40-year-old Woman with Orthostatic Hypotension

Celeste Thomas

November 29, 2012

History of Present Illness

- Diagnosed with Type 2 DM at age 21 years
- Treatment/Management
  - Initially treated with oral medications then transitioned to insulin
  - Infrequent use of insulin with liberal diet
- Control
  - Patient reports her average blood glucose level for many years has been in the 400s mg/dL
- Known complications
  - Nephropathy with Stage III CKD
  - Neuropathy with lower extremity pain, somewhat improved with gabapentin
  - Retinopathy (non-proliferative) based on last evaluation in 2009

History of Present Illness

- **Presented to the ED complaining of lightheadedness and headaches**
- **Fall one month prior to admission with avulsion fracture of left subscapularis**
- **Three days prior to ED visit, checked blood pressure at home when sitting and it was 86/50 mmHg → stopped anti-hypertensives**
- **In physical therapy on the day of ED visit**
  - **Supine: 141/86, HR 94**
  - **Sitting: 110/69, HR 105**
  - **Standing: 95/56, HR 107**

History

- **Past Medical History**
  - Type 2 DM, uncontrolled
  - Dyslipidemia
  - Hypertension
  - Asthma
  - Sickle Cell Trait
- **Past Surgical History**
  - I&D of multiple abscesses
  - Hysterectomy/Bilateral salpingo-oophorectomy
  - Repair of avulsion of left subscapularis (after fall)
- **Social History**
  - Lives alone
  - Has 3 children (23, 21, 19)
  - Not working currently
  - Never smoked
  - No alcohol or illicit drugs
- **Family History**
  - Mother has DM

Medications

- U-500 Insulin pump
  - Basal setting: MN-5:30 AM 1.45 units/hr, 5:30 AM-MN 1.8 units/hr
  - Carb ratio: I:C 1:7
  - Sensitivity factor (target 120) MN-4AM 20m 4AM-10PM 10, 10PM-MN 20
- Gabapentin 300 mg PO TID
- Albuterol prn
- Fexofenadine 180 mg daily
- Losartan-Hydrochlorothiazide 100-25 mg PO daily (not currently taking)
- Simvastatin 40 mg PO daily
- Premarin 0.625 mg PO daily

ED Course

- Three liters of normal saline
- Acetaminophen for headache
- Repeat blood pressure medications
  - Supine: 147/80, 96
  - Sitting: 162/89, 95
  - Standing: 151/104, 104
- Patient denied lightheadedness and discharged home

2 days later, return to Physical Therapy

- **"She felt better after her ER visit the other day *(Tuesday)*, but her symptoms returned on Thursday evening. She enters today with dizziness but not as severe as Tuesday. She has stopped taking her BP meds in the hopes that her BP would increase and she would not get dizzy.**
- **"She enters room today drinking a Pure drink high in sugar and chips high in salt. She notes dizziness upon standing from sitting. She has not fallen."**
- **BP (automatic)**
  - **Supine: 188/95**
  - **Sitting: 153/92**
  - **Standing: 126/79 with dizziness and unsteadiness**
- **Physical therapist escorted patient to ED**

ED Course

- Patient reported lightheadedness, dyspnea on exertion and orthopnea
  - Bedside ultrasound → no significant pericardial effusion
  - CT → no pulmonary emboli
  - Admitted to general medicine
- Repeat blood pressure measurements
  - Supine: 198/91, 92
  - Sitting: 169/92, 91
  - Standing: 134/74, 101

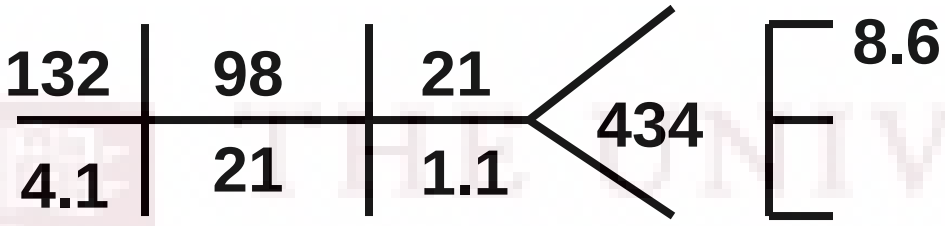
Review of Systems (pertinent)

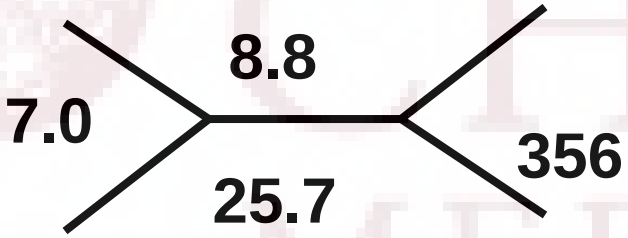
- **HEENT: + headaches, + blurry vision (intermittent)**
- **Neck: no masses**
- **Pulm: - cough**
- **CV: + decreased exercise tolerance, + lightheadedness, + chest pain, - palpitations**
- **GI: + nausea, + vomiting (intermittent)**
- **Neuro: + numbness tingling in b/l lower extremities and upper extremities**
- **Skin: no new rashes**

