THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

AT THE FOREFRONT OF MEDICINE®

69 y.o male presenting with AMS

Endorama

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

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I have no relevant financial relationships with any commercial interests

OBJECTIVES

- Discuss symptoms, signs and laboratory findings of myxedema coma
- Discuss the effects of T3 on cardiovascular system
- Discuss factors that interfere with thyroid function assays
- Discuss the management of Myxedema Coma

HPI

- 69 y.o male with PMH of CVA 2017 with residual bilateral weakness L>R, dementia (AAOx2 with decreased attention, concentration at baseline), HTN, hypothyroidism

  CC: lethargy and decreased responsiveness

  Consult: severe hypothyroidism

- Per his wife: he was not responding to questions and appeared to be very ill, preceded by cold-like symptoms
- He had near fall at home due to "legs giving out", denied syncopal events, denied head trauma. No recent fever, chills, pain, dysuria, chest pain, dyspnea, or other complaint
- CT scan did not show any acute findings and he was admitted for observation and UTI treatment with Cefepime

HYPOTHYROIDISM HISTORY

- 9 months PTA: admitted after a fall with L1 compression fracture and was found to be hypothyroid
- History of surgical hypothyroidism
- Thyroid was taken out at Cook County Hospital due to "overactive“
- Poor compliance

PMH:

- CVA (2017, L>R weakness and gait ataxia, concern for early vascular dementia)
- Hypothyroidism (s/p thyroidectomy)
- Prostate ca - being monitored prostate ca s/p radical prostatectomy (2006)
- OSA - on CPAP
- Psoriasis
- Reported PAD
- Lumbar spine fracture

PSH: thyroidectomy

PFH:no thyroid disease in the family

SH: lives with wife

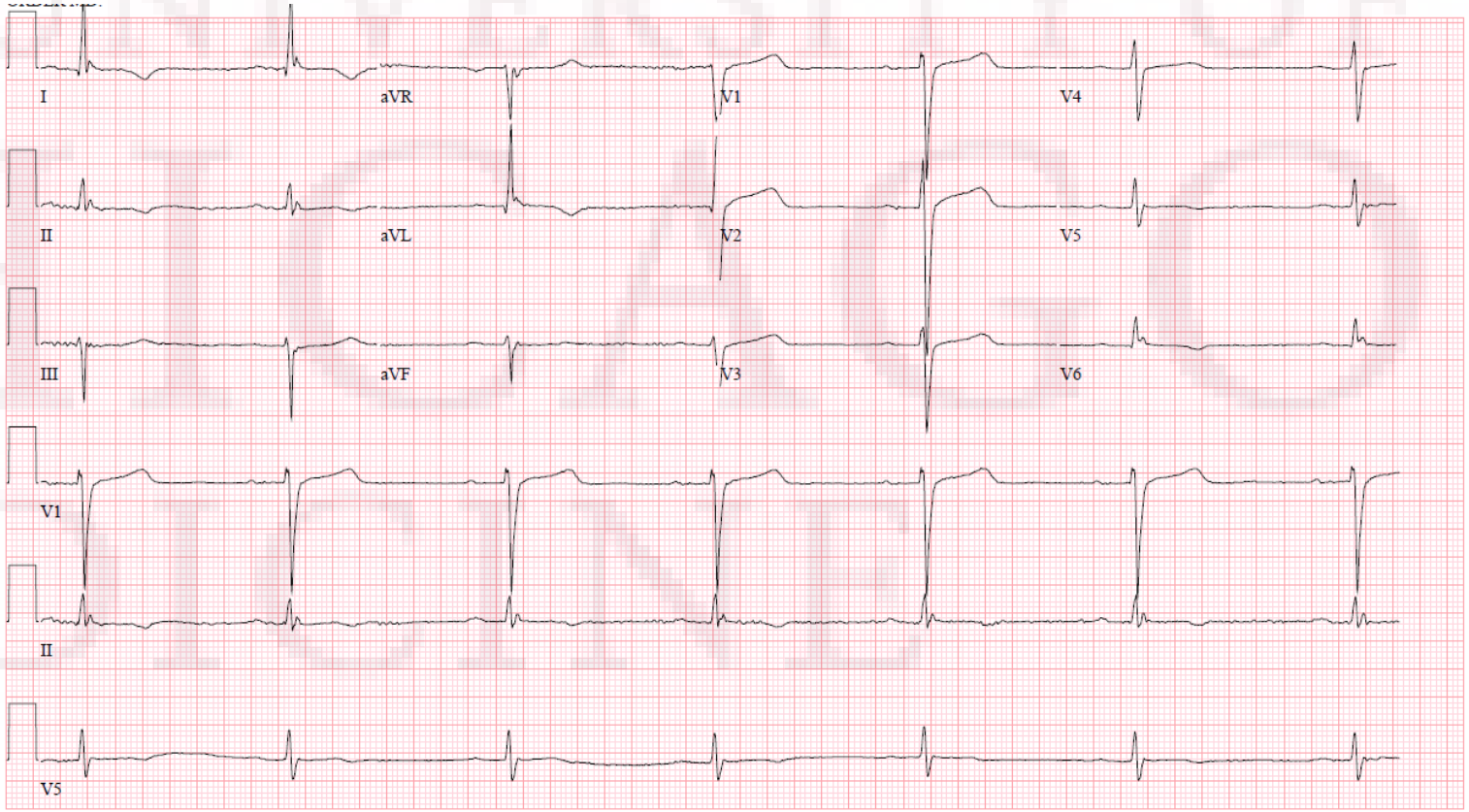
PTA Meds:

- acetaminophen (TYLENOL) 325 mg PO PRN
- amlodipine (NORVASC) PO 10 mg daily
- aspirin 81 mg PO chew daily
- atorvastatin (LIPITOR) 80 mg PO daily
- levothyroxine (SYNTHROID) 150 mcg PO daily

Allergies: NKDA

HOSPITAL COURSE

- During the night, his heart rate dropped to low 20s and EKG showed heart block
- 9-10 second pause
- Atropine given with improvement in his HR
- Transferred to CCU and was started on dopamine infusion
- While on dopamine infusion, HR remain at 50s and went down as low as 20s
- Was scheduled for cardiac cath in AM



REVIEW OF SYSTEMS

- Unable to perform ROS: due to mental status change

Per wife

- Constitutional: no fevers, chills
- HEENT: no Rhinorrhea, sore throat
- Cardiac: no chest pain, peripheral swelling
- Pulm: no cough, shortness of breath
- GI: no abdominal pain, nausea
- GU: no dysuria
- Skin: **+ rash - chronic psoriasis**
- Neuro: **+ diffuse weakness, somnolence**
- Heme: no bleeding

PHYSICAL EXAM

- BP 111/77 | Pulse (!) 55 | Temp 35.8 °C (96.6 °F) (NCIT) | Resp 18 | Ht 182.9 cm (6') | Wt 87.4 kg (192 lb 10.9 oz) | SpO2 98% | BMI 26.13 kg/m²

- Constitutional: on BIPAP, warming blanket
- HEENT: EOMI
- Neck: supple, no palpable thyroid tissue, could not appreciate neck scar
- Cardiovascular: **bradycardia**, no extra heart sounds
- Pulmonary/Chest: clear to auscultation bilaterally
- Abdomen: bowel sounds present, soft, non-tender
- Musculoskeletal: strength intact in RUE
- Neurological: **follows commands**
- Skin: warm, dry
- Psychiatric: not agitated

LABS

Trop (normal <22): 87➔138

Cortisol 4 AM 12.1 (add on)

How to manage this pt?

	3/21/2019 1143	6/25/2018 0802
CELL COUNT & DIFF		
WBC	2.2 *	4.4
RBC	4.18	3.23
Hemoglobin	12.5	9.8
Hematocrit	39.8	29.8
MCV	95.2	92.3
MCH	29.9	30.3
MCHC	31.4	32.9
RBC Dist Width	15.2	14.8
Platelet Count	71	158

BASIC & COMPREHENSIVE	
Glucose, Ser/Plasma	85 *
Sodium	143
Potassium, Ser/Plasma	4.7 *
Chloride	112
Carbon Dioxide	20
Anion Gap	11
BUN	25
Creatinine	1.1
GFR Estimate (Calc)	66 *
Calcium	9.0
Inorganic Phosphate	2.2
Magnesium	1.9

ARTERIAL BLOOD GAS	
FIO2	30
pH (Arterial)	7.29
PCO2 (Arterial)	56
PO2 (Arterial)	92
HCO3- (Arterial)	26.9
Base Excess (Arter...	MINUS 1
SO2 (Arterial)	97.4
Temperature	37.0
pH (Temp Corr Art)	7.29
PCO2 (Temp Corr Art)	56
PO2 (Temp Corr Art)	92

