



Neuropeptides in Autonomic Dysfunction and Syncope

David G Benditt MD

University of Minnesota, Minneapolis, USA

Pertinent Conflicts of Interest

None

Principal Neuropeptides

- **Brain-natriuretic peptide (BNP)**
- **Atrial natriuretic peptide (ANP)**
- **Vasoactive intestinal peptide (VIP)**
- **Vasopressin**
- **Adrenomedullin (ADM)**

CV and Renal Actions of Multiple Natriuretic Peptides

- **Natriuresis**
- **Diuresis**
- **Inhibit renin release**
 - ↓ **circulating angiotensin II**
 - ↓ **circulating aldosterone**
- **Systemic vasodilation**

BNP, ANP & ADM in Humans

- **Known vascular relaxation with diuretic properties.**
- **BNP is mainly of cardiac ventricular origin and ANP is mainly of atrial origin.**
- **Adrenomedullin (ADM) has been identified in:**
 - **adrenal medulla (thus the name)**
 - **cardiac tissues, lung, kidney and GI system**

Orthostatic Hypotension:

Definition

- **Sustained BP drop usually within 3-5 min standing or HUT to $\geq 60^\circ$**
 - **systolic BP fall ≥ 20 mmHg, or**
 - **diastolic BP fall ≥ 10 mmHg**
- **In hypertensive patients**
 - **systolic BP fall of ≥ 30 mmHg**

Causes of OH

- **Inadequate venous return**
 - Diminished cardiac output
 - Hypovolemia
 - Drugs (e.g., diuretics)

- **Other Possibilities?** **ular**

**Intrinsic
vasoactive / diuretic agents**

- Sinus Node Dysfunction
- Drugs (e.g., beta-blockers)

100 Referred OH Patients Co-Morbidities

		Percentage of patients		
Diagnosis		OH (N=100)	HTN (N=100)	P value
Neurologic disease				
	Multiple system atrophy	11	0	.001
	Parkinson disease	10	0	.001
	Cerebrovascular accident			
	Nonhemorrhagic	7	11	.05
	Hemorrhagic	2	0	.20
	Transient ischemic attack	6	1	.10
	Lewy body disease	2	0	.20
Cardiovascular disease				
	Preexisting hypertension	36	86	.001
	Hyperlipidemia	31	48	.02
	Cardiac arrhythmia	22	7	.005
	Left ventricular hypertrophy	20	36	.02
	Coronary artery disease	23	25	.75
Neoplasms				
	Prostate	11	3	.05
	Breast	4	22	.001
	Lung	2	0	.10
	Nasopharynx	4	2	.80
	Other	7	8	.80
Diabetes mellitus				
	Type 2	7	14	.20
	Type 1	4	0	.05
Carotid artery disease				
	Status after carotid			
	endarterectomy	5	1	.20
	Carotid artery stenosis	5	1	.20
Obstructive sleep apnea				
		0	1	.10
Peripheral vascular disease				
		5	1	.20

Neurogenic

Non-Neurogenic

Drugs

Peptides ?
(early studies)

UNKNOWN Approx 20%

*HTN = hypertension group; OH = orthostatic hypotension group.

100 Referred OH Patients Co-Morbidities

Diagnosis	Percentage of patients		P value
	OH (N=100)	HTN (N=100)	
Neurogenic			
Neurologic disease			
Multiple system atrophy	11	0	.001
Parkinson disease	10	0	.001
Cerebrovascular accident			
Nonhemorrhagic	7	11	.05
Hemorrhagic	2	0	.20
Transient ischemic attack	6	1	.10
Lewy body disease	2	0	.20
Non-Neurogenic			
Cardiovascular disease			
Preexisting hypertension	36	86	.001
Hyperlipidemia	31	48	.02
Cardiac arrhythmia	22	7	.005
Left ventricular hypertrophy	20	36	.02
Coronary artery disease	23	25	.75
Neoplasms			
Prostate	11	3	.05
Breast	4	22	.001
Lung	2	0	.10
Nasopharynx	4	2	.80
Other	7	8	.80
Diabetes mellitus			
Type 2	7	14	.20
Type 1	4	0	.05
Carotid artery disease			
Status after carotid endarterectomy	5	1	.20
Carotid artery stenosis	5	1	.20
Paraproteinemia			
Amyloidosis	2	0	.20
Multiple myeloma	2	0	.20
Obstructive sleep apnea	6	1	.10
Peripheral vascular disease	5	1	.20