Physical Exam

- **Vitals: BP 159/96 | Pulse 80 | Temp(Src) 36.8 °C (98.2 °F) (Tympanic) | Resp 18 | Ht 170.2 cm (5' 7") | Wt 72.576 kg (160 lb) | BMI 25.06 kg/m2 | SpO2 99% | LMP 03/23/1993**
- **Manual cuff BP readings**
  - **Seated: 150/90**
  - **Standing: 100/70**
- **General: no apparent distress. Appears stated age.**
- **Cardiovascular: regular rate and rhythm. +Palpable pulses BLE.**
- **Pulmonary/Chest: clear to auscultation bilaterally.**
- **Gastrointestinal: obese abdomen, no striae, bowel sounds present, non-tender**
- **Musculoskeletal: thin extremities, no edema**
- **Neurological: alert & oriented x 3, decreased vibratory sensation in lower extremities b/l**
- **Psychiatric: normal mood**

Laboratory Studies





MCV 75.8 fL
RDW 13.8 %
Iron 67 mcg/dL
TIBC 266 mcg/dL (230-430)
Vitamin B12 499 pg/dL

proBNP 723 pg/mL

HbA1c 11.7%

Random Cortisol (9:34AM) 4.7 mcg/dL

Cosyntropin Stim: 3.5→26.1→32.3 mcg/dL

Albumin/Creatinine Ratio: 2448.7 mcg/mg

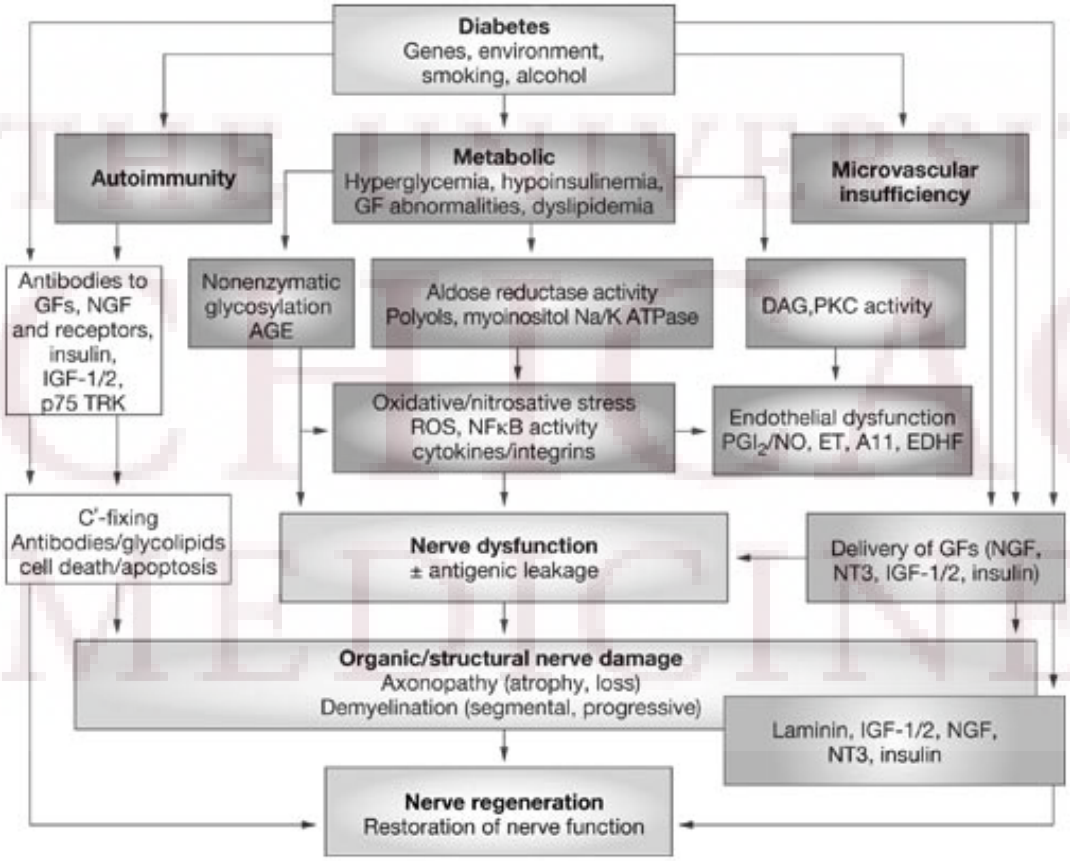
Why is her blood pressure dropping?