	Ref. Range and Units	3/22/2019 0138	3/21/2019 1143	8/16/2018 1502	6/25/2018 0802	6/22/2018 1407	6/22/2018 0803
THYROID FUNCTION							
Thyroxine, Free	Latest Range: 0.9 - 1.7 ng/dL	1.08	0.93	0.24	0.51		0.48
Thyroglobulin Ab	Latest Range: <0.4 KU/mL AbTgn					<0.4	
Thyroid Perox. Ab	Latest Range: <0.4 KU/mL AbTPO					<0.4	
Thyrotropin	Latest Range: 0.30 - 4.00 mcU/mL		92.04	100.50 *	89.34 *		133.50 *
Triiodothyronine	Latest Range: 80 - 195 ng/dL	52					
Thyroxine	Latest Range: 5.0 - 11.6 ug/dL						

Q1:
Is this myxedema coma with normal FT4 values?

MYXEDEMA COMA

Neurologic manifestations: usually takes the form of confusion with lethargy and obtundation
Hyponatremia: 50% of pts due to inappropriate secretion of ADH and/or adrenal insufficiency
Hypothermia: the lower the temperature, the higher the mortality
Hypoventilation: decreased responsiveness to hypoxia and hypercapnia
Hypoglycemia
Cardiovascular abnormalities: diastolic hypertension, severe hypothyroidism is associated with bradycardia, decreased myocardial contractility, a low cardiac output, and sometimes hypotension

Mathew V et al. Myxedema coma: a new look into an old crisis. *J Thyroid Res*. 2011;

MYXEDEMA COMA SCALE

- This scale has been proposed based on 21 patients diagnosed with myxedema coma
- MC data collected from retrospective cases as well as selected case reports from the literature

Table 4
Diagnostic Scoring System for Myxedema Coma[a]

Thermoregulatory dysfunction (temperature, °C)		**Cardiovascular dysfunction**	
>35 ✖	0	Bradycardia	
32-35	10	Absent	0
<32	20	50-59	10
Central nervous system effects		40-49	20
Absent	0	<40 ✖	30
Somnolent/lethargic ✖	10	Other EKG changes[b] ✖	10
Obtunded	15	Pericardial/pleural effusions	10
Stupor	20	Pulmonary edema	15
Coma/seizures	30	Cardiomegaly	15
Gastrointestinal findings		Hypotension	20
Anorexia/abdominal pain/constipation	5	**Metabolic disturbances**	
Decreased intestinal motility	15	Hyponatremia	10
Paralytic ileus	20	Hypoglycemia	10
Precipitating event		Hypoxemia	10
Absent	0	Hypercarbia	10
Present ✖	10	Decrease in GFR	10

Abbreviations: EKG = electrocardiogram; GFR = glomerular filtration rate.
[a] A score of 60 or higher is highly suggestive/diagnostic of myxedema coma; a score of 25 to 59 is suggestive of risk for myxedema coma, and a score below 25 is unlikely to indicate myxedema coma.
[b] Other EKG changes: QT prolongation, or low voltage complexes, or bundle branch blocks, or nonspecific ST-T changes, or heart blocks.

Popoveniuc Et al.,Endocr Pract. 2014

INTERFERING FACTORS WITH TFTS

↑TSH, normal FT4	TSH assay interference	Heterophilic antibody interference in the TSH assay may yield falsely elevated results; FT3 is normal
Persistent ↑TSH, with ↓, ↑ or normal FT4, despite treatment with high L-T4 dosages	Poor compliance	Owing to their differing half-lives, intermittent thyroxine ingestion may result in normal or even elevated TH concentrations, but fails to normalize TSH
Supraphysiologic L-T4 required to normalise TSH, but with resultant ↑FT4 (and ↑FT3)	Resistance to thyroid hormone	Typically seen following inappropriate thyroid ablation or concomitant primary hypothyroidism in a patient harbouring a mutation in the human thyroid hormone receptor β (*THRB*) gene

Koulouri Oet al., *Clin Endocrinol Metab*. 2013

ABS INTERFERENCE IN TH IMMUNOASSAYS

- Autoantibodies:
  - Can give abnormal values in thyroid function evaluation
  - These endogenous factors particularly interfere in T4, FT 4, T 3, and FT3 methods