Neurogenic

Non-Neurogenic

Drugs

Peptides ?
(early studies)

OH in Malignancy

- **First reports of potential role in Case reports in 1970's with Small Cell Ca**
- **Main neuropeptides of interest:**
 - **ANP**
 - **Vasopressin**

Table 4. ANP and AVP in Extensive Stage SCLC Patients

Patient no.	Sodium	ANP	AVP
27*	129‡	36.7	8.3‡
28	139	16	1.9
29	137	30	0.65
30*†	143	89‡	4.3
31	141	29	2.1
32	138	58	1.1
33	138	152‡	2.0
34*	128‡	88‡	1.0
35*	140	425‡	1.7
36	142	65	0.4
37*	137	65	1.7
38*†	140	82‡	12.0‡
39	141	115.5‡	0.4
40*†	140	159.0‡	0.47
41	138	59.3	1.4
42	139	57.0	1.4
43	141	46.0	ND
44	136	160‡	0.87
45	133	159‡	3.03
46	140	40.0	5.74‡
47	136	28	2.0
48	141	49	1.8
49	134	38	3.7
50	135	103‡	5.8
51	133	74‡	1.2
52	139	117‡	>100‡
53	140	143‡	1.3
54	140	113‡	1.8
55	142	7	1.5
56*	113‡	26	2.2
57	137	20	1.6
58*	129‡	30	1.2
59	138	25	3.5
60	139	26	1.9
61*†	129‡	43	1.5
62	139	42	2.1
63	139	23.8	4.08
64	136	49.9	0.54
65	139	141.8‡	0.23
66	137	64.4	0.71
67	130	29.4	0.53
68*	127‡	70.0	0.61
69*†	122‡	171.3‡	0.84

Secretion of Atrial Natriuretic Peptide and Vasopressin by Small Cell Lung Cancer

Barbara G. Campling, M.D.,*† Inder R. Sarda, Ph.D.,‡ Kathy A. Baer, B.Sc.,* Stephen C. Pang, Ph.D.,§ Heather M. Baker, B.A.,* Wycliffe S. Lofters, M.D.,† and T. Geoffrey Flynn, Ph.D.‡

Cancer 1995;75:2442-51.



