The Dilemma of Broken Heart Takotsubo Syndrome
Why is it More Prevalent in Women?

Right Care Initiative Virtual University of Best Practices
May 9, 2022, 12:00 to 2:00 p.m. PST

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Autonomic function slides courtesy of Jens Jordan, Charite, Berlin, Germany

Presenter Disclosure Information

Bairey Merz

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Consulting: iRhythm

Autonomic Nervous System

Coronary Microvascular Dysfunction (CMD)

Postural Orthostatic Tacycardia Syndrome (POTS)

Takotsubo Syndrome (TTS)

Coronary Microvascular Dysfunction (CMD)

Angina

Abnormal SPECT

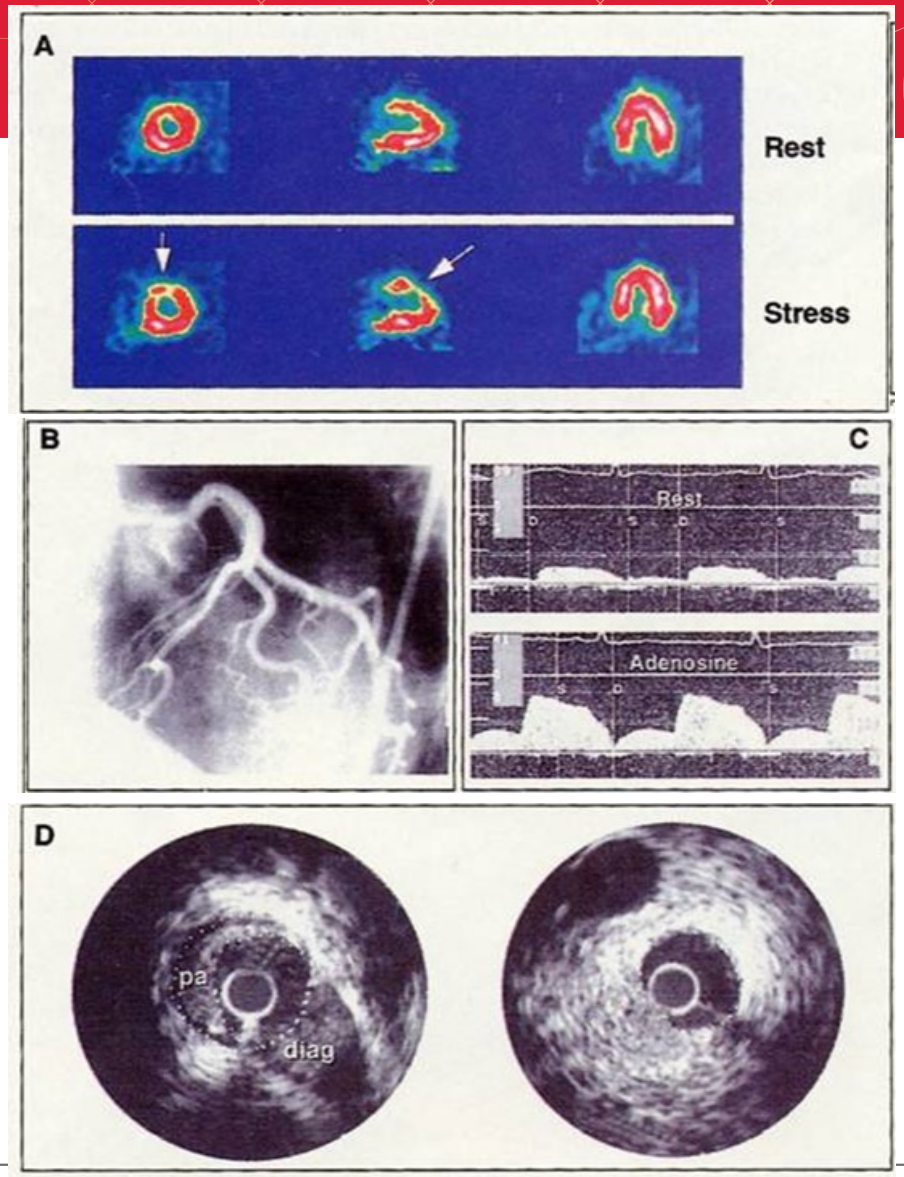
No obstructive CAD

Abnormal coronary flow reserve and elevated LVEDP

Diffuse atherosclerosis by IVUS

NCDR estimate 3 million women in the US – a larger problem than breast cancer.

70-80% women



Circulation. 1999;99:1774

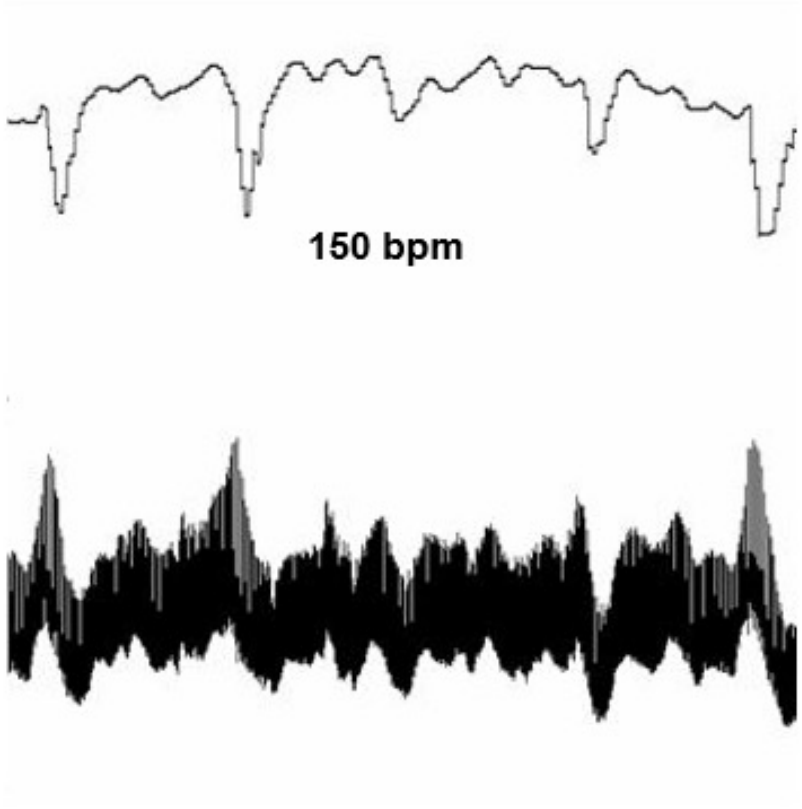
Postural Tachycardia Syndrome (POTS)

Diagnostic Criteria:

- Typical symptoms with standing
- Orthostatic heart rate increase ≥ 30 /min and/or upright heart rate ≥ 120 /min
- No orthostatic hypotension

Background:

- Most common dysautonomia
- Excessive beta-adrenergic stimulation
- Increased cardiac norepinephrine spillover