- Primary
  - Bradbury-Eggleston syndrome
  - Multiple System Atrophy (Shy-Drager syndrome)
  - Familial Dysautonomia (Riley-Day syndrome)
  - Dopamine--hydroxylase deficiency
- Secondary
  - Diabetes mellitus
  - Uremia
  - Guillain-Barre syndrome
  - Amyloidosis
  - Porphyria
- Transient Neurogenic (Autonomic) Syncope
  - Micturition syncope
  - Carotid sinus syncope
  - Vasovagal syncope
  - Bezold-Jarisch reflex activation
  - Glossopharyngeal neuralgia
- Endocrinologic Disorders
  - Pheochromocytoma
  - Hypoaldosteronism
  - Renal artery hypertension
- Vascular Insufficiency/Vasodilatation
  - Varicose veins
  - Arteriovenous malformations
  - Absent venous valves
  - Carcinoid
  - Mastocytosis
  - Hyperbradykininism
- Hypovolemic Disorders
  - Anemia
  - Decreased plasma volume
  - Hemorrhage
  - Anorexia nervosa
  - Diarrhea
  - Overdialysis
  - Overdiuresis
- Drugs (antihypertensives, diuretics, antidepressants, etc)
- Pregnancy
- Idiopathic

Diabetic Autonomic Neuropathy

- Cardiovascular Effects
- Gastrointestinal Dysfunction
- Sexual Dysfunction
- Bladder Dysfunction
- Sudomotor Dysfunction
- Impaired Visceral Sensation