Elev ANP + OH



Elev ANP alone

BNP in Unexplained OH

Krishnan et al, Univ Minnesota, Heart Rhythm 2015

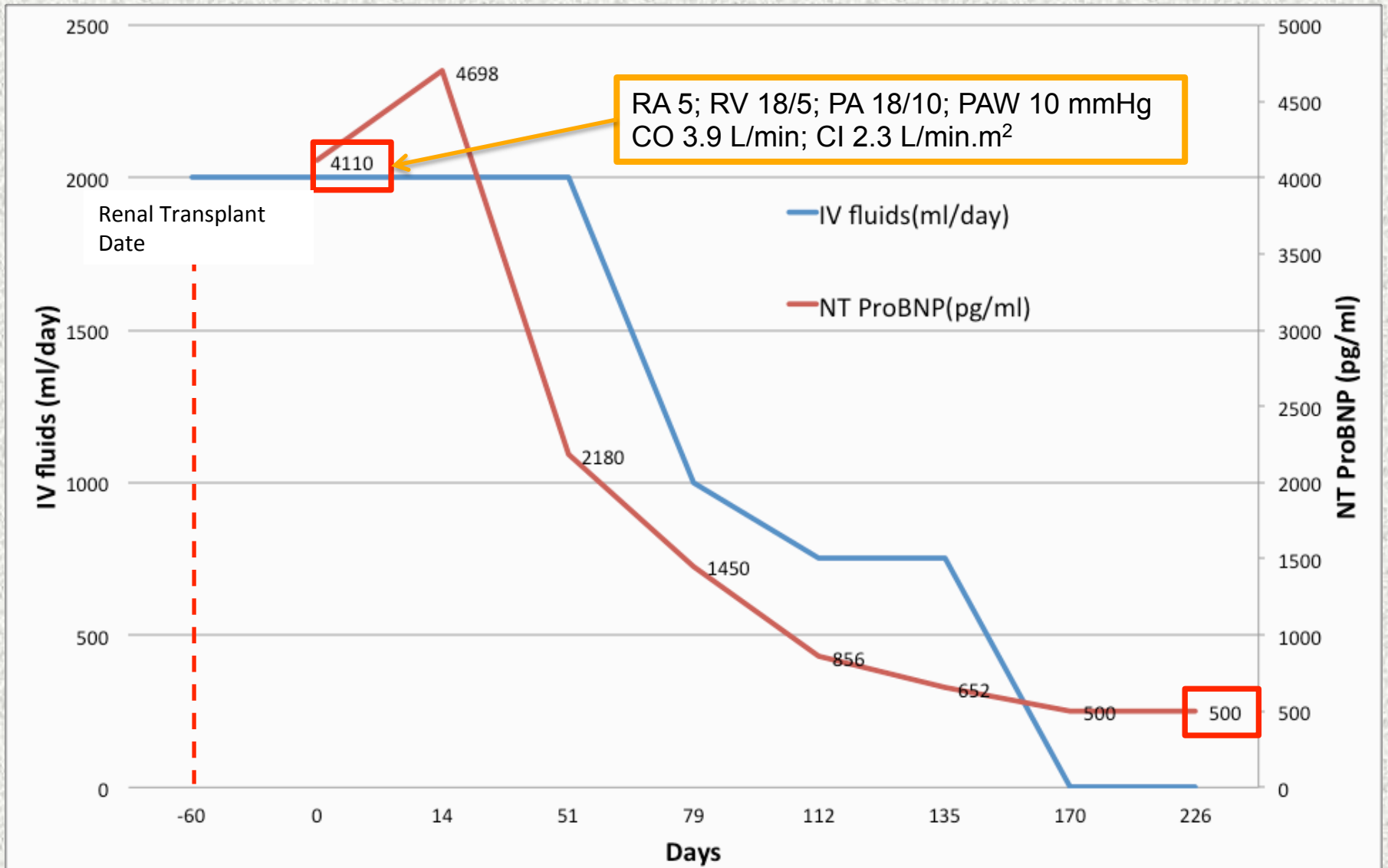
- **December 2012-December 2013**
- **84 patients referred to Syncope Unit for OH evaluation**
- **45 excluded due to determined cause**
- **39 had OH without evident cause**
 - **no patients with evident cardiac disease**
- **6 had markedly elevated BNP**
 - **all 6 euvolemic (RHC; 3 pts, Echo; 6 pts)**

Characteristic	Subjects Without elevated NT-proBNP (n=33)	Subjects With elevated NT-proBNP (n=6)
Age yrs	54 ± 20	61 ± 14
Male	10 (45%)	3 (50%)
Current medications		
Fludrocortisone	12 (55 %)	5 (83 %)
Midodrine	11 (50 %)	6 (100 %)
Physical examination findings		
Change(Δ) of heart rate(HR, bpm)	19 ± 10	17 ± 11
Change(Δ) of systolic blood pressure (SBP, mmHg)	29 ± 12	49 ± 7
Change(Δ) of diastolic blood pressure (DBP, mmHg)	17 ± 11	31 ± 14
Laboratory values		
CRP	4.5 ± 0.2	69 ± 0.2
ESR	16.7 ± 5.9	46 ± 35
NT-proBNP level, pg/ml (n = 30)	160 ± 124	6655 ± 4113
Creatinine level, mg/dl	0.93 ± 0.42	1.59 ± 1.31
eGFR level, ml/min/1.73 m ²	74 ± 19	51 ± 29