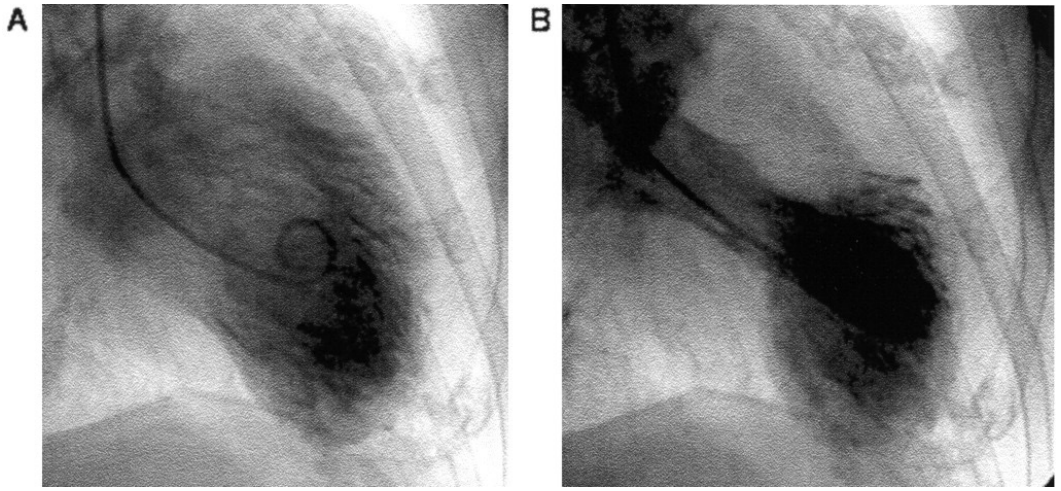


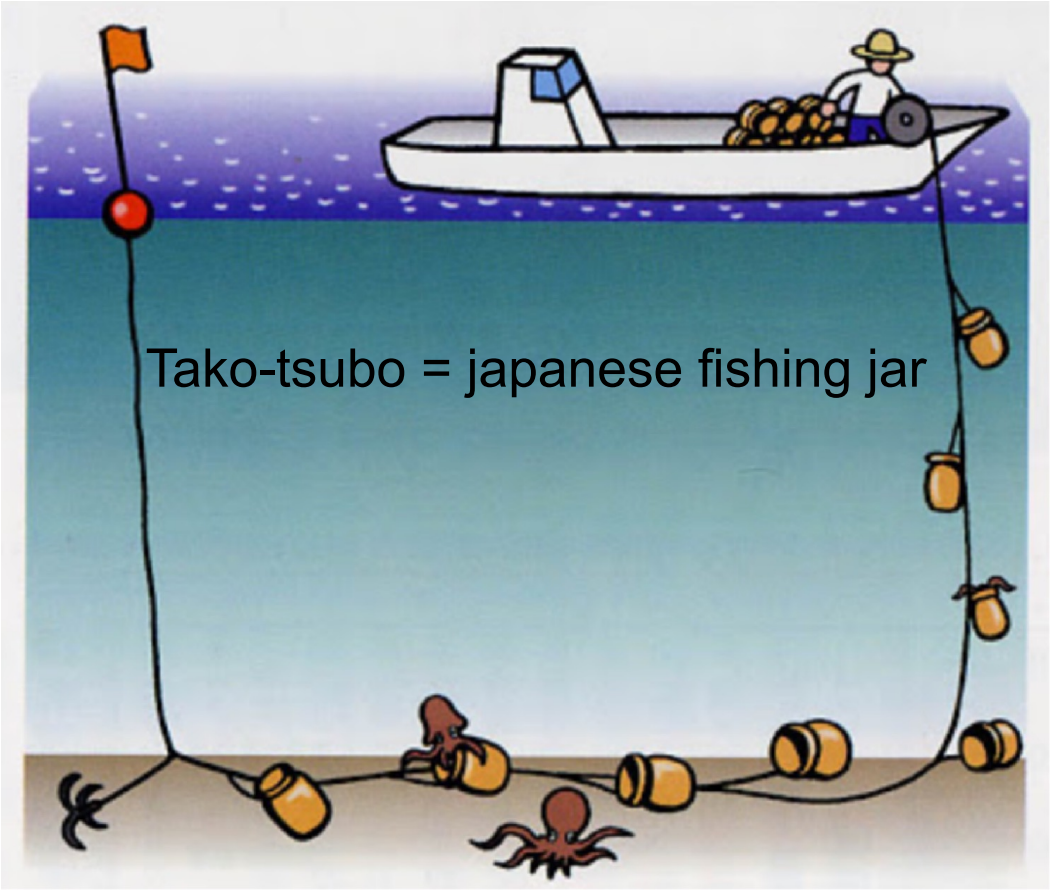
80-90% are women

Takotsubo Syndrome (TTS) – sometimes called Stress-induced Cardiomyopathy

- After psychological, physical or no stress
- Excessive sympathetic stimulation
- Apical ballooning of the left ventricle
- Recovery in days to weeks

80-90% women





Teraoka K et al. Circulation. 2005;111:e261-e262

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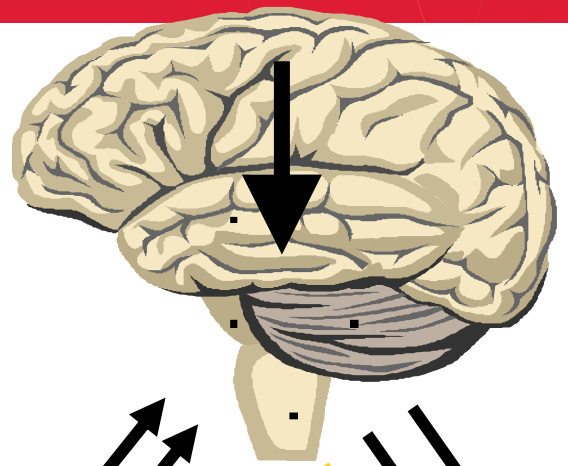
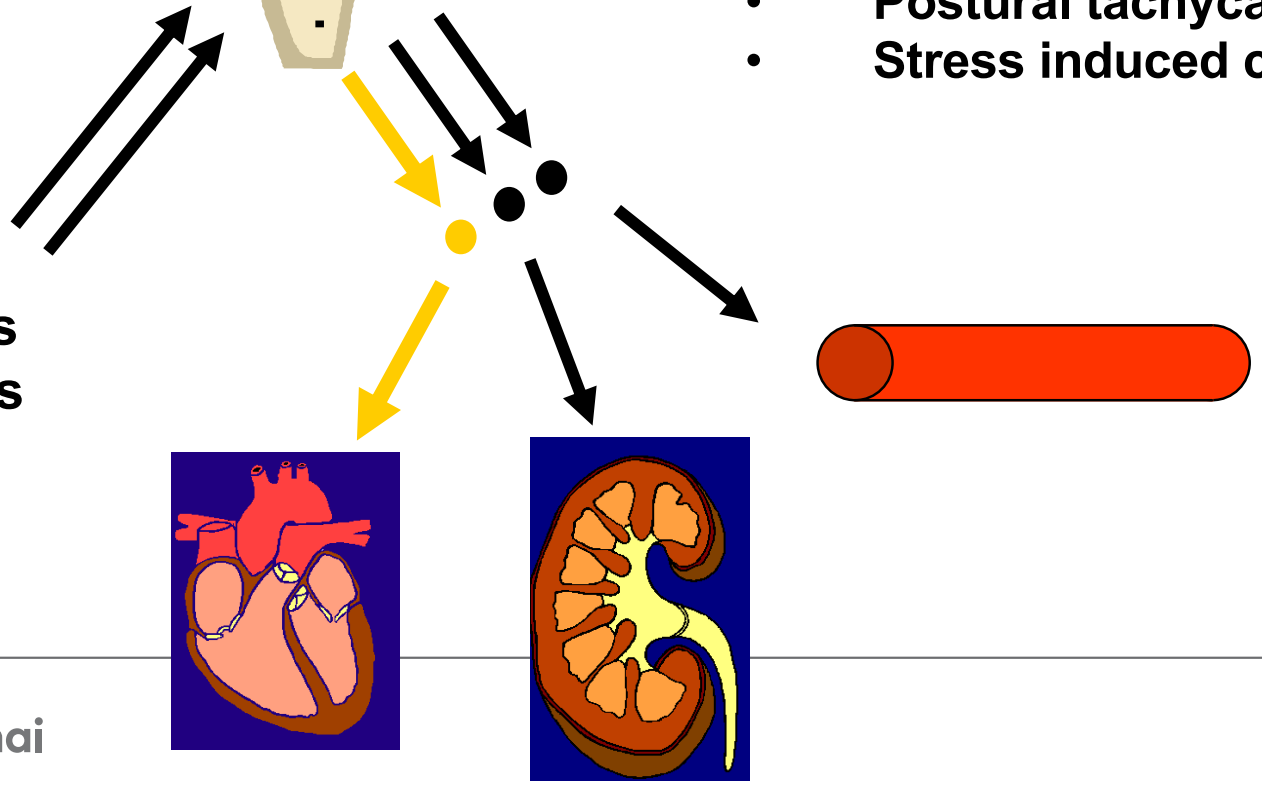
Sex and Sympathetic Autonomic Nervous System (SNS) activity

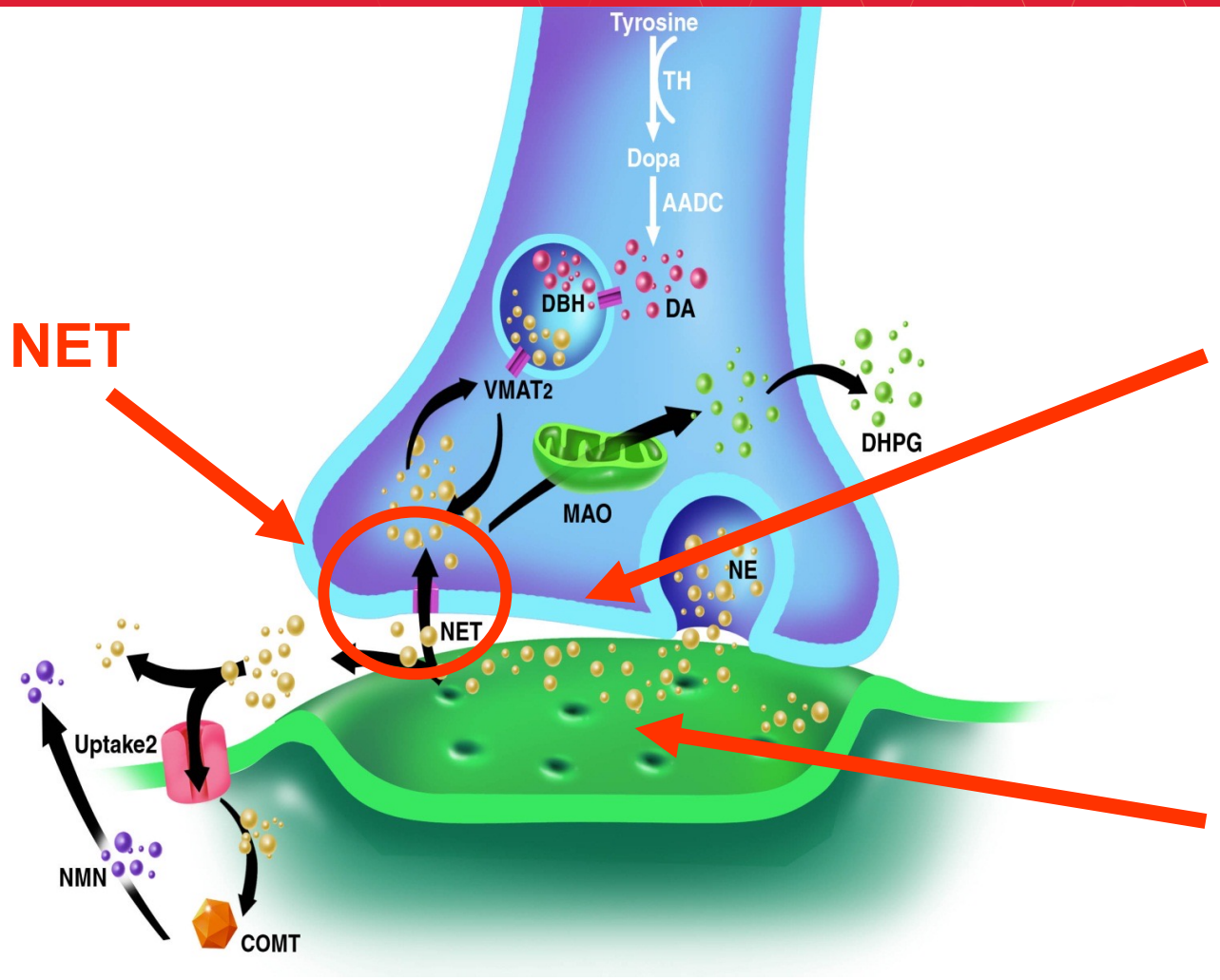




Baroreceptors
Chemoreceptors
Metaboreceptors

- **Microvascular coronary disease (MCD)**
- **Postural tachycardia syndrome (POTS)**
- **Stress induced cardiomyopathy (TAKOTSUBO)**