Pathogenesis of Diabetic Neuropathies



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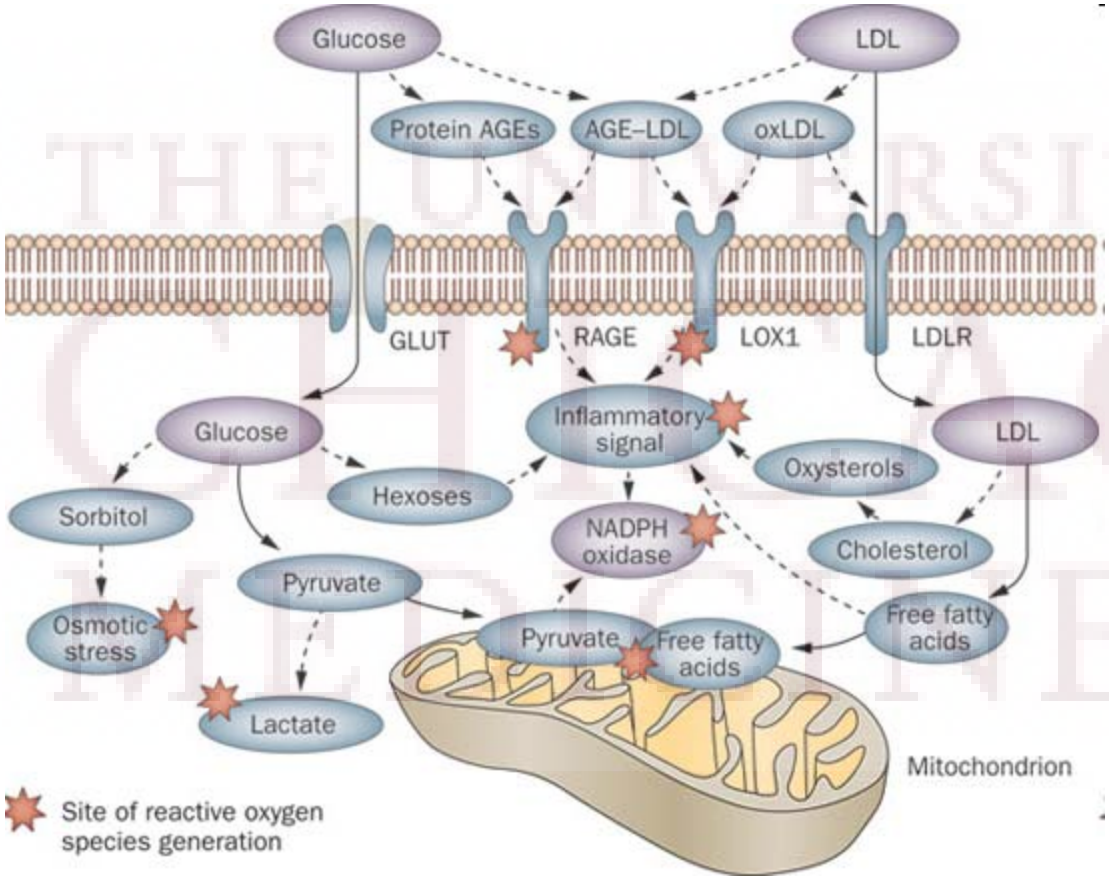
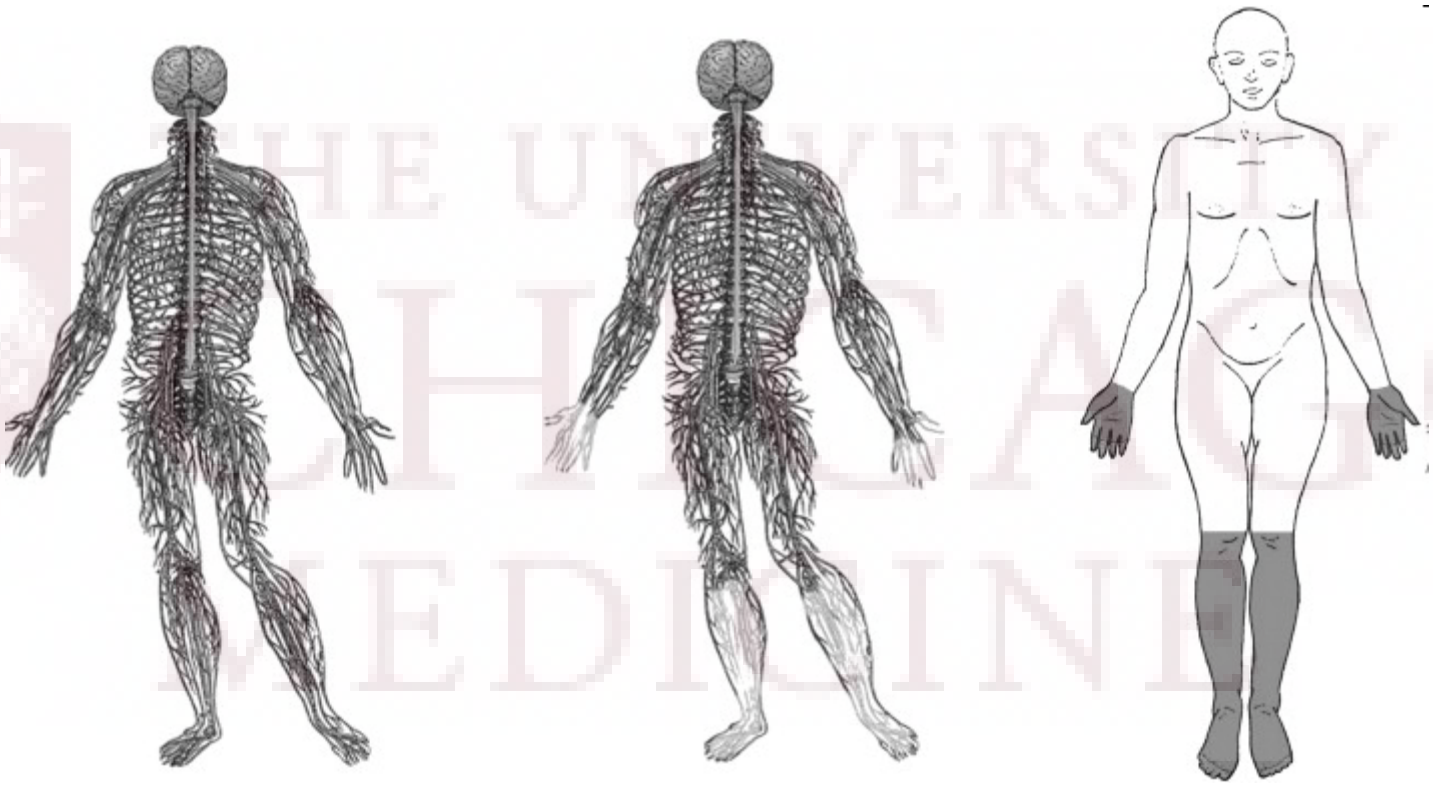
Nat Clin Pract Endocrino Metabol **2:** 269–281 doi:10.1038/ncpendmet0142