Patients with OH of Unknown Cause & High BNP

Age	HR and BP Supine	HR and BP Standing (3 minutes up)	NT-proBNP Baseline (Normal <300pg/ml)	NT-proBNP 12 months
49/F	HR 70 bpm BP 160/112 mmHg	HR 106 bpm BP 103/79 mmHg		
50/M	HR 75 bpm BP 153/76 mmHg	HR 84 bpm BP 71/42 mmHg		
74/F	HR 75 bpm BP 142/80 mmHg	HR 91 bpm BP 88/64 mmHg		
49/M	HR 87 bpm BP 160/96 mmHg	HR 105 bpm BP 80/53 mmHg		
64/M	HR 70 bpm BP 160/112 mmHg	HR 97 bpm BP 103/79 mmHg		
80/F	HR 88 bpm BP 140/85 mmHg	HR 93 bpm BP 89/57 mmHg		

Case: NT-proBNP & Fluid Requirement



Patient #1: 49/F

Summary: Neuropeptides in OH

- May contribute in rare cases
- Relation to solid organ transplant
 - particularly renal
- Further study needed

Neuropeptides in VVS

- **Vasopressin is increased, but function is unclear**
 - may degrade baroreceptor feedback
 - Vasodilation/vasoconstriction depends on vascular bed
 - Promotes water reabsorption in kidneys
- **Thromboxane and Prostacyclin are unchanged**
 - End products of arachidonic acid metabolism
 - Indirect vasodilator effects
- **Endothelin-1**
 - Increased in VVS but not Primary Autonom Failure
 - Poss compensatory response in VVS

Biochemical Changes Involved in the Mechanism of Vasovagal Syncope

Artemisia Theopistou, MD, Kostas Gatzoulis, MD, Emmanuel Economou, MSc, PhD, Skevos Sideris, MD, Kostas Hantzos, MD, Christodoulos Stefanadis, MD, and Pavlos Toutouzas, MD