- Heterophilic antibodies:
  - Abnormal concentrations of TSH resulting from heterophile antibody interference
  - The best-known heterophile antibodies are human anti-mouse antibodies (HAMA), which can react with the mouse monoclonal antibodies that are used in many immunometric assays
  - The prevalence in the general population between **0.2% and 15%**

- Rheumatoid factors (RF)

- HAMA and RF, interfere by a common mechanism and may give spuriously high values in two-site immunoassays (in TSH levels mainly, has also been described in a competitive FT4 assay)

Després et al., Clin Chem. 1998

ALTERED TBG CONCENTRATIONS

Changes in total but not free serum thyroid hormone

- Meds increase TBG synthesis:
  - Estrogen (oral, not transdermal), raloxifene, tamoxifen, mitotane, fluorouracil, methadone and heroin
- Meds decrease TBG synthesis :
  - Androgens, chronic glucocorticoid therapy and nicotinic acid have all been shown to inhibit TBG synthesis

Koulouri Oet al., *Clin Endocrinol Metab*. 2013

COMPETITION FOR TH BINDING SITES ON TBG

- Displace T4 and T3 from their binding and affect FT4 and FT3
- Drugs that compete for TH binding sites in TBG include:
  - Furosemide (especially with doses >80 mg/day and when given intravenously)
  - Aspirin
  - NSAIDs
  - Phenytoin
  - Heparin

Koulouri Oet al., *Clin Endocrinol Metab*. 2013

HEPARIN AND TH LEVELS

- Heparin interference with TH levels was first noticed in 12 patients undergoing hemodialysis
- Trial with IV heparin given to:
  - 9 healthy controls
  - 5 subjects with hypothyroidism
- FT4 increased up to 5 folds (within 2–15 min)
- Low dose IV heparin (maintain the patency of an indwelling cannula), and SubQ (LMWH) prophylaxis ➔ FT4 elevation

> *Heparin activates endothelial lipoprotein lipase in vivo ➔ increase serum non-esterified fatty acid (NEFA) ➔ increased NEFA generation in vitro during sample storage or incubation would compete for T4 and T3 binding sites on TBG*

- <u>Solution:</u> take blood sample more than 10 hrs after the last injection of heparin and analyze it without delay or, measurement of total TH levels together with TSH and TBG

Koulouri Oet al., *Clin Endocrinol Metab*. 2013

HOSPITAL COURSE

- When we were consulted, the patient was being transferred to cardiac cath

How would you proceed with treatment?

- We recommended giving him 75 mcg IV of levothyroxine before the cath lab along with 100 milligrams of hydrocortisone injection
- Recommend administering 100 mcg of Levothyroxine IV after the cath

CARDIAC CATH REPORT

Coronary arteries

- **Left main:** no disease
- **Left anterior descending artery:** mild luminal irregularities
- **Left circumflex:** mild luminal irregularities in the mid portion of the vessel and a 40% in the proximal portion
- **Right coronary artery:** up to 40-50% stenosis in the mid-vessel
  lateral branch contains a 90% stenosis (x 2 stents)
- LVEDP 8 mmHg (normal)
- No gradient across the aortic valve

Temporary pacemaker was placed in RIJ as well

TRANSTHORACIC ECHO (TTE)

1/26/2018 (13 months PTA) Advocate Aurora Health

SUMMARY:

- Left ventricle:
  - The cavity size is normal
  - Wall thickness is mildly increased
  - There is concentric hypertrophy
  - Systolic function is normal

- The estimated ejection fraction is 50-55%
- Doppler parameters are consistent with abnormal left ventricular relaxation (grade 1 diastolic dysfunction)

HEMATOLOGY

- Etiology of anemia and thrombocytopenia is unclear this time but likely multifactorial including underlying hypothyroidism
- Anemia/thrombocytopenia work up including infectious work up, hemolysis labs, nutritional and mineral tests initiated
- Peripheral smear with no concern for TTP

Case report of severe hypothyroidism and pancytopenia that was corrected after 1 month of LT4 treatment in hypothyroid patient with no other PMH

Tsoukas Et al., Am J Med. 2014

HOSPITAL COURSE

Next day:

- Appeared to be less responsive, he is not following commands
- HR in 40s (when pacer is off)
- S/P 100 mcg levothyroxine IV today
- still on dopamine drip

What would you do?