Neuronal Injury



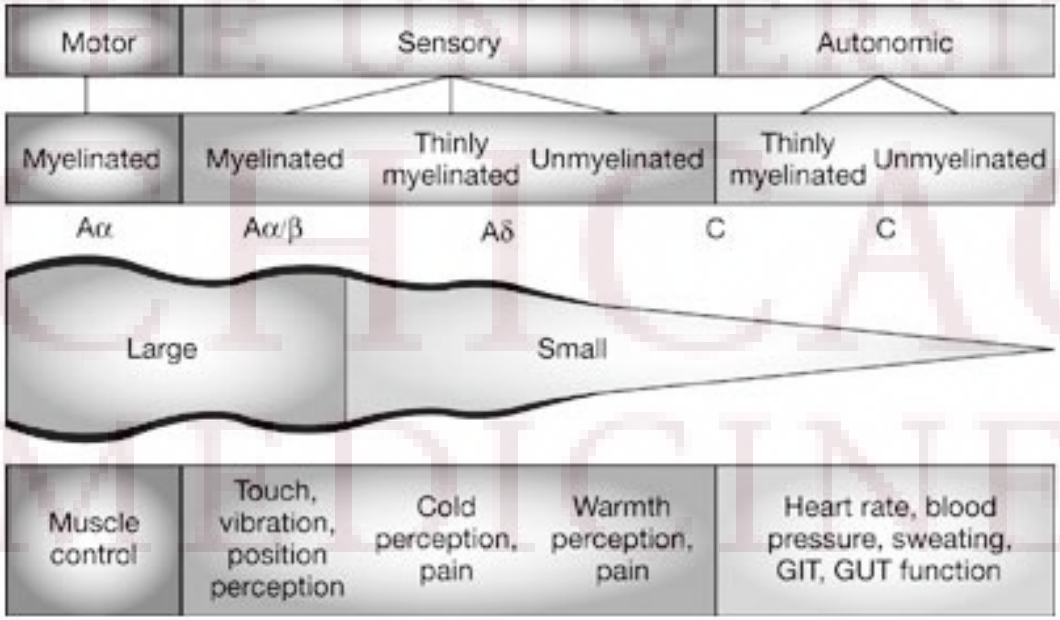
Vincent, A. M. *et al.* (2011) Diabetic neuropathy: cellular mechanisms as therapeutic targets
Nat. Rev. Neurol. doi:10.1038/nrneurol.2011.137

Dependent on Axon Length



James L. Edwards , Andrea M. Vincent , Hsinlin T. Cheng , Eva L. Feldman **Diabetic neuropathy: Mechanisms to management** Pharmacology & Therapeutics Volume 120, Issue 1 2008 1 – 34 http://dx.doi.org/10.1016/j.pharmthera.2008.05.005

Clinical Presentation of Small and Large Fiber Neuropathies



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Our Patient – NCV/EMG, 14 months prior to admission for RUE numbness

- **Findings**
  - **R median and R ulnar SNAPs were unobtainable. R radial SNAP showed moderately decreased amplitude and moderately slowed conduction velocity.**