Adrenergic synapse
(J Jordan, Berlin Heart Institute)

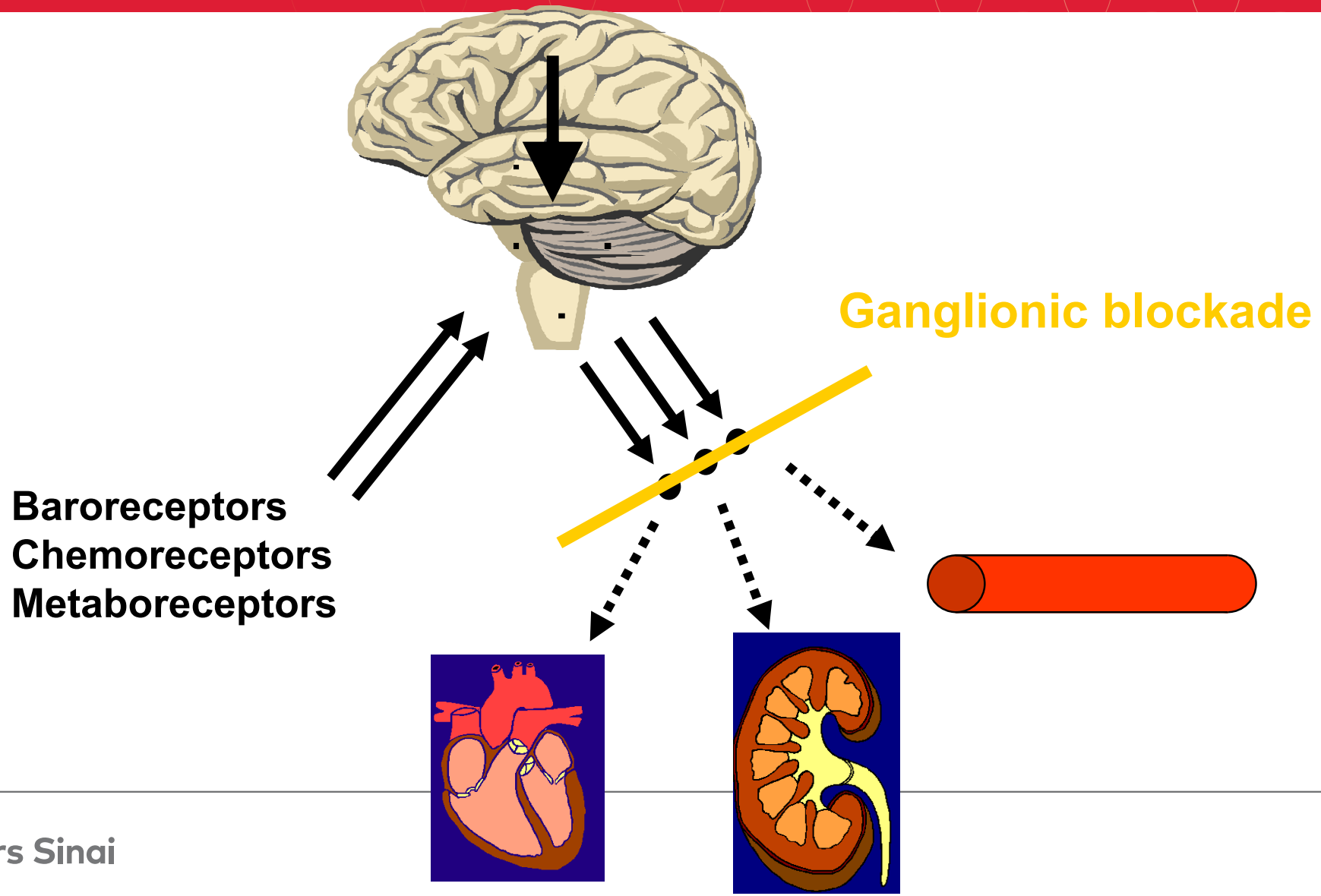


Presynaptic receptors (α_2, β_2)

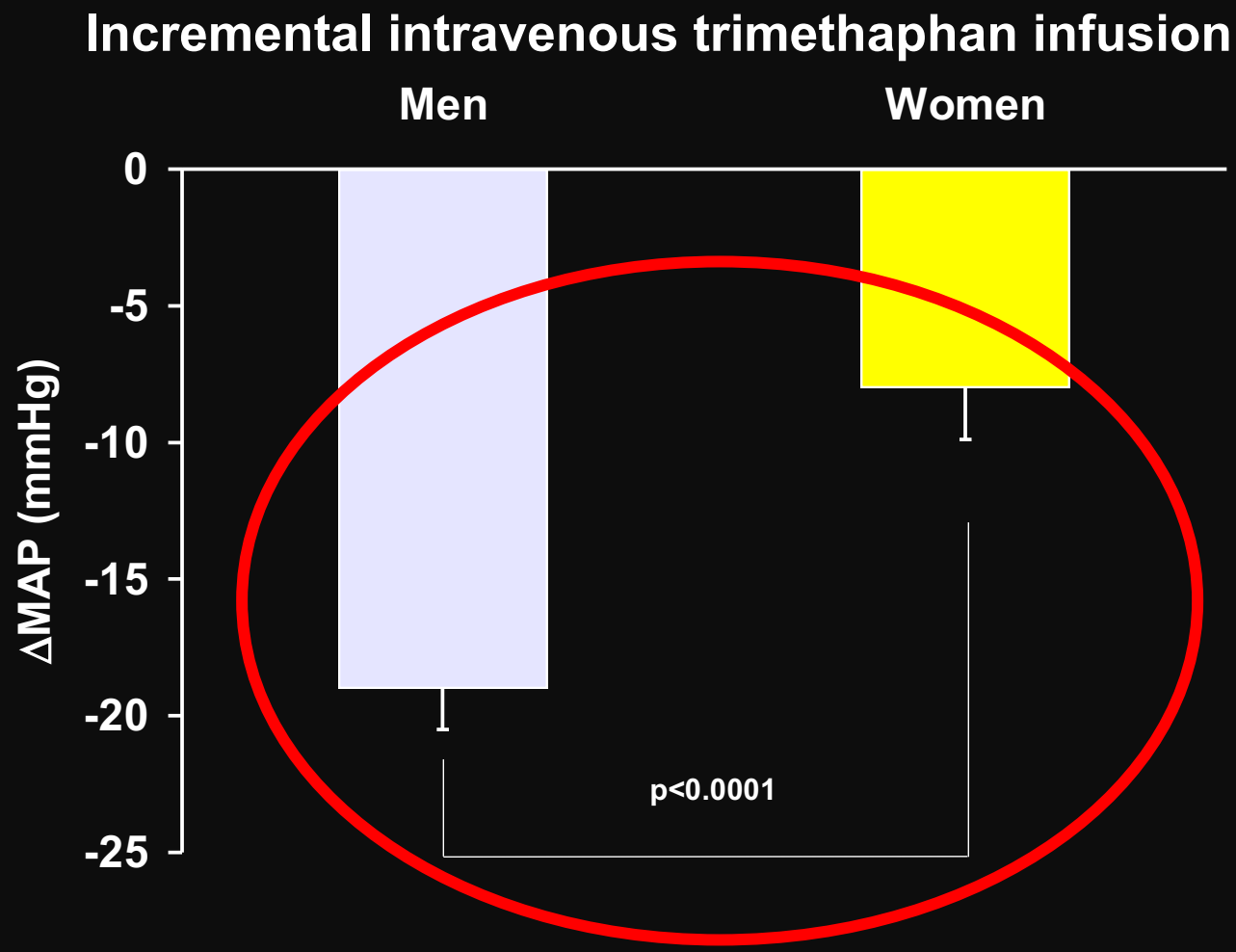
Norepinephrine Transporter (NET)

Postsynaptic receptors ($\alpha_{1/2}$, $\beta_{1/2}$)

