DIABETIC NEUROPATHIES

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Disclosures-Pfizer

(Familial Amyloid Polyneuropathy)

Off label use of medications will be discussed

Peripheral Neuropathy

- Common problem
  - non-traumatic peripheral neuropathy
  - prevalence of 2.4% in population
  - prevalence of 8% over the age of 55

Peripheral Neuropathy

- Most common cause (in developed nations) is diabetic mellitus
- Prevalence of diabetic peripheral neuropathy expected to rise in the U.S.

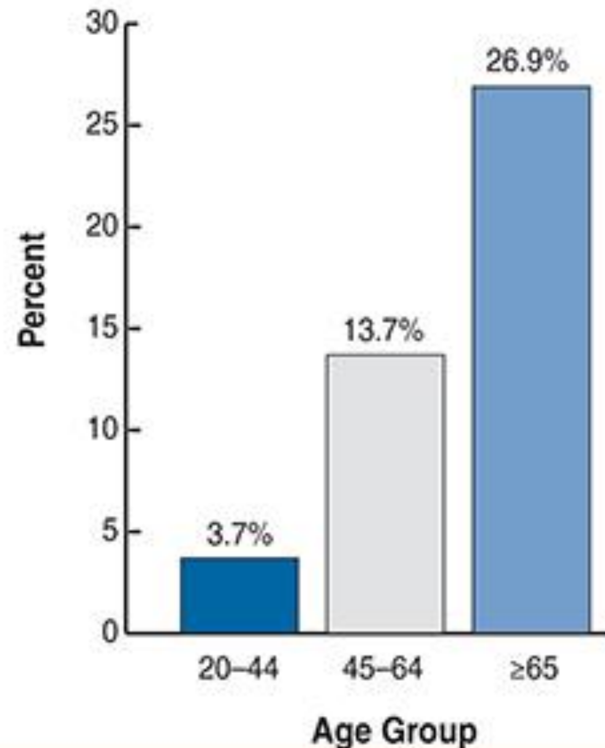
(http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/)

Diabetes affects:
25.8 million people of all ages
8.3 percent of the U.S. population

DIAGNOSED
18.8 million people

UNDIAGNOSED
7.0 million people

(http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/)



(http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/)