MYXEDEMA TREATMENT

- Initially IV levothyroxine given intravenously
  - A loading dose of 200–400 μg of levothyroxine may be given (lower doses for older patients/ CAD or arrhythmia)
  - Daily replacement dose 75% of 1.6 μg/kg body weight
  - Switch to oral after patient improves clinically
- Empiric glucocorticoid (stress dose) coverage preceding levothyroxine administration

Strong recommendation, Low-quality evidence:

IV liothyronine (LT3) may be given in addition to levothyroxine

- High doses should be avoided given the association of high serum triiodothyronine during treatment with mortality
  - A loading dose of 5–20 μg ➔maintenance dose of 2.5–10 μg every 8 hours
  - Lower doses for older patients/ CAD/ or arrhythmia
  - Therapy can continue until the patient is clearly recovering

OUR APPROACH

- Continued levothyroxine 100 mcg IV daily (75% of expected oral physiologic replacement of 1.6 mcg/kg/d)
- Recommended starting IV liothyronine due to worsening MS and persistent bradycardia
- Avoided loading dose of LT3 since he is an elderly with proven recent CAD and already s/p loading dose of levothyroxine
- Started LT3 2.5 mcg IV Q 8 hrs and monitor for arrhythmia closely

HOSPITAL COURSE

liothyronine (TRIOSTAT) IV 2.5 mcg	
03/24/19 0800	Given
03/24/19 1400	Given
03/24/19 2200	Given
03/25/19 0600	Given
03/25/19 1400	Given
03/25/19 2200	Given
03/26/19 0600	Given

BP	HR
95/55	46
101/65	43
134/98	60
127/88	66
56/43	145

MS improved, awake, responded to his name and was able to squeeze hand on request, off BIPAP

Paced rhythm, awake and spoke incoherently, off dopamine drip

- **<u>Polymorphic VT</u> was noted on the tele monitor. He subsequently lost pulse and Dr. Cart was called for cardiac arrest**
- **Intubated and ROSC was achieved after ~30 minutes**
- **Cath lab for LHC where a DES was placed in the mid RCA**

TFTs

	Ref. Range and Units	3/26/2019 1432	3/25/2019 0203	3/24/2019 0309	3/23/2019 1257	3/23/2019 0300	3/22/2019 0138	3/21/2019 1143
THYROID FUNCTION								
Thyroxine, Free	Latest Range: 0.9 - 1.7 ng/dL	*1.50 **	*1.06*	*1.08*	*1.18*		*1.08*	*0.93*
Thyroglobulin Ab	Latest Range: <0.4 KU/mL AbTgn							
Thyroid Perox. Ab	Latest Range: <0.4 KU/mL AbTPO							
Thyrotropin	Latest Range: 0.30 - 4.00 mcU/mL	*13.89* ▲	*18.89* ▲	*15.47* ▲				*92.04* ▲
Triiodothyronine	Latest Range: 80 - 195 ng/dL	*68* ▼	*61* ▼	*49* ▼	*49* ▼	*47* ▼	*52* ▼	
Thyroxine	Latest Range: 5.0 - 11.6 ug/dL					6.5		

Schrier et al., J Am Soc Nephrol. 2006

Q2:
What are the effects of T3 on the cardiovascular system?