Sex Differences in Sympathetic Activity – Healthy Subjects



Sympathetic support of blood pressure: women are less SNS dependent



Christou et al. Circulation 2005

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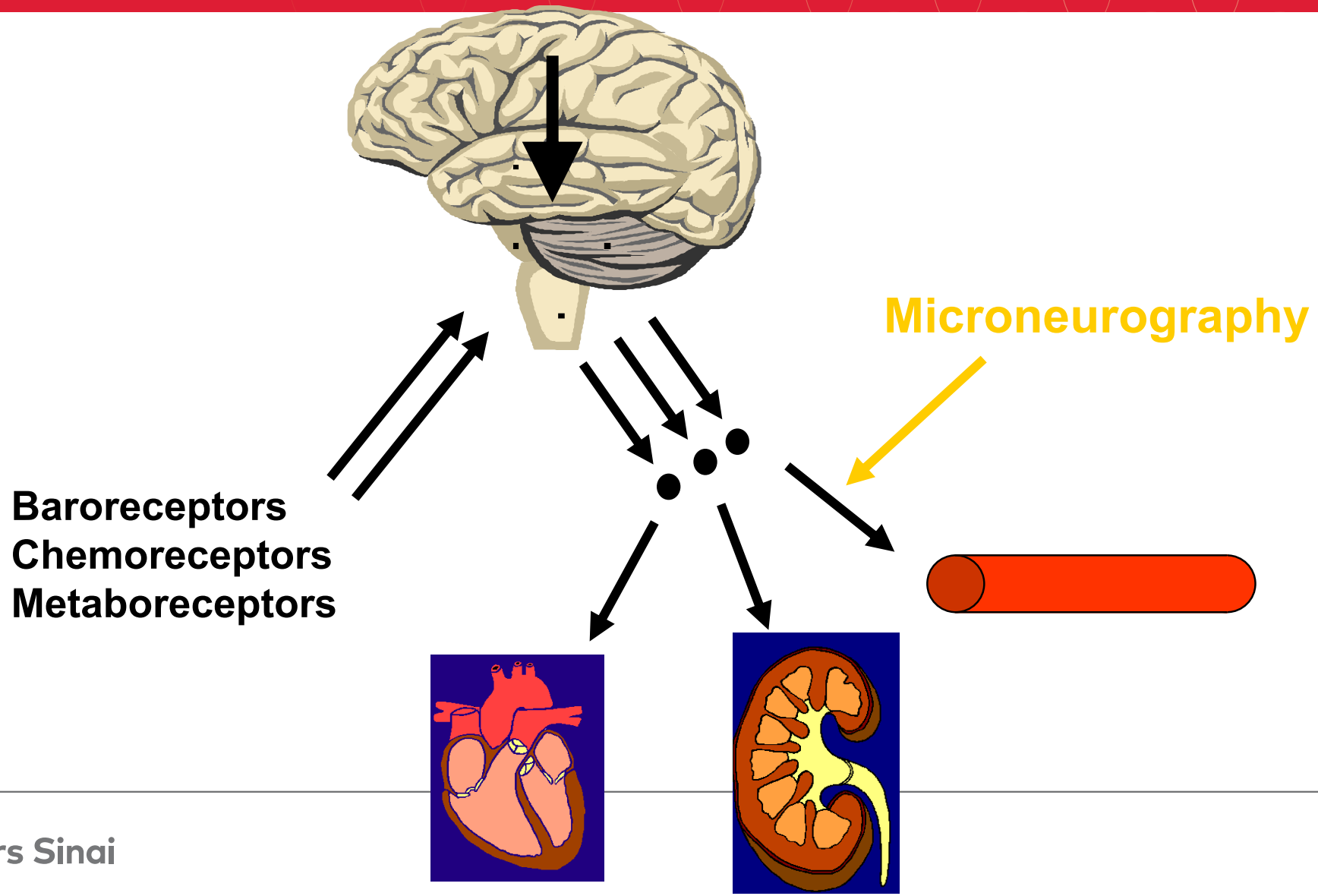
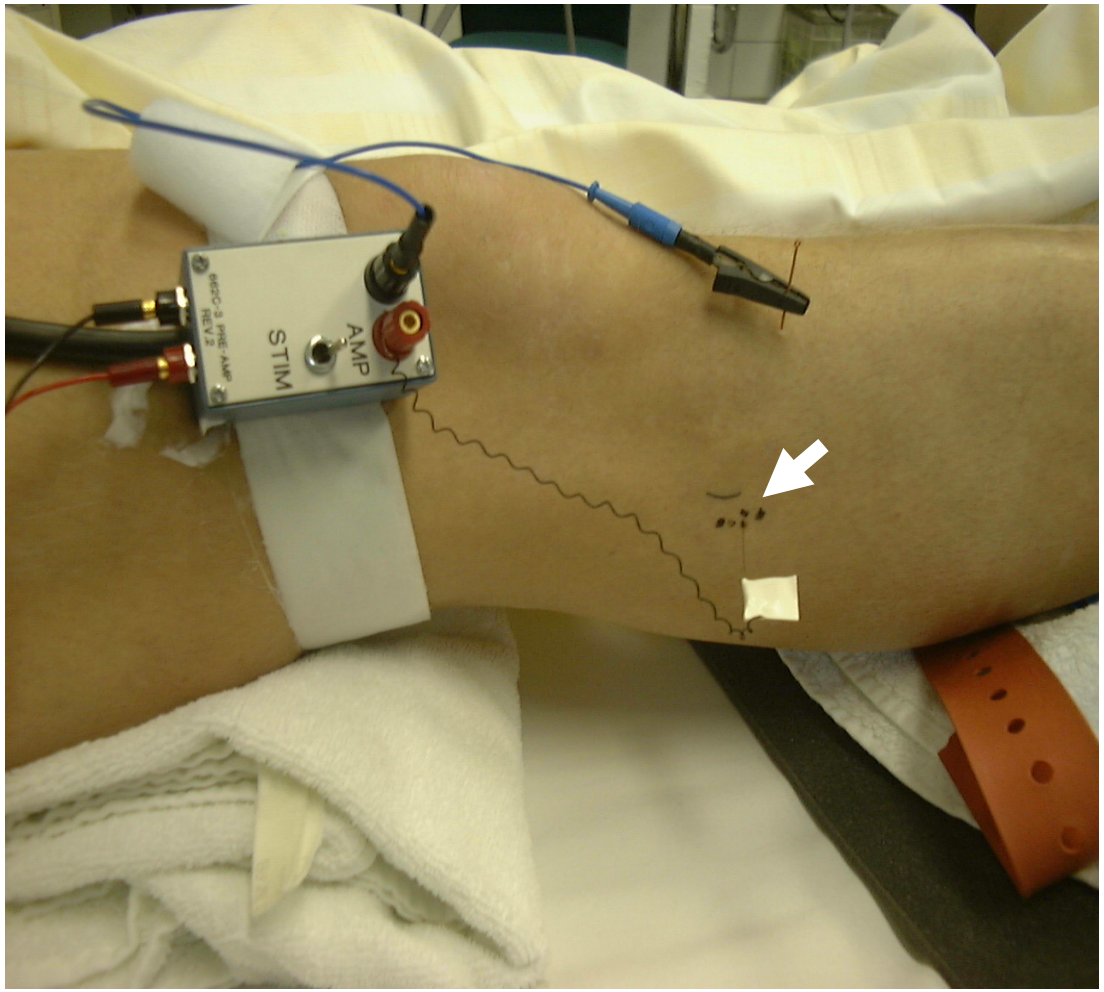
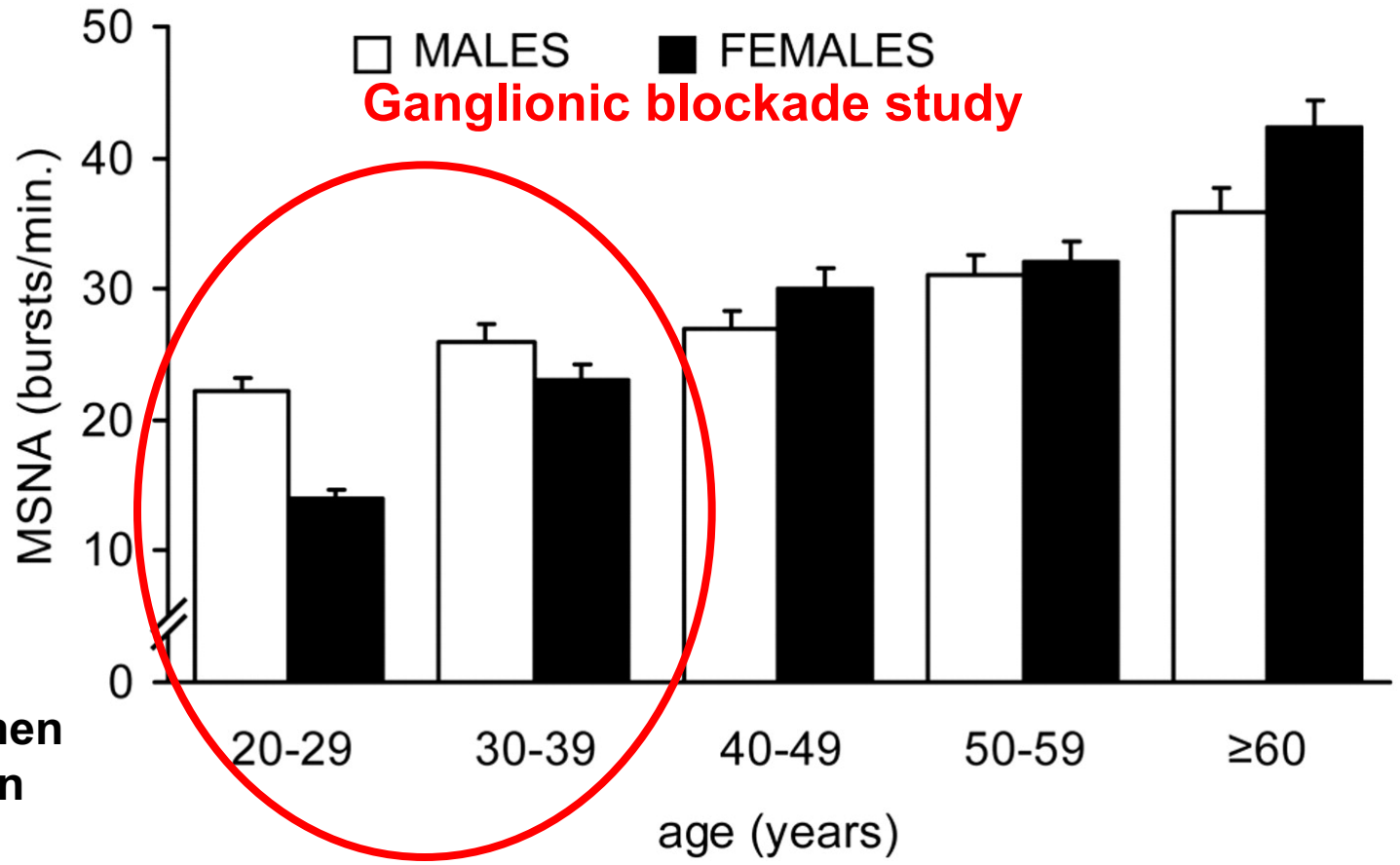
Brain or peripheral mechanisms?