Complications of Diabetes

Neuropathy

60-70%

Polyneuropathy, Autonomic Neuropathy, CTS, etc

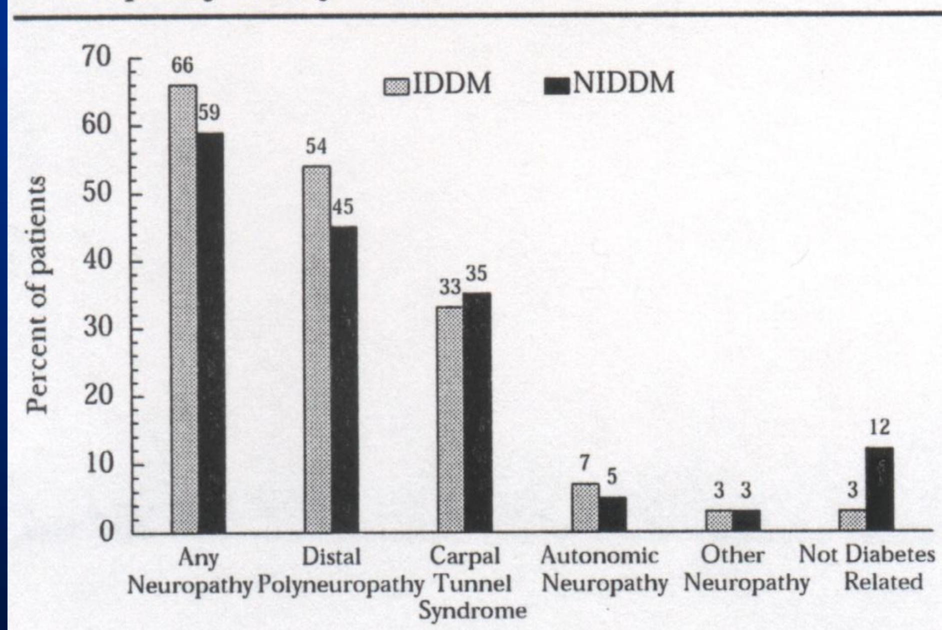
Major contributor of amputations

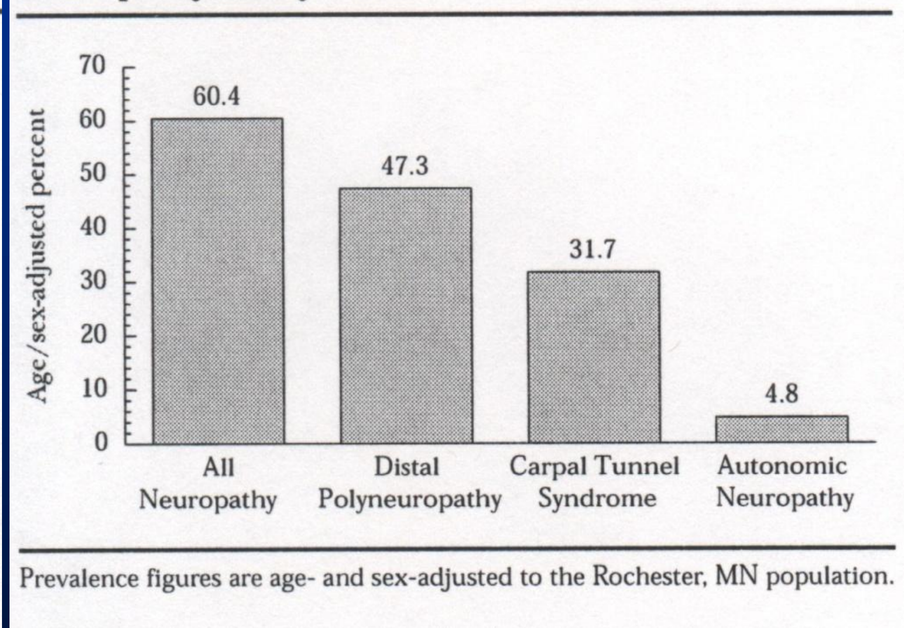
Lower Limb Amputations

>60% of non-traumatic amputations

65,700 amputations from 2006

Prevalence of Diabetic Neuropathies





(Dyck PJ et al. Neurology 1993; 43(4):817-24.)

Diabetic Neuropathies

Table 1—*Classification of diabetic neuropathy*

Generalized symmetric polyneuropathies
- Acute sensory
- Chronic sensorimotor
- Autonomic

Focal and multifocal neuropathies
- Cranial
- Truncal
- Focal limb
- Proximal motor (amyotrophy)
- Coexisting CIDP

Adapted from Thomas (4). Note: Clinicians should be alert for treatable neuropathies (CIDP, monoclonal gammopathy, vitamin B_{12} deficiency, etc.) occurring in patients with diabetes.

(Boulton et al, 2005)

Overview-Diabetic Neuropathies

- Diabetic Polyneuropathy and Autonomic Neuropathy
  - Symptoms
  - Signs
  - Complications
  - Evaluations
  - Management
  - Treatment

Diabetic Neuropathy

Risk Factors

- High blood sugars
- Coronary artery disease
- Increased triglyceride levels
- Body mass index > 24
- Smoking
- High blood pressure

Pathophysiology

- HYPERGLYCEMIA
- Cardiovascular risk factors
- Lipid alterations
- Increased polyol flux
- Accumulation of advanced glycation end products
- Oxidative stress

Diabetic Polyneuropathy (DPN)

Definition of DPN for clinical practice:

“the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes”.

Diabetic Polyneuropathy

Diagnosis cannot be made without a careful clinical examination of the lower limbs, as absence of symptoms should never be assumed to indicate an absence of signs

Symptoms of DPN

- Tingling
- Burning pain
- Electrical or stabbing sensations
- Hypersensitivity
- Deep aching pain

- Weakness
- Imbalance
- Fatigue
- Falls

- Worse in feet
- Worse at night

Signs of DPN

- Distal sensory loss:
  - vibration
  - pinprick
  - temperature
  - absent or reduced ankle reflexes
- Distal weakness
  - Toes
  - Fingers

Complications of DPN

- Risk of injury due to lack of sensation
- Charcot joints
- Foot ulcers
- Amputations

DPN

- Absence of retinopathy and nephropathy
- Exclusion of other causes
- Other causes of polyneuropathy
  -Hypothyroid, Vitamin B12 deficiency, hepatitis C, HIV, medications

(Mauermann and Burns 2008)

