HRV in Diabetes and Other Disorders

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Control

Propranolol

Atropine

The natural history of diabetic autonomic neuropathy
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%

Low et al, Neurology 2004; 27:2942-2947
Prevalence of abnormal R-R variation Kuopio study

E:I ratio < 1.10

The natural history of diabetic autonomic neuropathy

## Mortality of autonomic neuropathy

<table>
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<tr>
<th>Author</th>
<th>Follow-up</th>
<th>Mortality with AN (%)</th>
<th>Mortality without AN (%)</th>
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<td>Navarro et al., 1990</td>
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<td>Rathman et al., 1993</td>
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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)

Witte DR et al  Diabetologia 2005
Risk factors for cardiac autonomic neuropathy in type 1 Diabetes:

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Witte DR et al. Diabetologia 2005

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

Witte DR et al. Diabetologia 2005

Carnethon et al. Diabetes Care 2006
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
- Hypocarbia
- Medications
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

Low et al. Muscle and Nerve, 1997
HRV with deep respiration:
Ave Max    86.8
Ave Min    60.1
E:I        1.45
Max-Min    27
SD HR      9.26
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. 
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. 
CARDIAC PARASYMPATHETIC FUNCTION

Heart rate variability in response to:

- Respiration
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- Postural change
- Apneic facial immersion
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**

- **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

Stimulus: Expiratory pressure 40 mm Hg for 15 seconds

Afferent: Vagus and glossopharyngeal

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Vasoconstriction

Sensitive and specific
Valsalva Ratio = 1.45

Valsalva Ratio = 1.01

Intrathoracic pressure: 20-60 mm Hg
Duration of expiration: 7-20 sec.
Open glottis
Phase of respiration
Patient cooperation
Number of trials
Age
Sympathetic activity
Severe proliferative retinopathy
Reproducibility
Valsalva Ratio = 1.45

Valsalva Ratio = 1.01

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CARDIAC PARASYMPATHETIC FUNCTION

Heart rate variability in response to:

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- 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
- **Measurements:** HR response
- **Limited sensitivity and specificity**

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Vasoconstriction

Measurements: HR response
Limited sensitivity and specificity

Measurements
- "30:15" ratio
- Acceleration and brake index
Heart rate variability in the frequency domain
Heart rate power spectrum

Supine

Tilt
Power spectral analysis of heart rate in diabetic autonomic neuropathy.

Power spectral analysis of heart rate in diabetic autonomic neuropathy.
Power spectral analysis of heart rate in diabetic autonomic neuropathy.
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

Transfer function analysis of respiratory sinus arrhythmia: a measure of autonomic function in diabetic autonomic neuropathy

Heart rate power spectrum
Heart rate power spectrum

Sympathetic Nervous System and Parasympathetic Nervous System
Heart rate power spectrum

Frequency [Hz]

Tilt

Sympathetic Nervous System

Parasympathetic Nervous System

Mild orthostatic intolerance

Orthostatic tachycardia

Sympathotonic orthostatic hypotension

Hyperdynamic -adrenergic state

Idiopathic hypovolaemia

Postural tachycardia syndrome

POTS

Terminology
Postural tachycardia

Terminology

- Mild orthostatic intolerance
- Orthostatic tachycardia
- Sympathotonic orthostatic hypotension
- Hyperdynamic β-adrenergic state
- Idiopathic hypovolaemia
- Postural tachycardia syndrome
- POTS
A sustained heart rate increase of greater than 30 beats per minute within the first 10 minutes of tilt table testing without orthostatic hypotension.
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Postural tachycardia

Orthostatic tachycardia

BP (mmHg) vs HR (bpm) over time (seconds):
- Control: n=8
- POTS: n=9
A sustained heart rate increase of greater than 30 beats per minute within the first 10 minutes of tilt table testing without orthostatic hypotension.

**Postural tachycardia**

**Definition**

![Graph showing heart rate over time with control n=8 and POTS n=9](image)

- Heart Rate (Beat/min)
- Time (sec)
- Control n=8
- POTS n=9
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

Gain = 10.4 msec/mmHg

Farquhar et al. Circulation, 2000
Cardiac Vagal Baroreflex Gain

Farquhar et al. Circulation, 2000

p < 0.01
SBP (mmHg)  
100 120 140 160  
R-R interval (msec)  
500 600 700 800 900  
Gain = 10.4 msec/mmHg

Baroreflex response - Patient  
Farquhar et al. Circulation, 2000

Patients Controls  
p < 0.01

Cardiac Vagal Baroreflex Gain  
Farquhar et al. Circulation, 2000

Healthy Subjects  
Frequency (Hz)  
0.00 0.05 0.10 0.15  
Transfer Modulus (ms mmHg⁻¹)  
0 5 10 15 20 25 30  
25th 50th 75th

POTS Patients  
Frequency (Hz)  
0.00 0.05 0.10 0.15  
Transfer Modulus (ms mmHg⁻¹)  
0 5 10 15 20 25 30  
25th 50th 75th