Microneurography



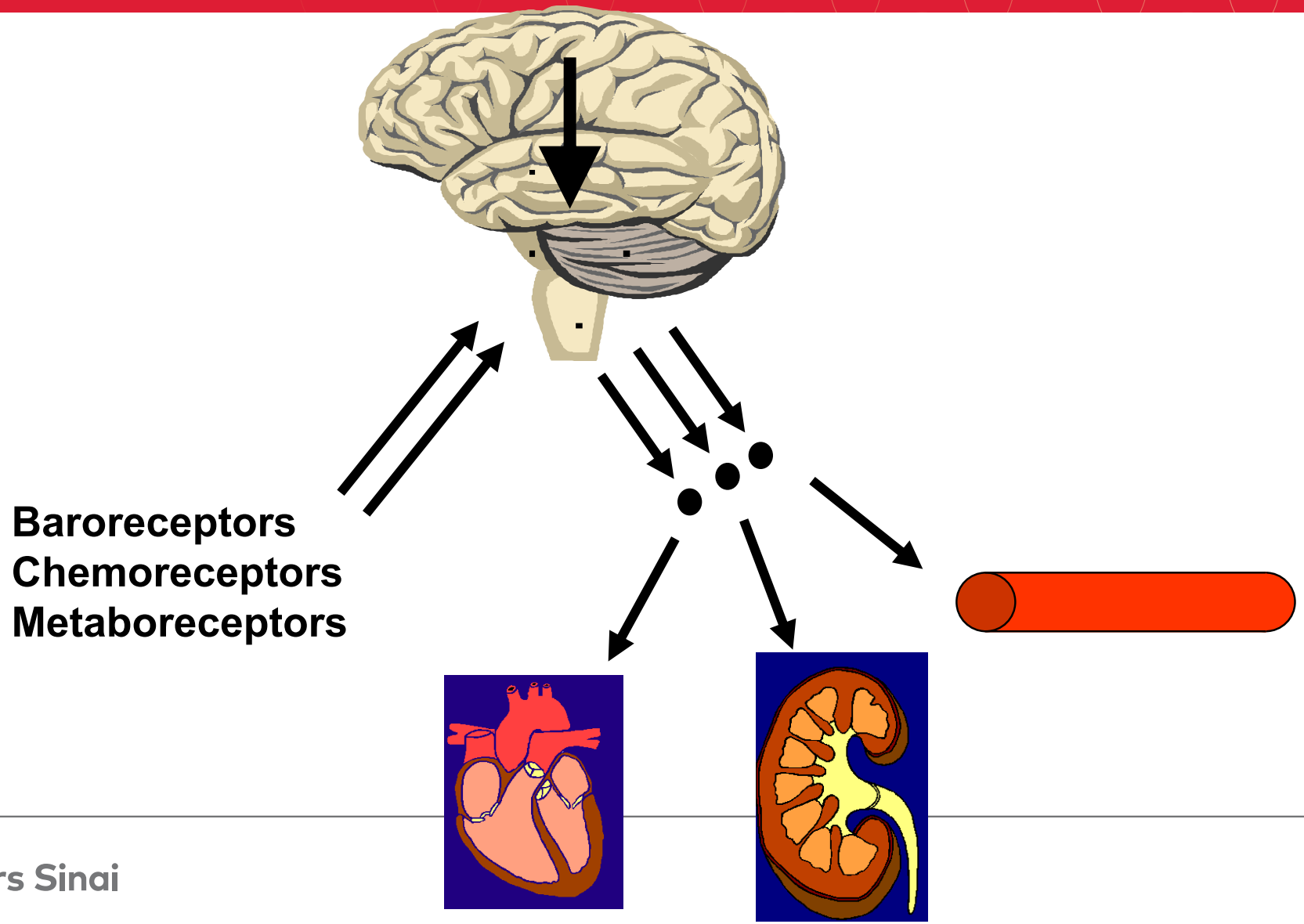
Sex, age, and MSNA: young women are also less SNS dependent peripherally



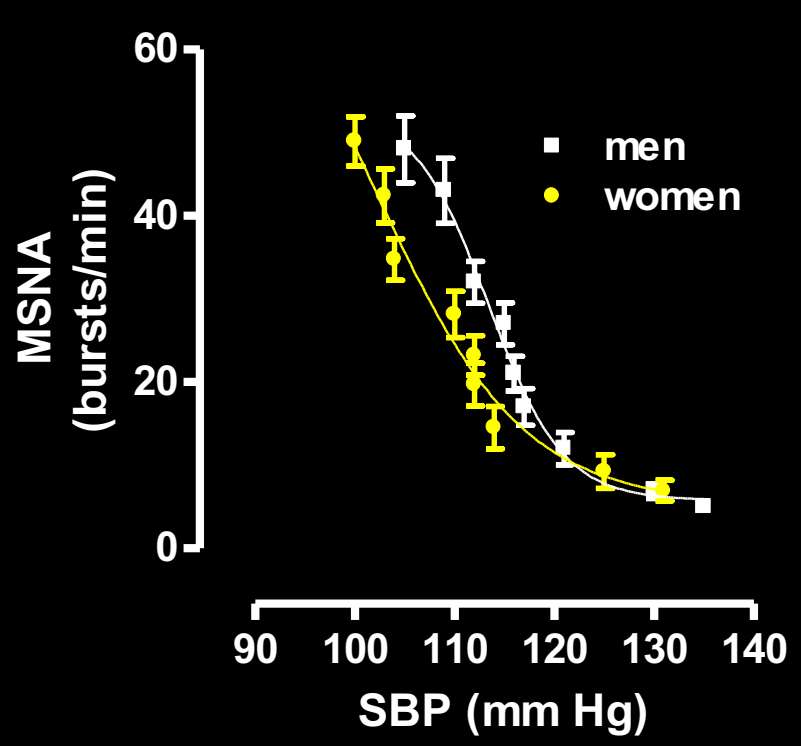
96 women
120 men

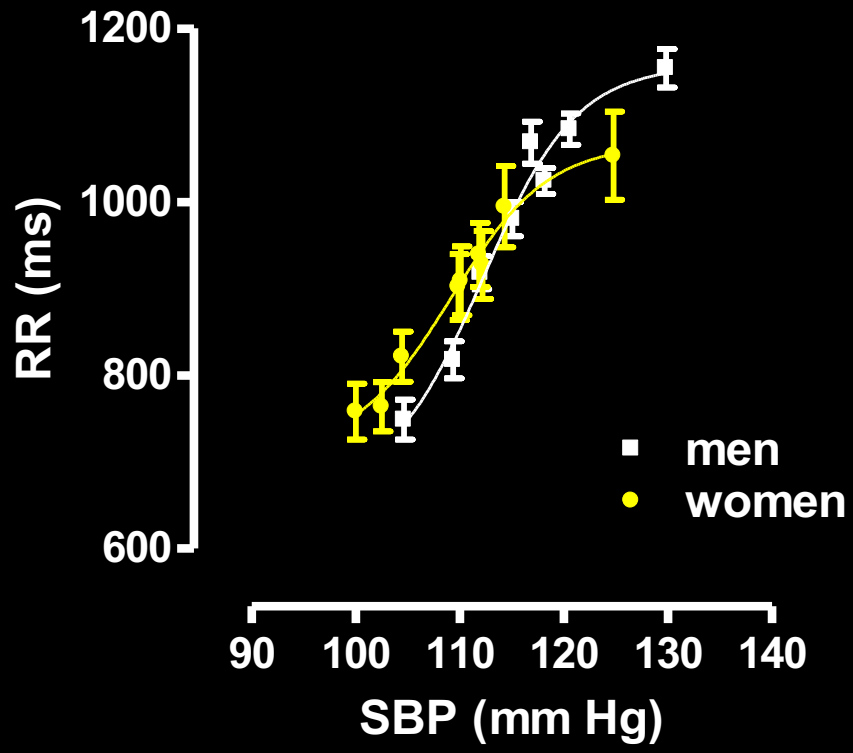
Narkiewizc K et al. Hypertension 2005

Does sex influence the distribution of sympathetic activity between organs?