	Inherited	Acquired ("M I N I")			
		Metabolic	Immune	Neoplastic	Infectious
"What"	Motor or sensorimotor; PNSS uncommon	Sensory > motor; PNSS very common	Variable		
"Where"	distal, symmetric	distal, symmetric	Not distal, symmetric	Not distal, symmetric	
"When"	Insidious/gradual onset, slow progression	Insidious/gradual onset, slow progression	Definite date of onset, more rapid progression	Definite date of onset, more rapid progression	Definite date of onset, more rapid progression
"What Setting" "Why"	Family history, foot deformities, foot ulcers	Risk factors, diseases or exposures?	Symptoms of vasculitis or systemic illness?	Symptoms of cancer? Paraproteinemia?	Symptoms / risks for infection?
Differential Diagnosis	CMT/HMSN HNPP HSN	Diabetic Uremic Alcohol B12 deficiency B1 deficiency Hypothyroid Meds	Non-vasculitic: GBS, CIDP, MMN, Sarcoid, Sjogren's Vasculitic	Paraneoplastic Paraproteinemic	Hepatitis C Lyme HIV Sarcoid West Nile Syphilis Diphtheria Leprosy

Differential Diagnosis in Diabetic Polyneuropathy

- Small fiber neuropathy
- Cervical myelopathy
- Lumbosacral radiculopathy
- Plantar fasciitis
- Osteoarthritis

Diagnosis

- EMG
- Quantitative Sensory Testing
- Skin biopsy

- Autonomic Testing

Electromyography (EMG)

- Two part test:
  - Nerve conduction studies
  - Needle electromyography

- Establish diagnosis of polyneuropathy
- Distinguish demyelinating from axonal
- Differentiate radiculopathy, plexopathy

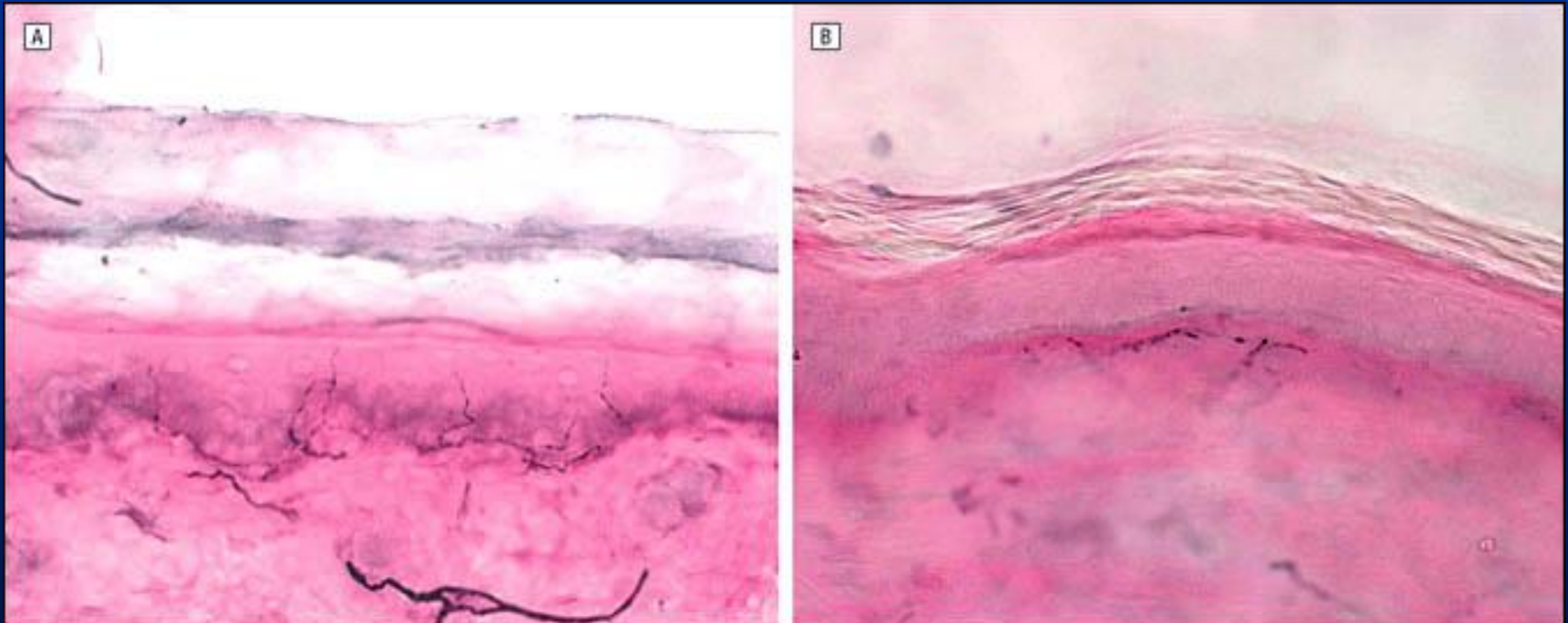
- Normal in small fiber and autonomic neuropathy