  - **R median CMAP showed mildly prolonged distal latency, mildly decreased amplitude, and moderately slowed conduction velocity.**
  - **R ulnar CMAP showed mildly prolonged distal latency, normal amplitude, and moderately slowed conduction velocities.**
  - **Limited needle examination of selected muscles in the RUE (C5-C8 myotomes) and R C5-6 paraspinal muscle was normal.**
- **Impression: This is an abnormal study showing evidence of a sensorimotor polyneuropathy with axonal and demyelinating features, that could be consistent with diabetic neuropathy. There is no definite electrophysiologic evidence of R cervical radiculopathy in this study.**

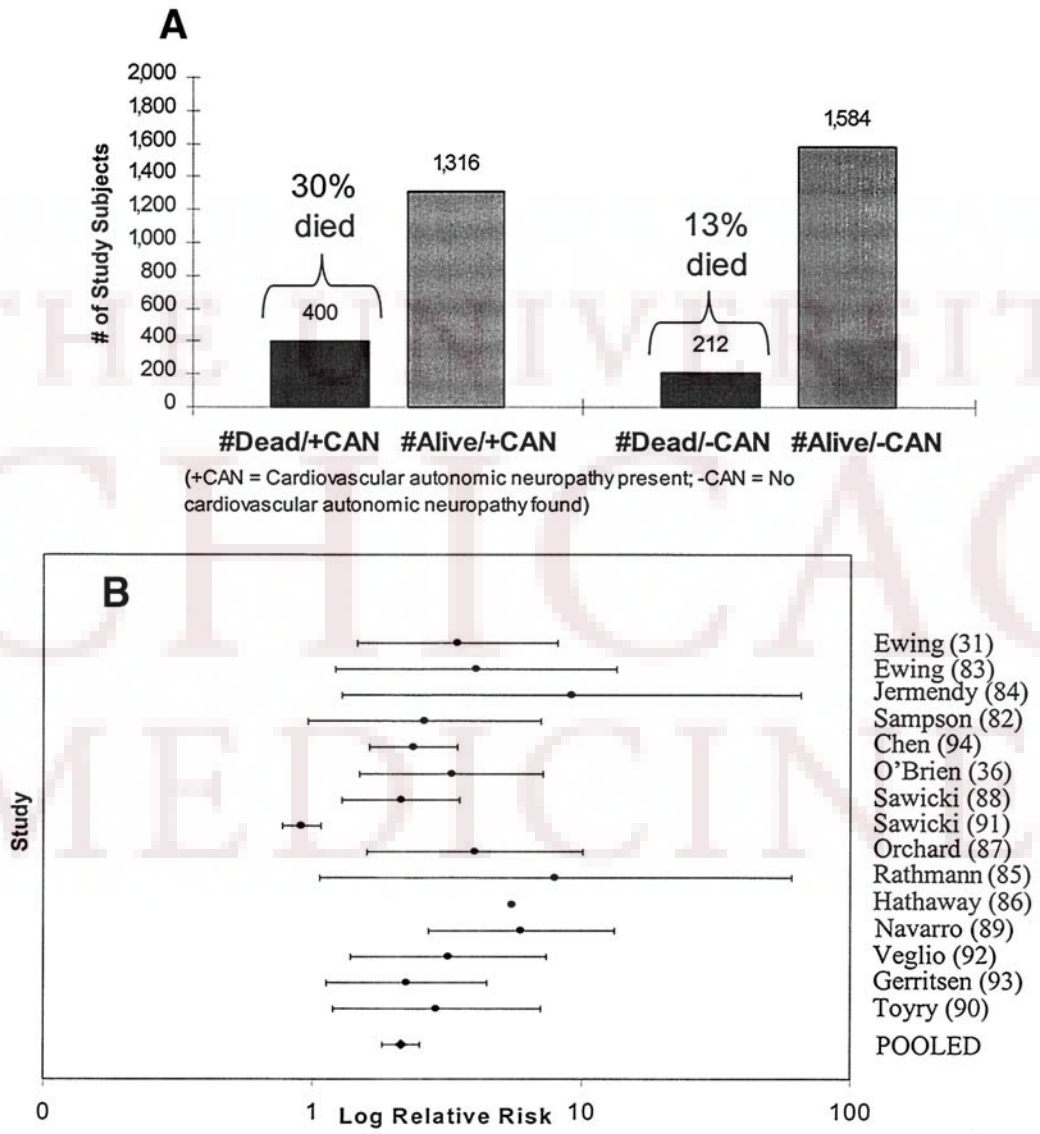
Cardiovascular Autonomic Neuropathy (CAN)

