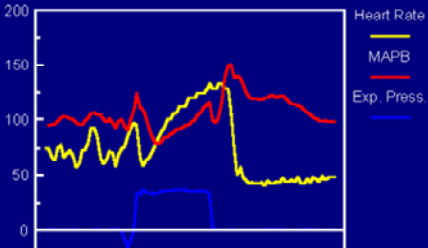
- Respiration
- Valsalva manoeuvre
- Postural change
- Apneic facial immersion

VALSALVA MANOEUVRE

- Stimulus: Expiratory pressure
- 40 mm Hg for 15 seconds
- Afferent: Vagus and glossopharyngeal
- Efferent: Vagus and sympathetic efferents
- Response: Biphasic HR and BP changes
- Vasoconstriction
- Sensitive and specific

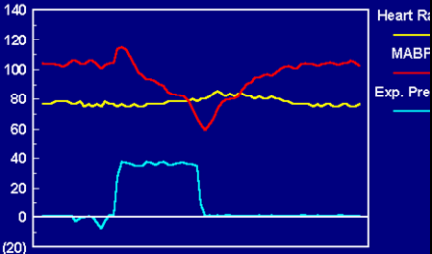
VALSALVA MANEUVER

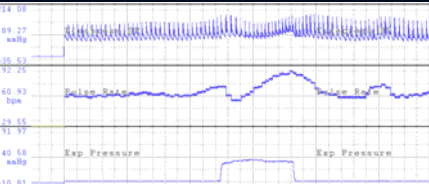
Normal Subject

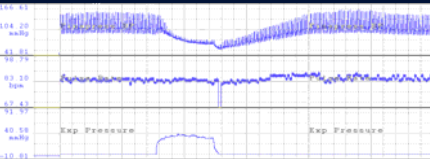


VALSALVA MANEUVER

Autonomic Failure







VALSALVA MANOEUVRE

- Intrathoracic pressure: 20-60mm Hg
- Duration of expiration: 7-20 sec.
- Open glottis
- Phase of respiration
- Patient cooperation
- Number of trials
- Age
- Sympathetic activity
- Severe proliferative retinopathy
- Reproducibility

CARDIAC PARASYMPATHETIC FUNCTION

Heart rate variability in response
to:

- Respiration
- Valsalva manoeuvre
- Postural change
- Apneic facial immersion

POSTURAL CHANGE

- Stimulus: Active stand or passive tilt
- Afferent: Muscle, vagus and glossopharyngeal nerves
- Efferent: Vagus and sympathetic efferents
- Response: Biphasic HR and BP changes
- Vasoconstriction
- Measurements: HR response
- Limited sensitivity and specificity

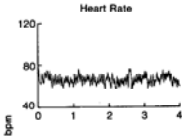


Measurements

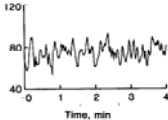
- "30:15" ratio
- Acceleration and brake index

Heart rate variability in the frequency domain

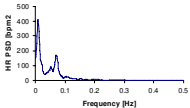
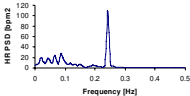
Supine

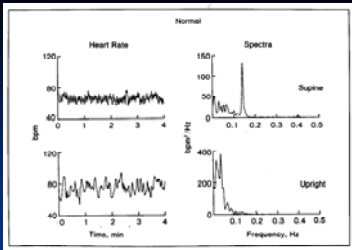


Tilt

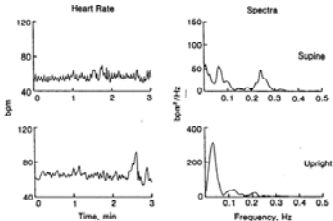


Heart rate power spectrum

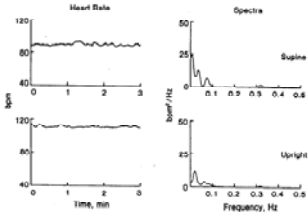




Power spectral analysis of heart rate in diabetic autonomic neuropathy.
Freeman R. et al. Archives of Neurology 1991;48:185-190.

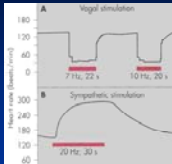
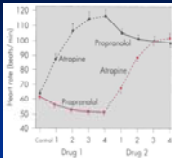


Power spectral analysis of heart rate in diabetic autonomic neuropathy.
Freeman R. et al. Archives of Neurology 1991;48:185-190.