Quantitative Sensory Studies

- Quantitative outcomes in research
- Small fiber neuropathy

- Computer assisted sensory testing
  - Vibration
  - Cold
  - Heat-pain

Fixed cryosections of skin biopsy specimens from the distal part of the leg of a healthy subject (A) and patient 4 (B), who has an abnormally low epidermal nerve fiber density (immunoperoxidase stain of protein gene product 9.5 [a panaxonal marker], original magnification x400)



(Brannagan, T. H. et al. Arch Neurol 2005;62:1574-1578.)

Management

- Control of blood sugar levels
  - More frequent monitoring
  - Change in medication
  - HbA1c < 7%

- Avoidance of extreme glucose fluctuations
  - Hyperglycemia
  - Hypoglycemia
  - Nutritional education

(http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/#Nervous)

Diabetic Polyneuropathy: Management

- In general, every percentage point drop in A1C (e.g. from 8.0 to 7.0%) can reduce the risk of microvascular complications—eye, kidney, and nerve diseases—by 40 %.

Management

- Care of feet
  - Inspect feet daily (mirror)
  - Keep feet clean and moisturized
  - Foot care with podiatrist
  - Molded shoes
  - Avoid walking barefoot
  - Checking temperatures of water/sand

Management

- Rehabilitation for weakness and balance
  - Physical therapy
    - maintain strength and flexibility
    - Balance,
    - Fall avoidance
    - cane, braces, walker, motorized vehicle
  - Occupational Therapy
    - Activities of daily living

Treatment

- Analgesics (ASA, acetaminophen, NSAIDS)
- Antidepressants medications
- Anesthetic medications
- Narcotics
- Antioxidant medications (ALA 600 mg)

Table 1. Summary of recommendations

(Evidence based Guidelines: MN 2011)

	Recommended drug and dose	Not recommended
Level A	Pregabalin, 300–600 mg/day	
Level B	Gabapentin, 900–3600 mg/day	Oxcarbazepine
	Sodium valproate, 500–1200 mg/d	Lamotrigine
	Venlafaxine, 75–225 mg/day	Lacosamide
	Duloxetine, 60–120 mg/day	Clonidine
	Amitriptyline, 25–100 mg/day	Pentoxifylline
	Dextromethorphan, 400 mg/day	Mexiletine
	Morphine sulfate, titrated to 120 mg/day	Magnetic field treatment
	Tramadol, 210 mg/day	Low-intensity laser therapy
	Oxycodone, mean 37 mg/day, max. 120 mg/day	Reiki therapy
	Capsaicin, 0.075% four times per day	
	Isosorbide dinitrate spray	
	Electrical stimulation, percutaneous nerve stimulation for 3–4 weeks	

Treatment

- Prevention of secondary issues
  - Osteoporosis
  - Depression
  - Social isolation

Diabetic Autonomic Neuropathy

Autonomic Symptoms

- Orthostatic (lightheadedness)
- Visual (blurred vision, glare, reduced night vision)
- Secretomotor (dry eyes and dry mouth)
- Gastrointestinal (satiety, diarrhea, constipation)
- Urogenital (bladder dysfunction, ED)
- Sudomotor (decreased/increased)
- Vasomotor (cold extremities)

Postural hypotension

- Fall in SBP>20 mm Hg
- Lightheadedness, dizziness, weakness, fatigue, cognitive changes, syncope
- May be exacerbated by insulin
- Worse postprandial
- Exacerbated by anemia

Diabetic Autonomic Neuropathy (DAN)

- Cardiovascular symptoms
- Unexplained tachycardia
- Orthostatic hypotension
- Poor exercise intolerance

- 2.5-50% prevalence

DAN

- Predictors:
  - Duration of diabetes
  - Glycemic control
  - Polyneuropathy/retinopathy/nephropathy

DAN

- Associated with :
  - Intraoperative cardiovascular instability
  - Silent myocardial infarction and ischemia
  - Increased mortality

(Boulton et al. Diabetes Care 2005;28(4):956-62.)