- **Epidemiology**
  - **DCCT: 2.5% in recently diagnosed T1DM**
  - **Increases with duration up to 35% in the former conventional treatment arm of DCCT reported in the EDIC trial**
- **Clinical Features**
  - **Resting tachycardia**
  - **Decreased heart rate variability**
  - **Exercise intolerance**
  - **Postural Hypotension/Syncope**

CAN Mortality Risk

- **Meta-analysis, evaluating 15 clinical studies (2900 subjects), found a pooled relative risk for death of 3.45 (95% CI 2.66–4.47;*P* <0.001)**
- **In EURODIAB IDDM Complications Study, CAN was the strongest predictor of mortality during a 7-year follow-up, exceeding the effect of traditional CV risk factors**
- **ACCORD**
  - **Presence strongly predicts all-cause (HR 2.14) and CVD mortality (HR 2.62) independent of traditional CV risk factors**

Relative risks and 95% CIs for association between CAN and mortality in 15 studies

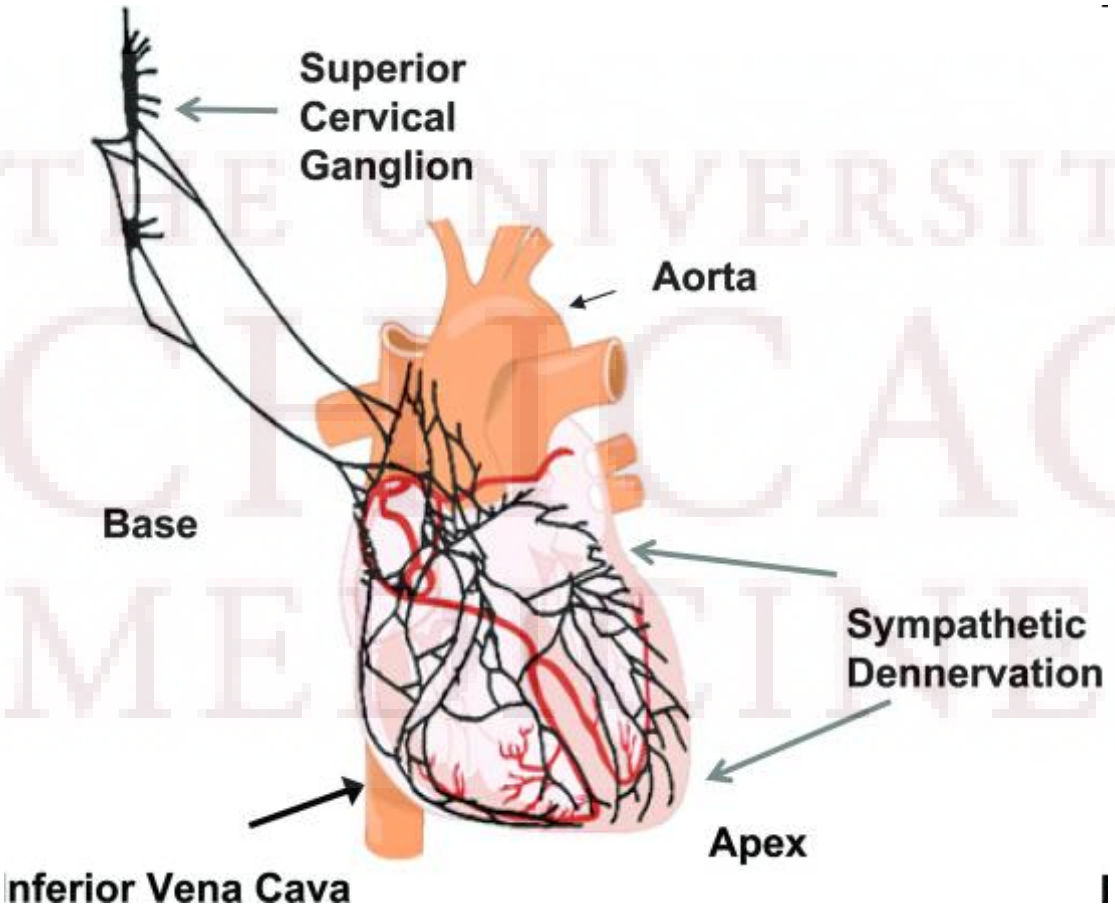


Vinik A I et al. Dia Care 2003;26:1553-1579

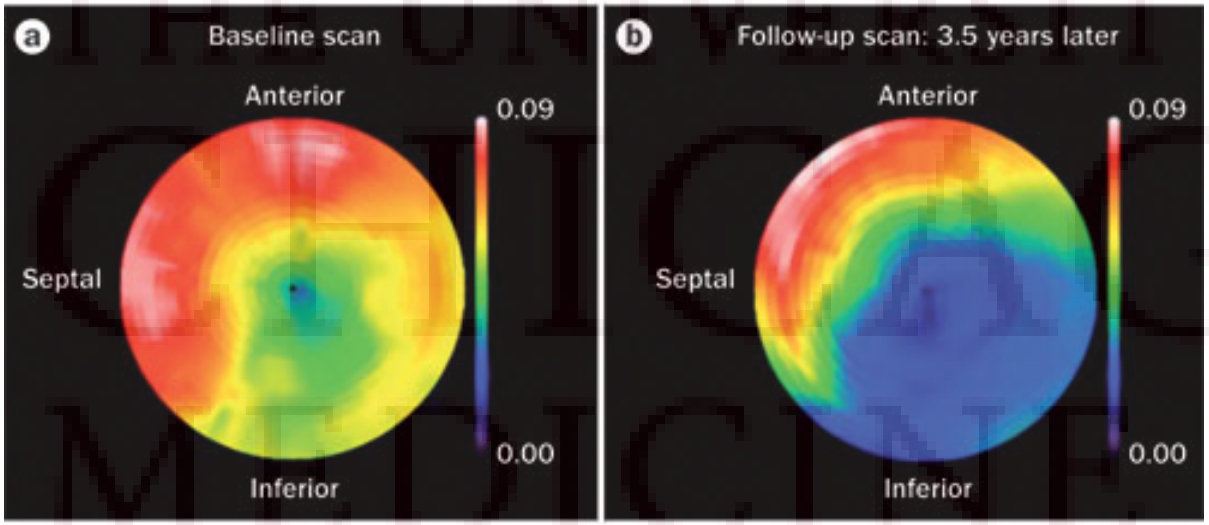
Assessment for Cardiovascular Autonomic Neuropathy

- Conventional cardiovascular autonomic reflex tests (CARTs) assess cardiovascular parasympathetic function by the temporal differences of heart rate response to
  - Deep breathing
  - Valsalva maneuver
  - Postural change
- Results are compared against age-related normal values
- The presence of one abnormal HRV test suggests the development of early CAN
- At least two abnormal tests are required to confirm the diagnosis CAN

Autonomic Innervation of Heart



Progression of cardiac denervation in a female patient with T1DM, CAN and poor glycemic control



Kuehl, M. & Stevens, M. J. (2012) Cardiovascular autonomic neuropathies as complications of diabetes mellitus *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2012.21