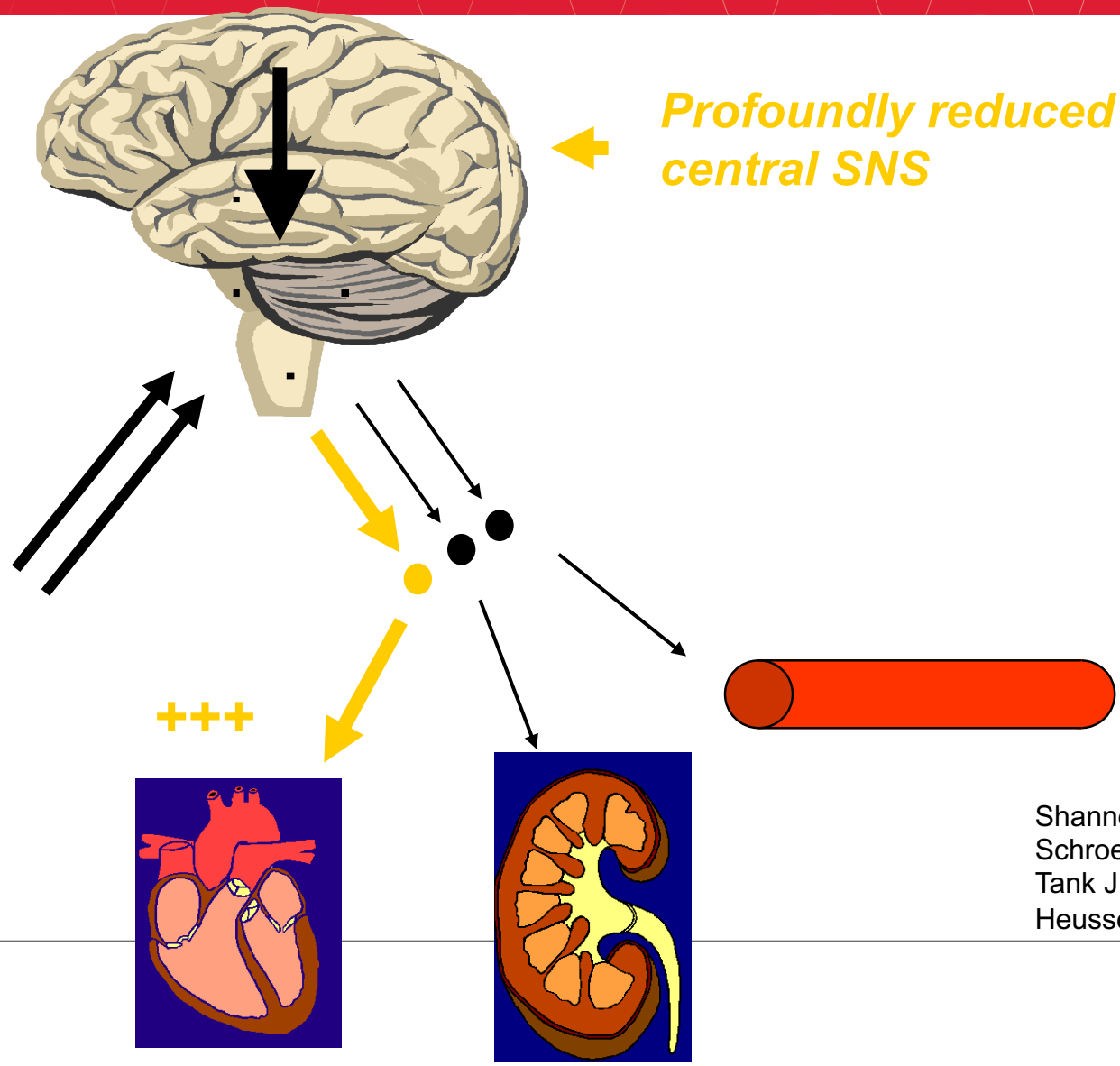


Sex and Cardiac Baroreflex Regulation



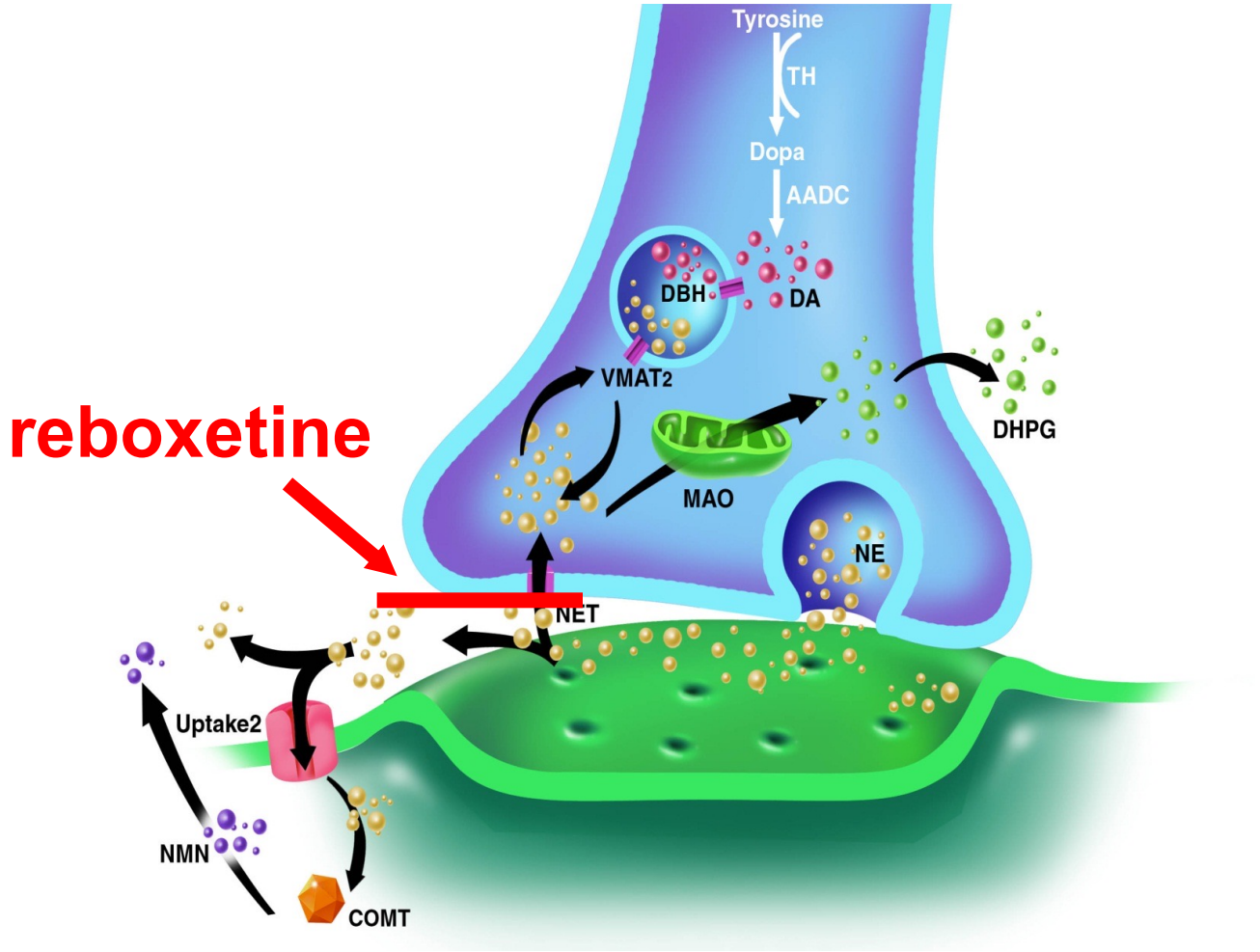


Norepinephrine Transporter (NET) Dysfunction



Shannon J. NEJMED 2000
Schroeder C. Circulation 2002
Tank J. Circulation 2003
Heusser K. CPT 2006

Pharmacological Model



Less Cardiac NET Activity in Women?

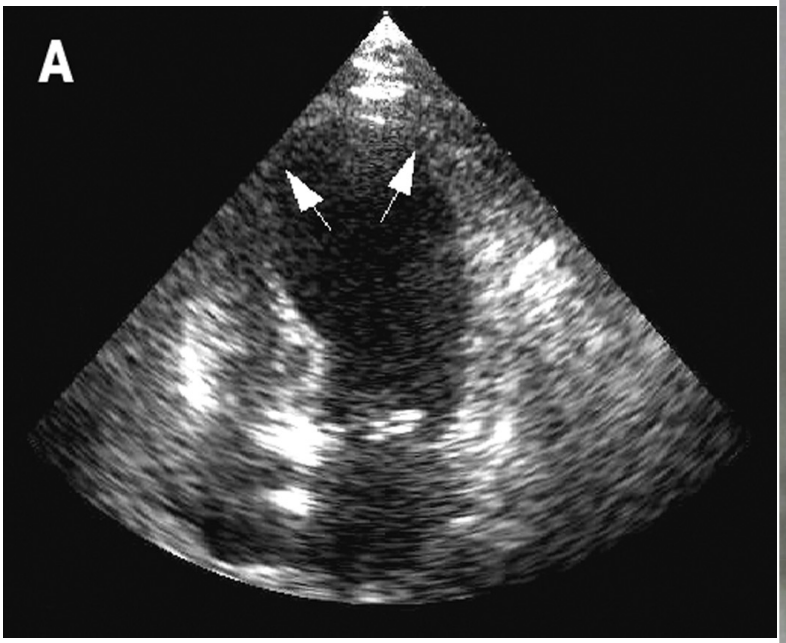
Men become hypertensive: women do not

Conclusions – Sex Differences in Sympathetic Nervous System

Women:

- Overall sympathetic activity ↓↔ compared to men
- Redistribution of sympathetic traffic to heart
- Norepinephrine transporter may be involved
- Role in:
  - coronary microvascular dysfunction (CMD) – paced breathing intervention?
  - POTS - female space-suits, alpha-beta blockers?
  - Takotsubo Syndrome (TTS) – NET intervention?

Why is Takotsubo Cardiomyopathy More Prevalent in Women?



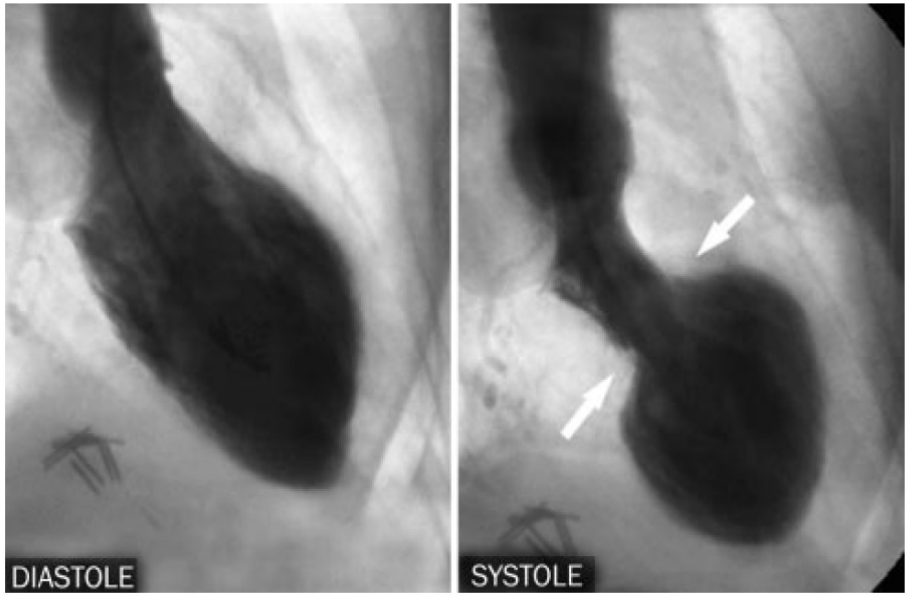


Fig. 2. Takotsubo. (Printed with permission from the Morikami Museum and Japanese Gardens, Delray Beach, Florida).