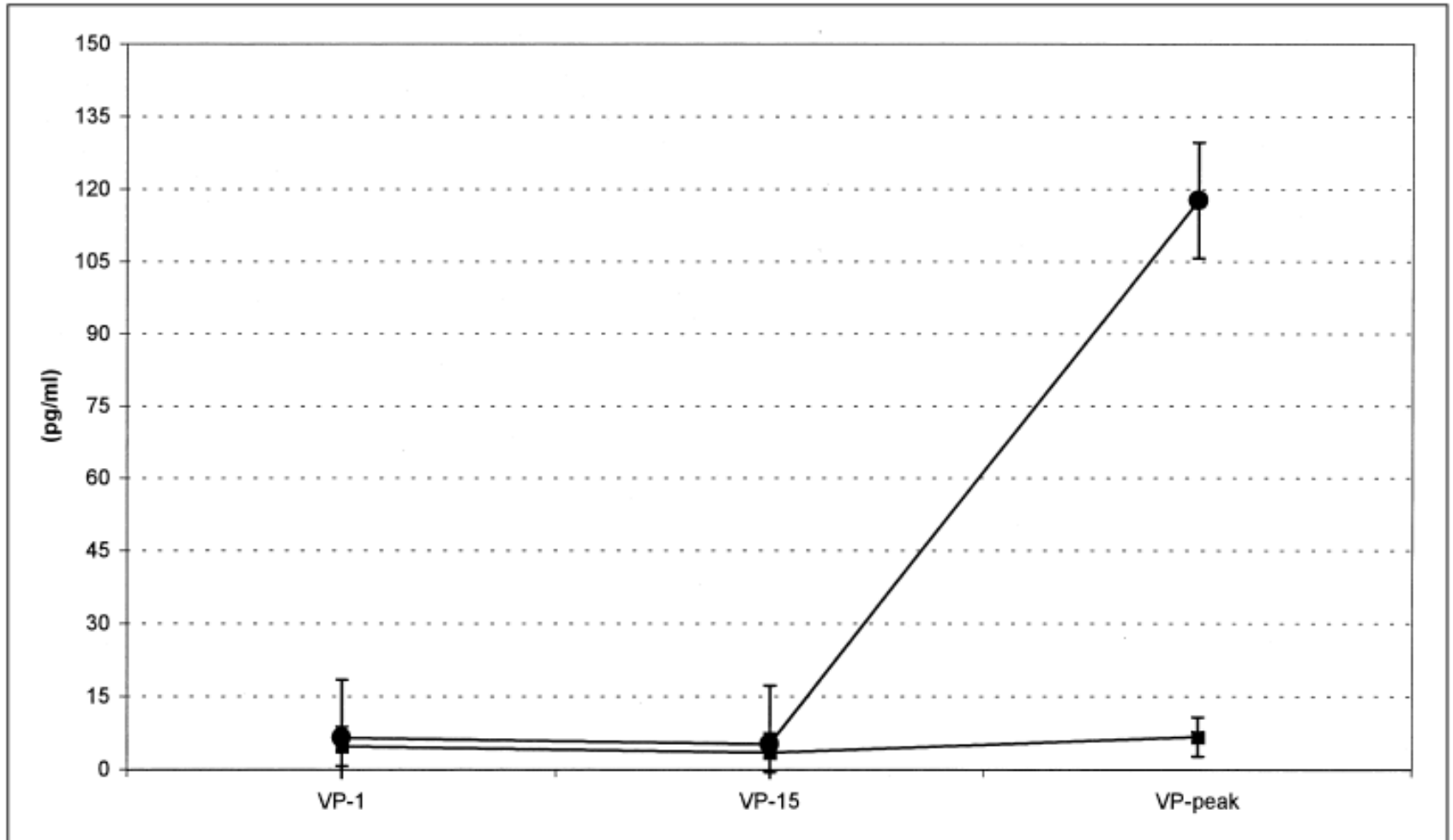


FIGURE 1. VP (pg/ml) plasma levels at baseline (VP-1), at 15 minutes (VP-15), and at peak (VP-peak) of tilt testing. Circles represent patients with positive results, and squares those with negative results.

Plasma endothelin during upright tilt: relevance for orthostatic hypotension?