Testing for DAN

- Screening at diagnosis of type 2 DM
- 5 years after diagnosis of type 1 DM
- Severe DAN-worse prognosis

Autonomic Testing

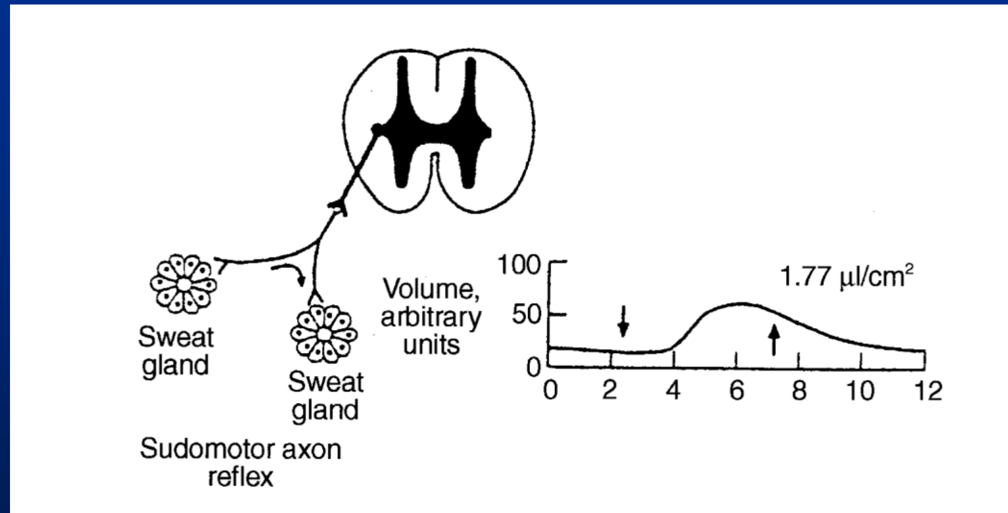
- Battery of non-invasive tests

- Sympathetic cholinergic (sudomotor)
- Parasympathetic cardiovagal
- Sympathetic adrenergic

Autonomic Testing

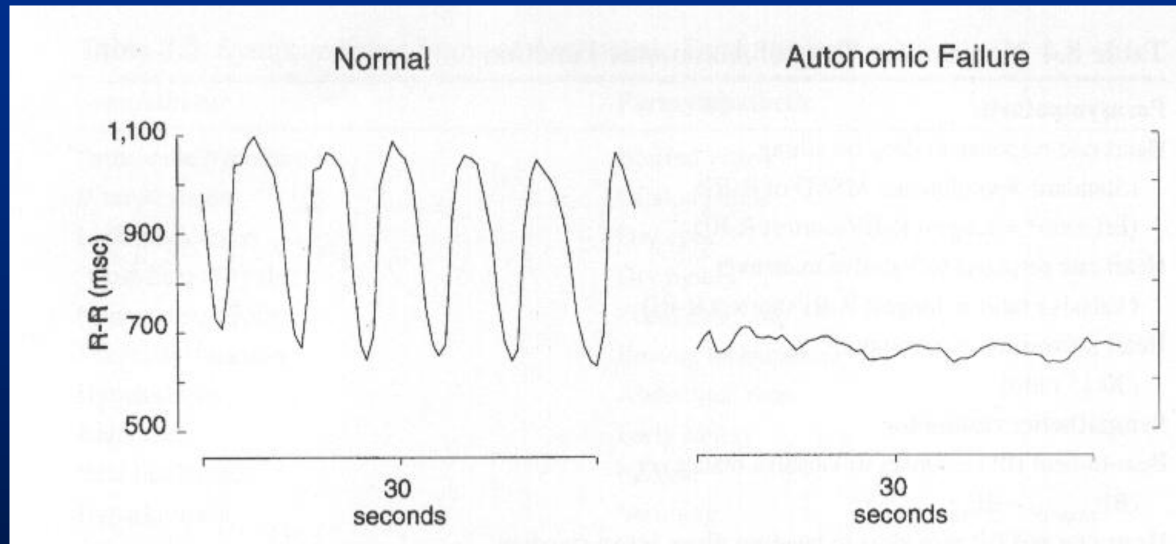
- Quantitative Sudomotor Axon Reflex Test
- Heart rate response to deep breathing
- Valsalva Maneuver (not retinopathy)
- Tilt Table