Pilgrim TM. IJC 2008; 124: 283

TTS Prevalence, Acute Mortality, Recurrence and Morbidity

- **Prevalence:** 1.7-2.2% of patients who had suspected acute coronary syndrome were subsequently diagnosed with Takotsubo
- **Acute Mortality**: 1-5% comparable to AMI
- **Recurrence**: 5-22% at 5 years
- **Morbidity:** 50% long-term morbidity of persistent cardiac symptoms and subclinical cardiac dysfunction

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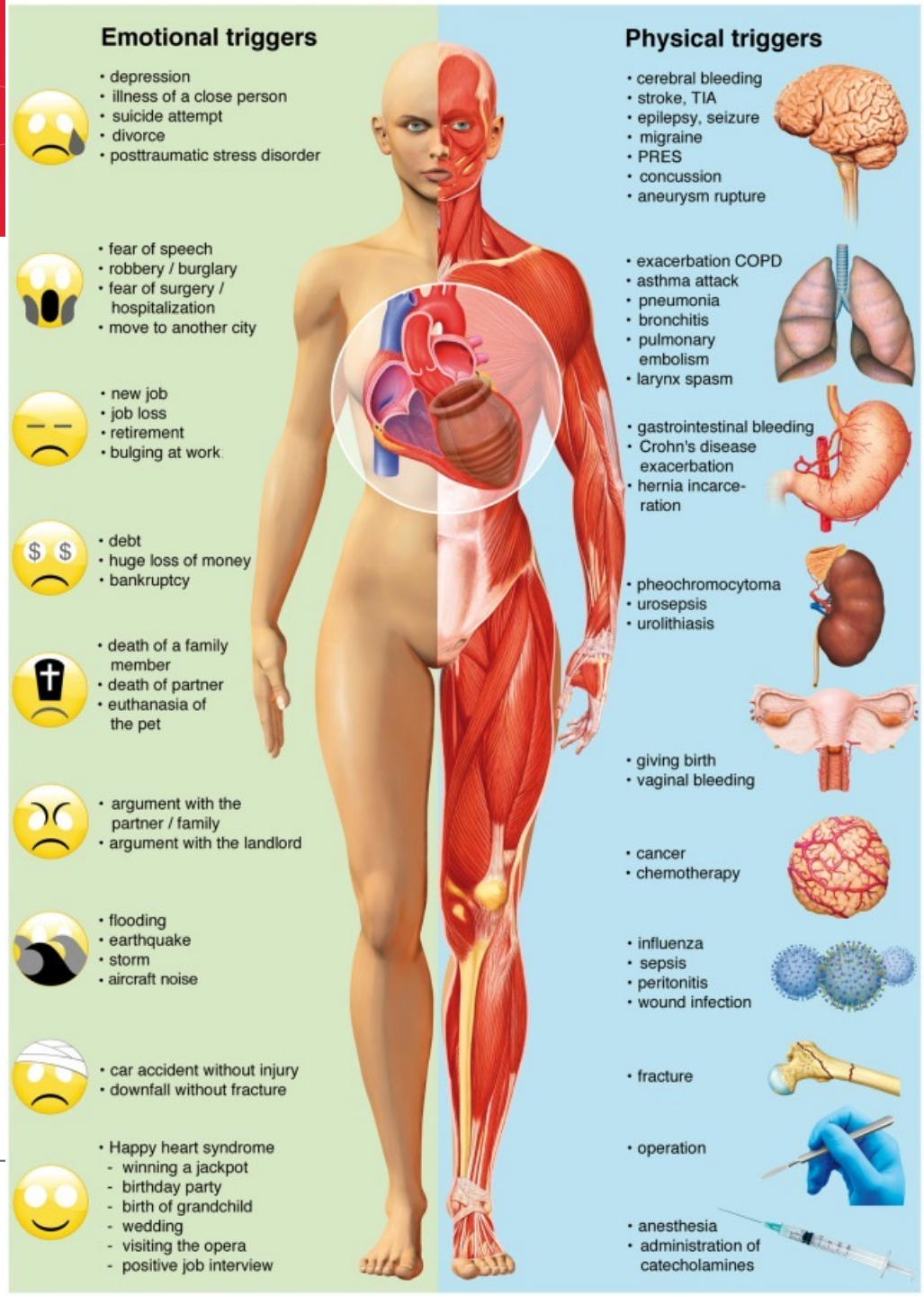
J Med Life. 2020;13(1):3-7. doi:10.25122/jml-2018-0067; *J Am Coll Cardiol*. 2016;67(16):1937-1940. doi:10.1016/j.jacc.2016.03.006; *Heart Br Card Soc*. 2018;104(2):96-102. doi:10.1136/heartjnl-2017-311579; . Eur J Heart Fail. 2016;18(1):8-27. doi:10.1002/ejhf.424; Journal of the American Heart Association, 2021; DOI: 10.1161/JAHA.120.019583

TTS Presentation and Triggers

- Post Menopausal Woman
- Chest Pain, SOB, Nausea, Weakness; mimics acute MI
- EKG Changes Vary
- Troponin Positive
- Echo with LV Dysfunction/Wall Motion Abnormalities, usually in the distal LV
- Angiogram – No Obstructive Coronary Atherosclerosis
- LV Dysfunction reverses over days to months
- Emotional triggers more common in women; physical triggers in men more common



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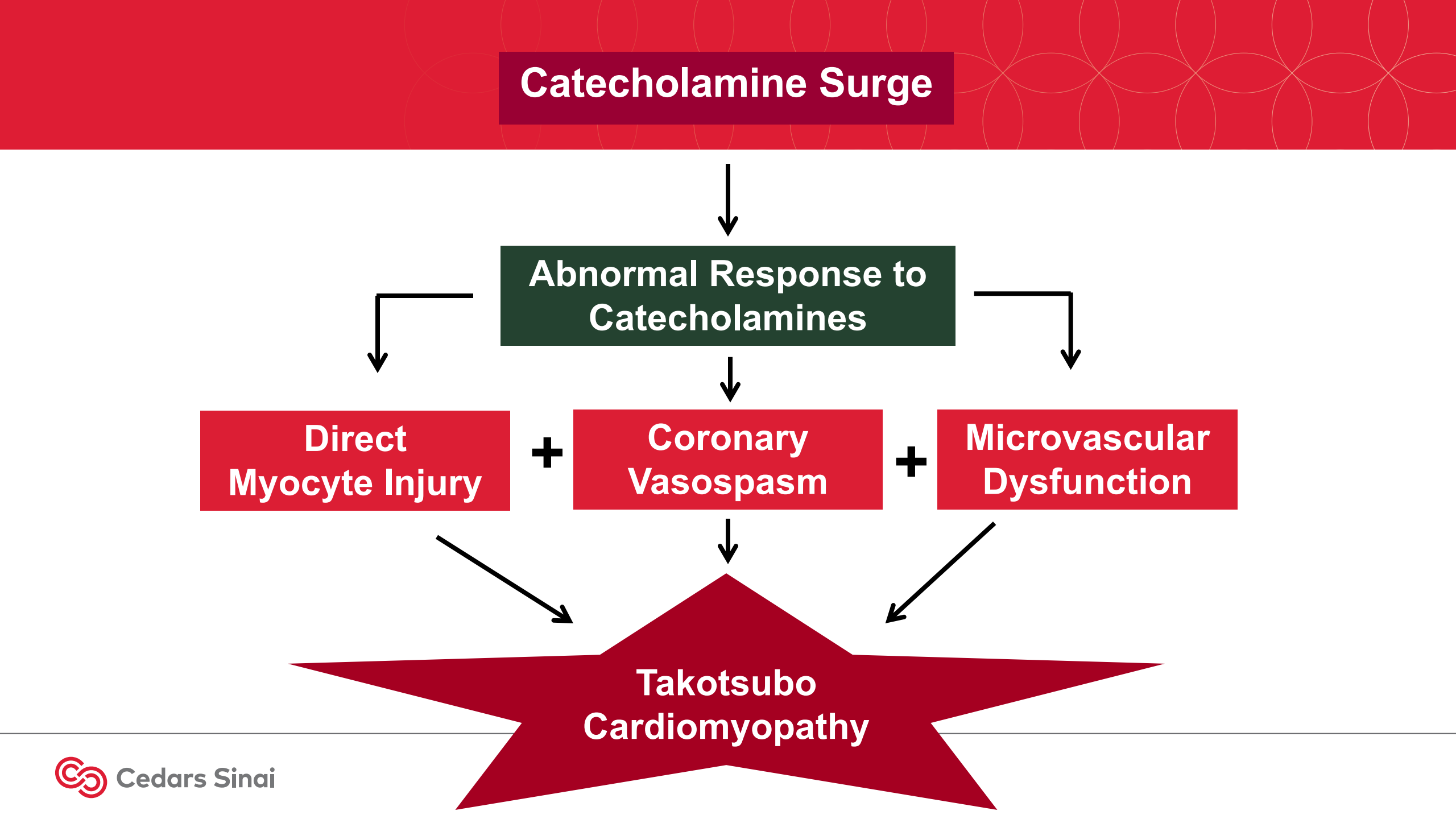

Catecholamine Surge
Abnormal Response to Catecholamines
Direct Myocyte Injury
+
Coronary Vasospasm
+
Microvascular Dysfunction
Takotsubo Cardiomyopathy

Why is it More Prevalent in Women? Two Speculations: (Totally Opposite !!)