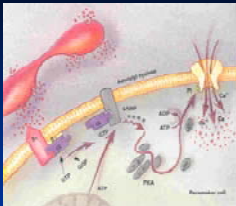
Power spectral analysis of heart rate in diabetic autonomic neuropathy.
Freeman R. et al. Archives of Neurology 1991;48:185-190.

Parasympathetic and Sympathetic Neurotransmission



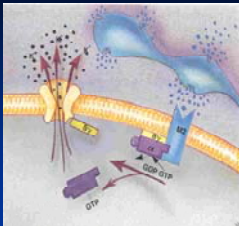
Sympathetic neurotransmission

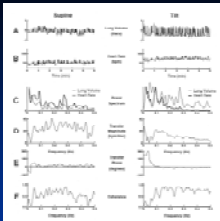
- Beta-adrenergic receptor coupled to Gs protein
- Adenylate cyclase activation
- cAMP formation
- Protein kinase activation
- Calcium channel phosphorylation
- NE reuptake and diffusion



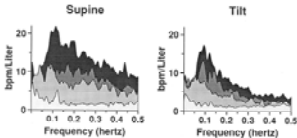
Parasympathetic neurotransmission

- Distribution: SA and AV node
- Overlapping innervation
- 200 msec latency
- No second messenger system
- Short duration response



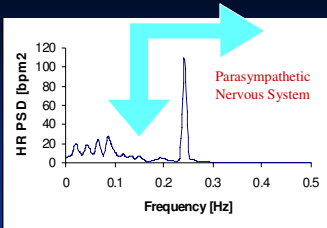


Transfer function analysis of respiratory sinus arrhythmia: a measure of autonomic function in diabetic autonomic neuropathy
Freeman R et al. Muscle and Nerve 1995;18:74-84.

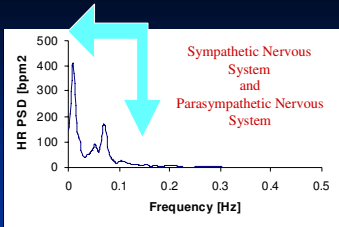


Transfer function analysis of respiratory sinus arrhythmia: a measure of autonomic function in diabetic autonomic neuropathy
Freeman R et al. Muscle and Nerve 1995;18:74-84.

Heart rate power spectrum



Heart rate power spectrum





Postural tachycardia

Terminology

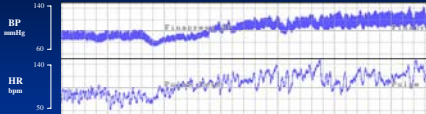
- Mild orthostatic intolerance
- Orthostatic tachycardia
- Sympathotonic orthostatic hypotension
- Hyperdynamic β -adrenergic state
- Idiopathic hypovolaemia
- Postural tachycardia syndrome
- POTS

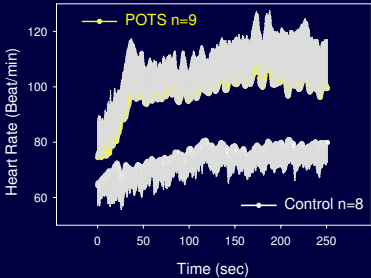
Postural tachycardia

Definition

A sustained heart rate increase of greater than 30 beats per minute within the first 10 minutes of tilt table testing without orthostatic hypotension.

Orthostatic tachycardia



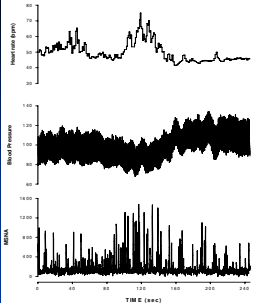


Orthostatic intolerance

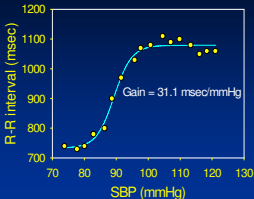
Features

- Postural tachycardia
- Palpitations
- Fatigue
- Gastrointestinal symptoms
- Anxiety
- Female predominance

The modified
Oxford method for
determination of
baroreflex gain.

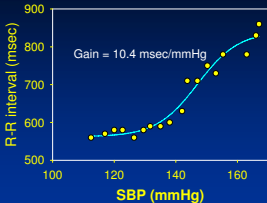


Baroreflex response - Control

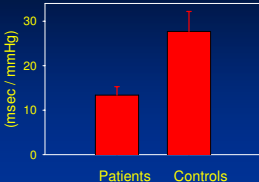


Farquhar et al. Circulation, 2000

Baroreflex response - Patient



Cardiac Vagal Baroreflex Gain



$p < 0.01$

Farquhar et al. Circulation, 2000