Quantitative Sudomotor Axon Reflex Test



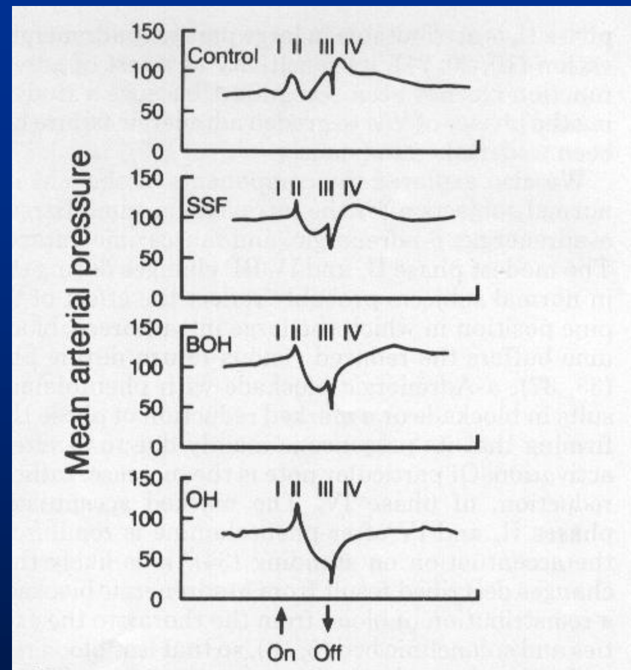
(Low et al. Ann Neurol 1983;14:573)

Heart rate response to deep breathing



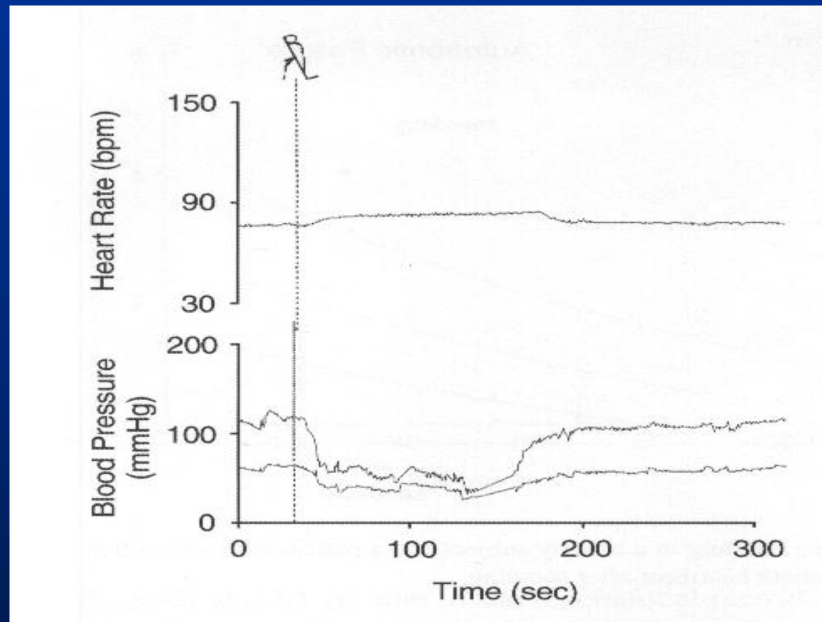
(Wang and Kaufmann. Clinical Evaluation and Diagnostic Tests for Neuromuscular Disorders. TE Bertorini ed.)

Valsalva Maneuver



(Sandroni et al. J Appl Physiol 1991;71:1563)

Tilt Table



(Wang and Kaufmann. Clinical Evaluation and Diagnostic Tests for Neuromuscular Disorders. TE Bertorini ed.)

Management

- Cardiac Evaluation
- Review medications (adverse effects)
- Avoid dehydration
- Avoid extreme temperatures

Management

- Orthostatic hypotension
  - Sit on edge of bed/dorsiflex feet
  - Fluids (8 cups/day)
  - Salt
  - 6 small meals
  - Cross legs
  - Compression stockings/Abdominal binder
  - Walker/wheelchair

Treatment

- Fludrocortisone
  - Mineralocorticoid
  - 0.1-0.4 mg/day
  - Monitor potassium
  - Supine hypertension
  - Edema

Treatment

- Midodrine
  - Alpha adrenoreceptor agonist
  - 10 mg three times daily
  - Up to every 4 hours
  - Avoid after 6 pm
  - Goosebumps (piloerection)

Questions