- **Men are biologically protected against stress**
  - Sympathetic adrenergic innervation is different
  - Sympathetic adrenergic receptor density on the cardiomyocyte is higher in men compared to women
  - Autonomic stress response system is different

- **Men are biologically less resistant against stress**
  - Males die from LV dysfunction in the acute phase (sudden death is more frequent in men)
  - Cardiomyocyte repair after damage is better in women

Stollberger C at al. Int J Cardiol 2011;147:175

Takotsubo Knowledge Gaps

- **Occurrence:** it is unknown why women are predominantly impacted and what sex and gender variables may contribute to TTS.
- **Recurrence:** large TTS studies of acute episodes using electronic medical records have failed to identify recurrence and morbidity predictors beyond age, low body mass index (BMI) and depression
- **Subclinical CVD**: poorly characterized in small populations not adequate for understanding and development of treatment targets
- **Tools**: We have demonstrated that remote patient monitoring (RPM) using biosensors, biomarkers and patient reported outcomes (PROs) can fill knowledge gaps outside the hospital walls, capturing real life settings and is ideal for studying low prevalence, episodic, and important cardiovascular disease (CVD)
- **Strategy:** We have demonstrated that sex/gender investigation within women (rather than comparisons to men) can provide understanding leading to improved care for women

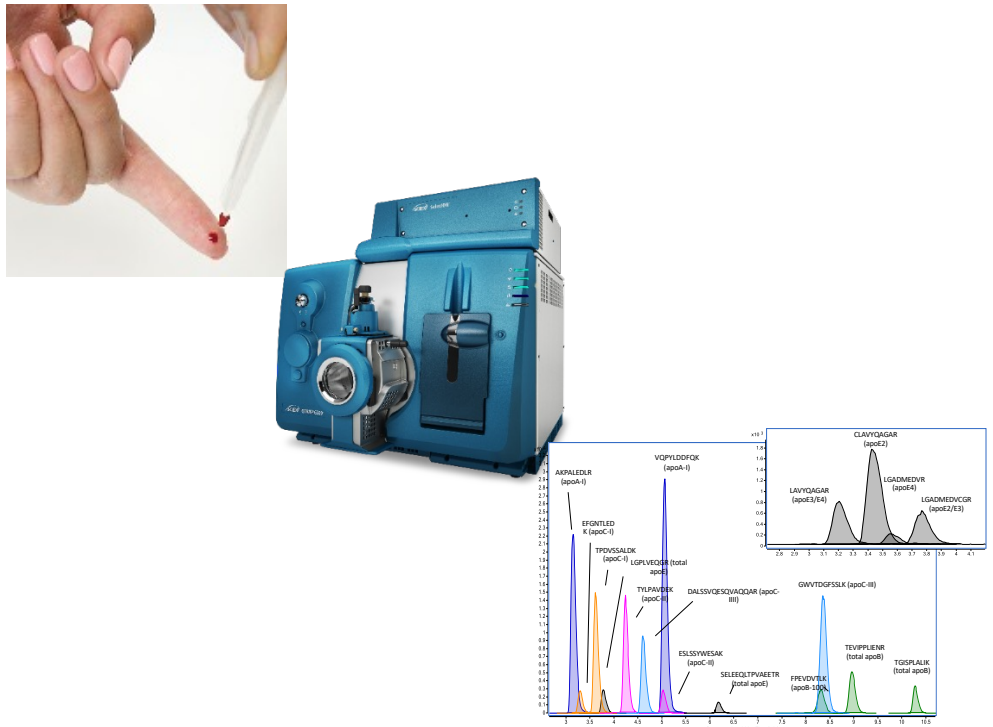
Sex and gender-specific Takotsubo Syndrome phenotyping to identify contributors to recurrence and long-term morbidity to formulate treatment strategies (Bairey Merz PI, submitted)

Smidt Heart Institute Takotsubo Registry

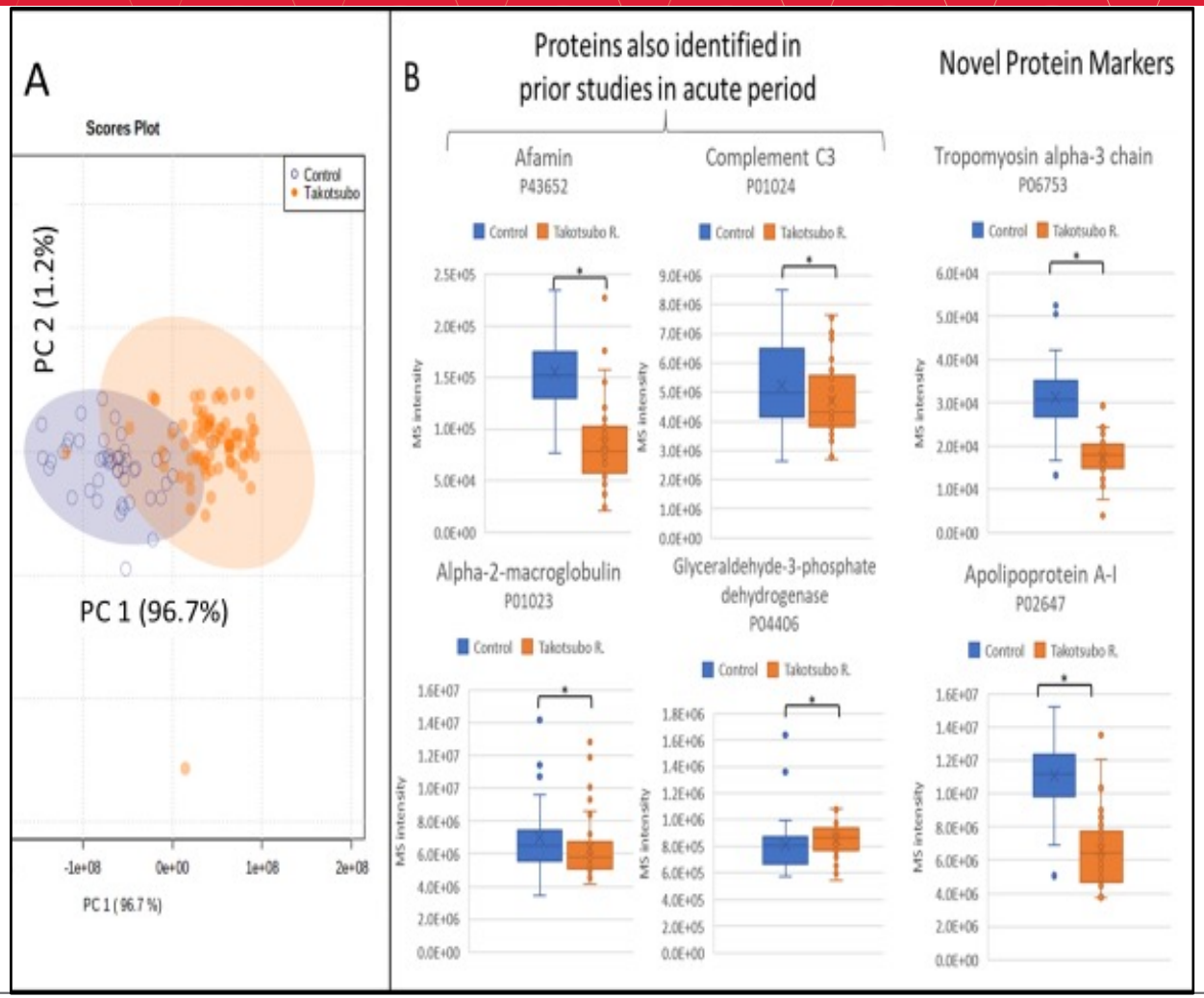
We have developed a TTS Registry of self-reported volunteer survivors (n=150) using a SHI pilot grant:

- Mean age 61.3 ± 10.0 yrs, 99% female, 68% with identifiable emotional and/or physical triggers.
- 85% are physician-adjudicated/confirmed TTS & 15% non-TTS (disease controls)
- Notable TTS Registry characteristics include:
  - History of childhood trauma/abuse (~50%)
  - Posttraumatic stress disorder (PTSD) symptoms (~60%)
  - Low rates of menopausal hormone therapy/high vasomotor symptoms
  - Recurrent TTS (24%, median 3.3 yrs after index event)
  - Concordant repeat emotional triggers.
- Using remote blood sampling proteomic analysis of TTS survivors after recovery, we have identified potential residual cardiomyopathy

Separation of circulating protein expression in TTS vs controls (Panel A) and identification of novel candidate markers (Panel B)



Identification of Novel Protein Markers



Marano and Washington, JACC (submitted)

The Dilemma of Takotsubo Cardiomyopathy: Why More Prevalent in Women?

- **Sex differences the sympathetic nervous system contribute to patterns of cardiovascular health and disease, including CMD, POTS, Takotsubo Syndrome (TTS)**
- **Pilot results in the SHI TTS Registry suggest sex and gender variables including hormones, SNA, microvascular dysfunction and behaviors can provide dense phenotyping**
- **Ongoing work evaluating SABV and GASV mechanisms of health and disease is directed at understanding TTS occurrence, recurrence and long-term morbidity in order to develop treatment targets**

Thanks to the Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars Sinai Medical Center

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Thank you for SHI pilot funding, website on-line programming, website and participant recruitment, volunteering and consenting, medical record retrieval, TTS adjudication, data management, Mitra tip mailing/receiving, freezer management, proteomic assays, proteomic analysis, investigator collaborations, abstract, poster, manuscript and application writing, budgeting and administrative submission.