HORACIO KAUFMANN EMILIO ORIBE JUAN A. OLIVER

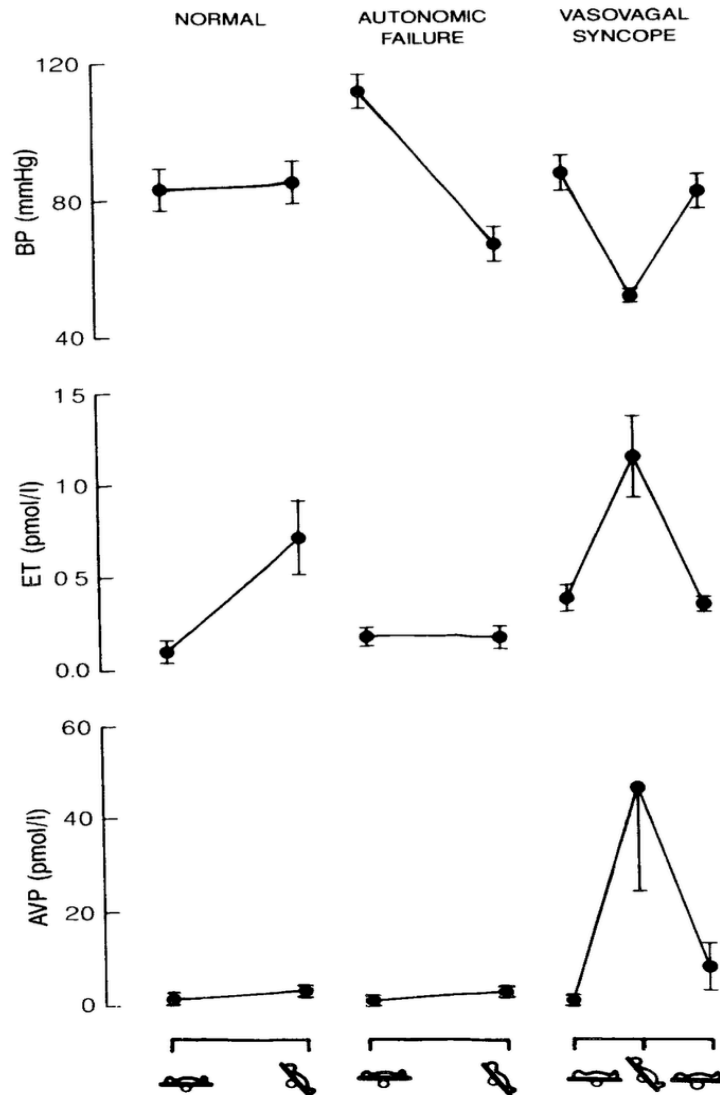


Fig 1—Mean arterial pressure (BP) and plasma concentrations of endothelin (ET) and vasopressin (AVP) in normal subjects and in patients with autonomic failure before and during upright tilt and in patients with vasovagal syncope before, during, and after upright tilt.

- Is ET rise compensatory?

Adrenomedullin—in Vasovagal Syncope

Gajek J; Zysko D; Halawa B.

Polski Merkurusz Lekarski. 17(99):267-70, 2004 Sep

- **Adrenomedullin (ADM) is a potent vasodilator**
- **Pts age 45.0+/-16.1 years with VVS reactions on HUT**
- **VVS in 6 pts in passive phase, 17 after NTG**
 - Passive: ADM 1.3+/-0.8 vs 2.7+/-1.3 pg/0.1 ml
 - NTG: ADM 3.2+/-3.4 vs 1.7+/-1,4 pg/0.1 ml

Novel cardiovascular biomarkers in unexplained syncopal attacks: the SYSTEMA cohort

■ A. Fedorowski^{1,2,3}, P. Burri¹, J. Struck⁴, S. Juul-Møller² & O. Melander¹

- 255 syncope patients
- 4 potential vasoactive substances measured
 - MR-proANP
 - MR-proADM
 - Vasopressin
 - Endothelin-1
- Diagnosis based on HUTT
- VVS was independently associated with:
 - Low MR-proANP
 - Low ET-1

Novel cardiovascular biomarkers in unexplained syncopal attacks: the SYSTEMA cohort