T3 AND THE CVS

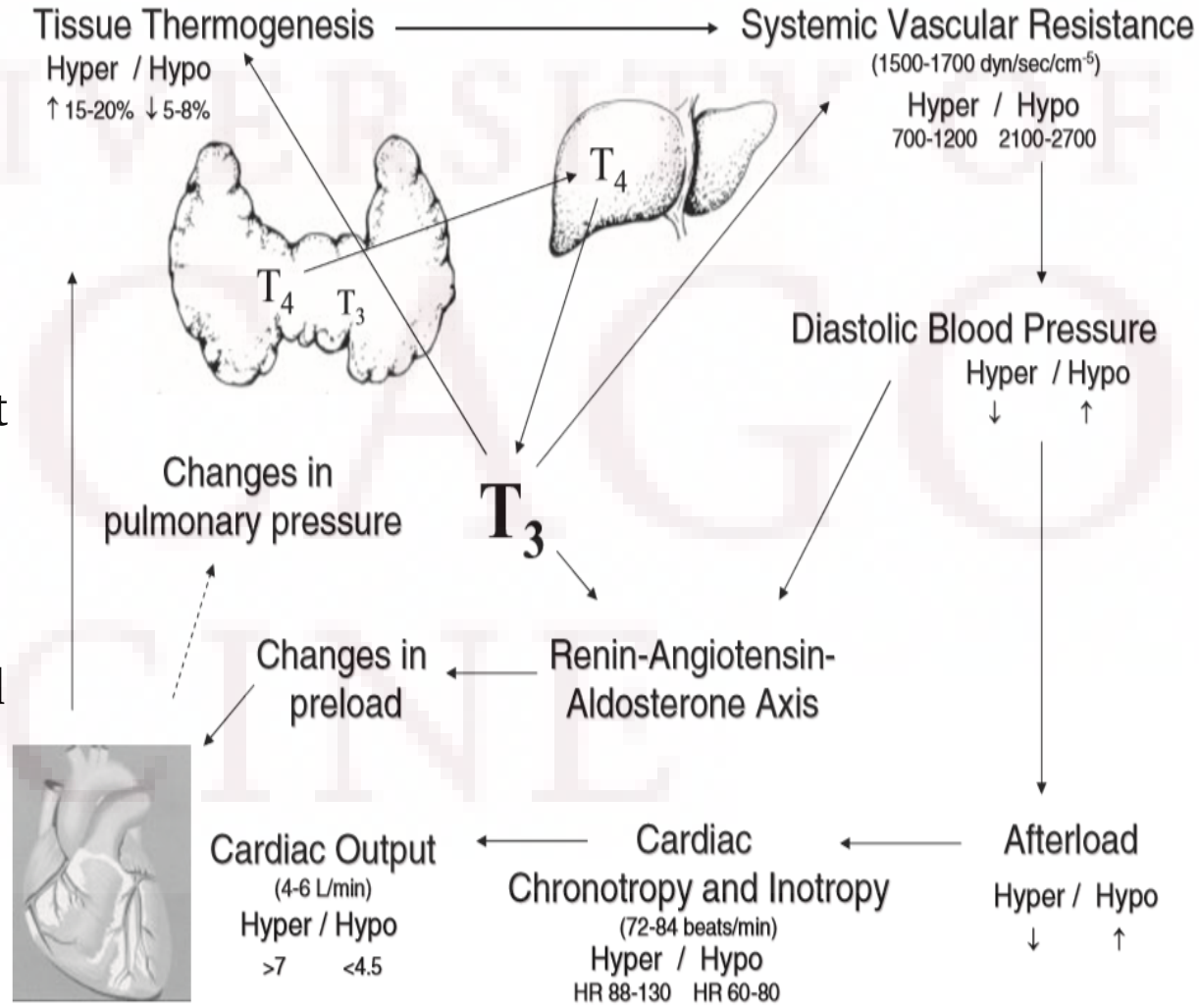
Key role of thyroid hormones on the homeostasis of the cardiovascular system is regulated by three different routes:

- Direct effect on cardiomyocytes
- Peripheral effects on the vasculature
- Modulation of sympathetic systems

Pingitore A aeal., Acute effects of (T3) therapy in pts with CHF and low-T3 syndrome, J Clin endo Metab. 2008

T3 AND CVS

- Thyroid hormone has effects on both the peripheral circulation and the myocardium
- The cardiac myocyte (in normal condition) has no appreciable deiodinase activity (but +mRNA) and therefore relies on the plasma as the source of T3
- Diastolic hypertension is a common accompaniment of hypothyroidism
- TH effects on the heart is mediated indirectly via acceleration of VO2 throughout the body
- TH causes vasodilation by increasing global demand for oxygen, that requires an increase in cardiac output to sustain mean arterial blood pressure