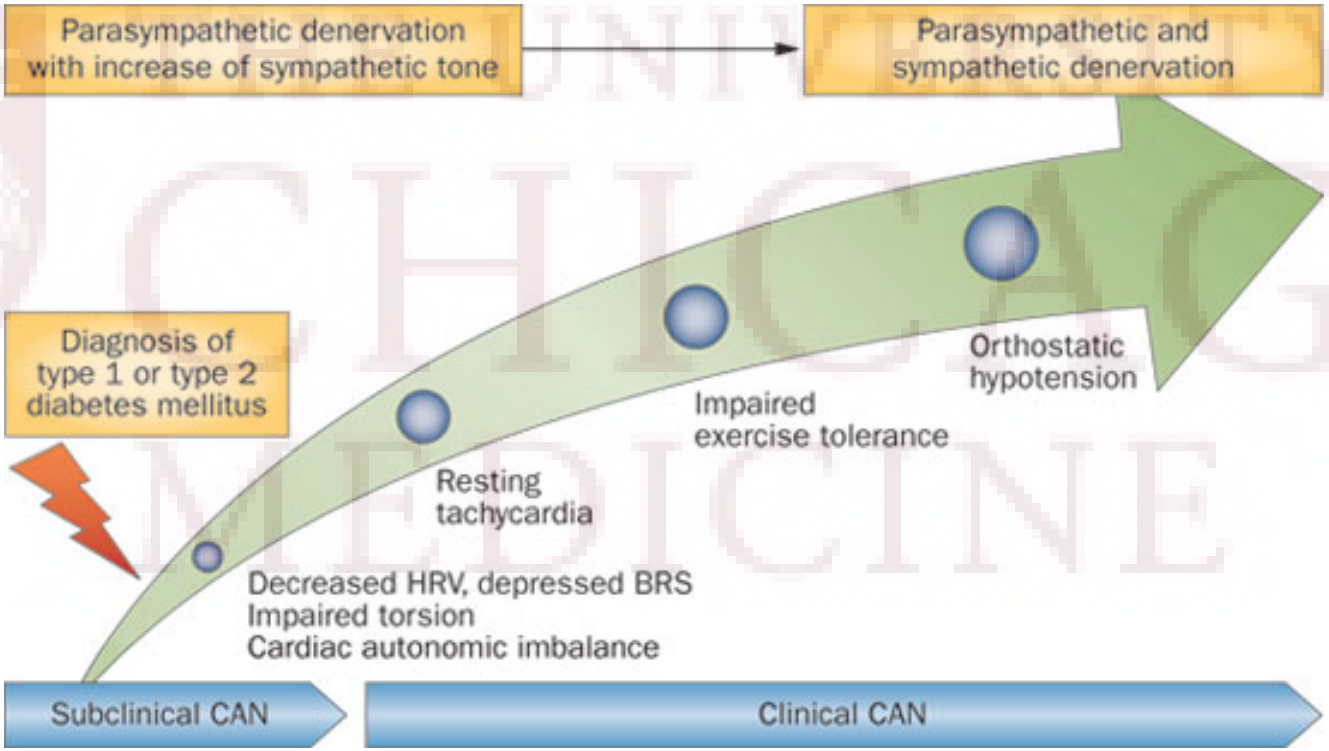
Our Patient – TTE, 6 months prior to admission, complaining of DOE

- **The left ventricle is normal in size**
- **There is mild left ventricular hypertrophy**
- **LV mass when indexed for body surface area is moderately increased**
- **Doppler estimated LV filling pressures are elevated**
- **Left ventricular ejection fraction by single plane method of discs is 53.0 %**
- **Left ventricular performance is mildly reduced**
- ***There is apical hypokinesis***

Nuclear Stress Test

- Time In Exercise Phase: 60 S
- Max. Systolic BP: 161 mmHg
- Max Diastolic BP: 86 mmHg
- Max Heart Rate: 116 BPM
- Max Predicted Heart Rate: 180 BPM
- Baseline ECG: ST-segment within normal limits
- Protocol: Regadenoson
- Stress ECG: No significant ST depression (<1mm)
  - The test was negative for Ischemic ECG changes
  - There were no arrhythmias

Progression of Cardiovascular Autonomic Neuropathy



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Treatment of orthostatic hypotension

Treatment	Dose regimen	Possible side effects
Support garments		
Behavioral advice		
Avoid sudden changes of body posture		
Avoid hot baths and predisposing medications		
Eat frequent small meals		
Take insulin injections lying down		
Fludrocortisone	**0.1 mg titrated to 0.5 to 2.0 mg/day**	**May predispose to congestive heart failure, hypertension**
Sympathomimetics		
Ephedrine	**15 - 45 mg, TID**	**Sympathetic symptoms**
Midodrine	**2.5 - 10 mg, TID**	**Fewer centrally-mediated side effects**
Clonidine	**0.1 - 0.5 mg at bedtime**	**Hypotension**
Octreotide	**0.1 - 0.5 ug/kg/day**	**Injection site pain, diarrhea**

Our Patient

- **Supine Hypertension**
  - **Verapamil – 180 mg PO QHS**
  - **Clonidine – 0.1 mg PO QHS**
- **Upright Hypotension**
  - **Compression stockings or abdominal binder**
  - **Salt tabs – 1 gram upon awakening, 1 gram with lunch**

Teaching Points

- **CAN significantly affects quality of life and intensive glucose control early in diagnosis of DM is the best way to prevent it**
- **Patients often die from sudden cardiac death attributed to dysrhythmias**
- **Multifaceted approach is necessary to treat CAN including behavioral modifications**

References

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