Irwin Klein, and Sara Danzi Circulation. 2007;116:1725-1735

EFFECTS OF THYROID HORMONES ON THE VENTRICLES

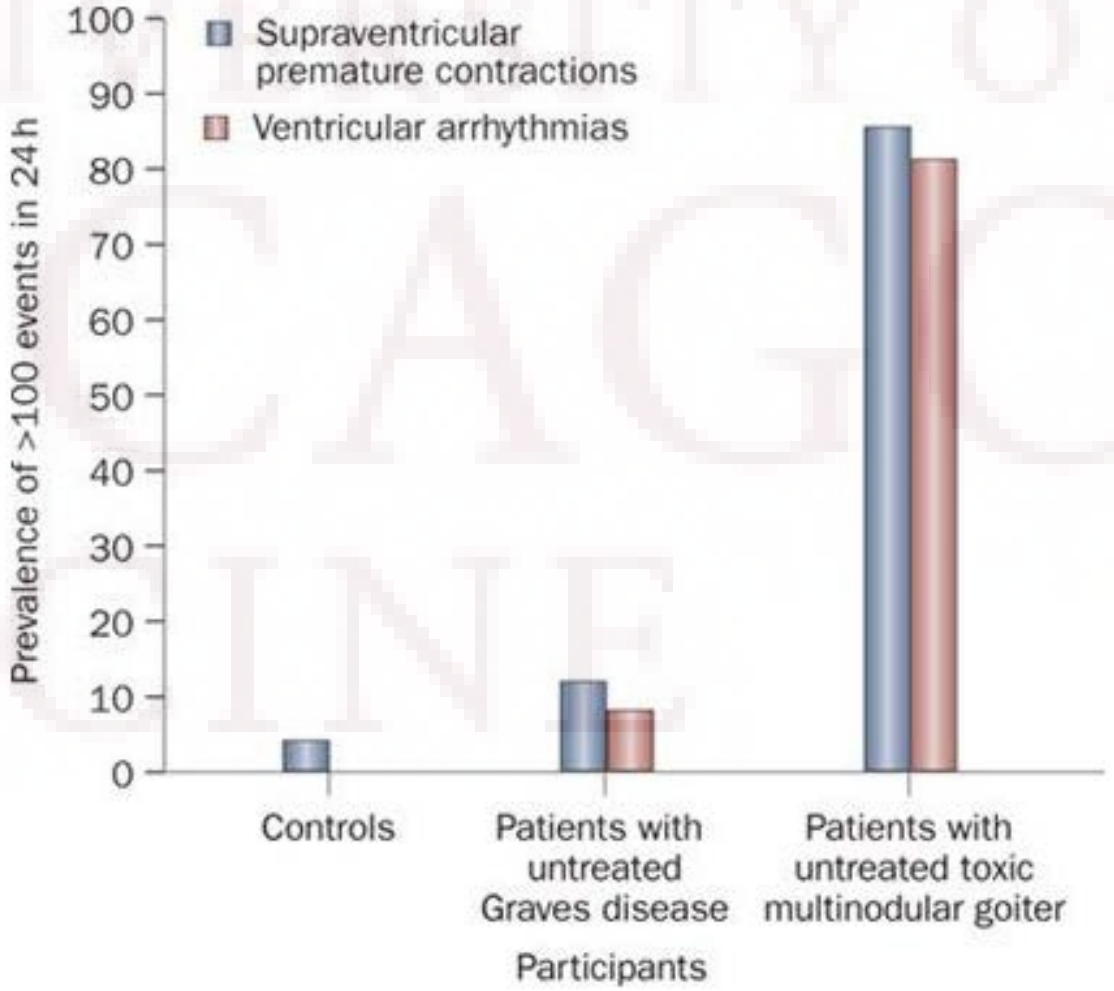
- Ventricular arrhythmias are uncommon in thyrotoxicosis and are found with a frequency similar to that in the normal population
- Ventricular tachycardia and ventricular fibrillation are exceptional in those with thyrotoxicosis and usually occur only in those with marked heart failure or associated cardiac disease, typically because of ischemic heart disease

Osman Et. al, *Jour Clin End & Meta* 2002

T3 AND VENTRICULAR ARRHYTHMIA

- Review article on 150 pts
- None of the controls had ventricular arrhythmias, which were present in 29 untreated patients with toxic multinodular goiter and in three untreated patients with Graves disease (all three had CAD)

- The presence of ventricular arrhythmias in patients with hyperthyroidism frequently reflects underlying heart disease, particularly in patients with toxic multinodular goiter



Biondi Et al., Nature Rev Endocrinol. 2010

BACK TO PATIENT

- Remained intubated on 3 vasopressors
- Developed multi-organ failure after the cath lab
- Family they elected for comfort care
- Vasopressors support was withdrawn on 3/26/19
- Subsequently expired
- Records acquired form Cook County Hospital revealed:
  - US in March 2001: diffuse thyromegaly
  - Total thyroidectomy in September 2001
  - LT4 175 mcg/d and good TFTs and F/U ends in 2005

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THANK YOU

Questions/comments?