■ A. Fedorowski^{1,2,3}, P. Burri¹, J. Struck⁴, S. Juul-Møller² & O. Melander¹

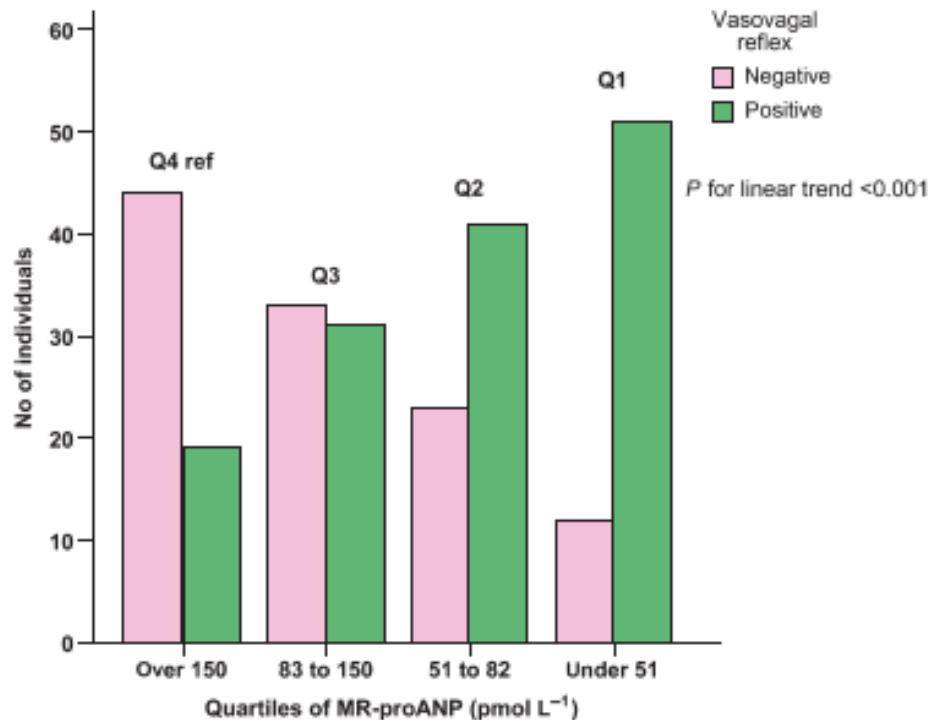


Fig. 2 Vasovagal reflex and MR-proANP levels. Distribution of vasovagal reflex (VVS, $n = 142$) across quartiles of resting MR-proANP among 255 patients with unexplained syncope. Odds ratio for VVS in quartile with lowest (Q1) vs. quartile with highest MR-proANP concentration (Q4 ref) was 5.57 (95% CI 1.86–16.74; $P = 0.002$). To determine

ANP low
in VVS

Novel cardiovascular biomarkers in unexplained syncopal attacks: the SYSTEMA cohort

■ A. Fedorowski^{1,2,3}, P. Burri¹, J. Struck⁴, S. Juul-Möller² & O. Melander¹

-pro-ET1
-baseline
low in VVS

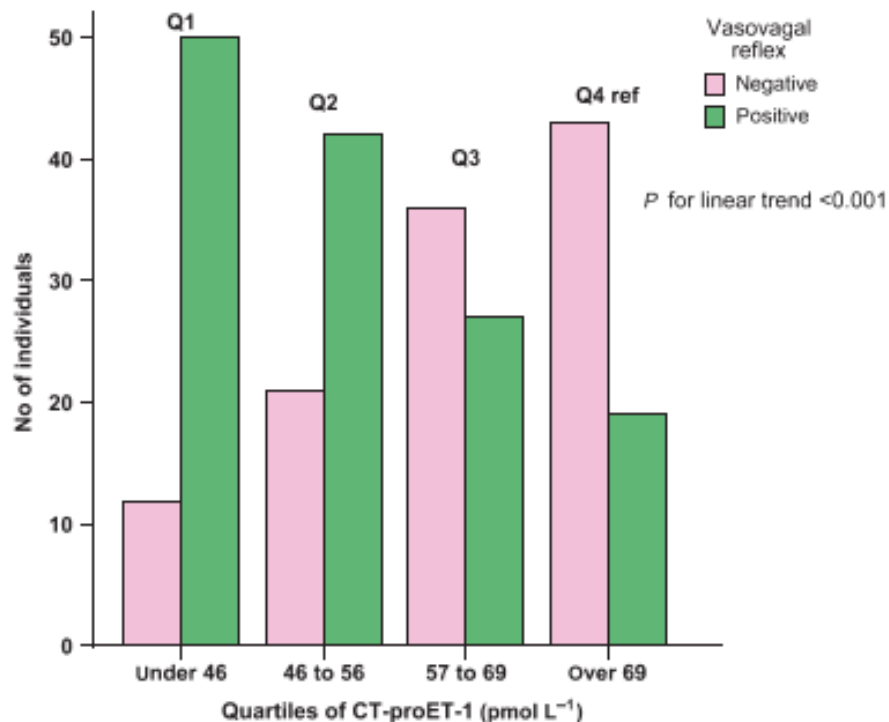


Fig. 3 Vasovagal reflex and CT-proET-1 levels. Distribution of vasovagal reflex (VVS, $n = 142$) across quartiles of resting CT-proET-1 among 255 patients with unexplained syncope. Odds ratio for VVS in quartile with lowest (Q1) versus quartile with highest CT-proET-1 concentration (Q4 ref) was 7.17 (95% CI 2.43–21.13; $P < 0.001$). Odds ratio

Conclusions

- **Many neuropeptides exhibit vasorelaxant and diuretic properties**
 - diagnostic utility debated
- **OH has multiple potential causes; 20% are unknown**
 - intrinsic vasoactive agents (e.g., BNP) may play a role in an as yet ill-defined subset
 - unexpected increase BNP was found in 15% of unknown cases
- **Neuropeptide Role in VVS uncertain**
 - physiology of low MR-ANP and Endothelin-1 remains to be better understood
 - change from baseline may be key

Thank You

Diurnal BP / HR in OH Patients: Nocturnal Hypertension, Inappropriate HR Variation

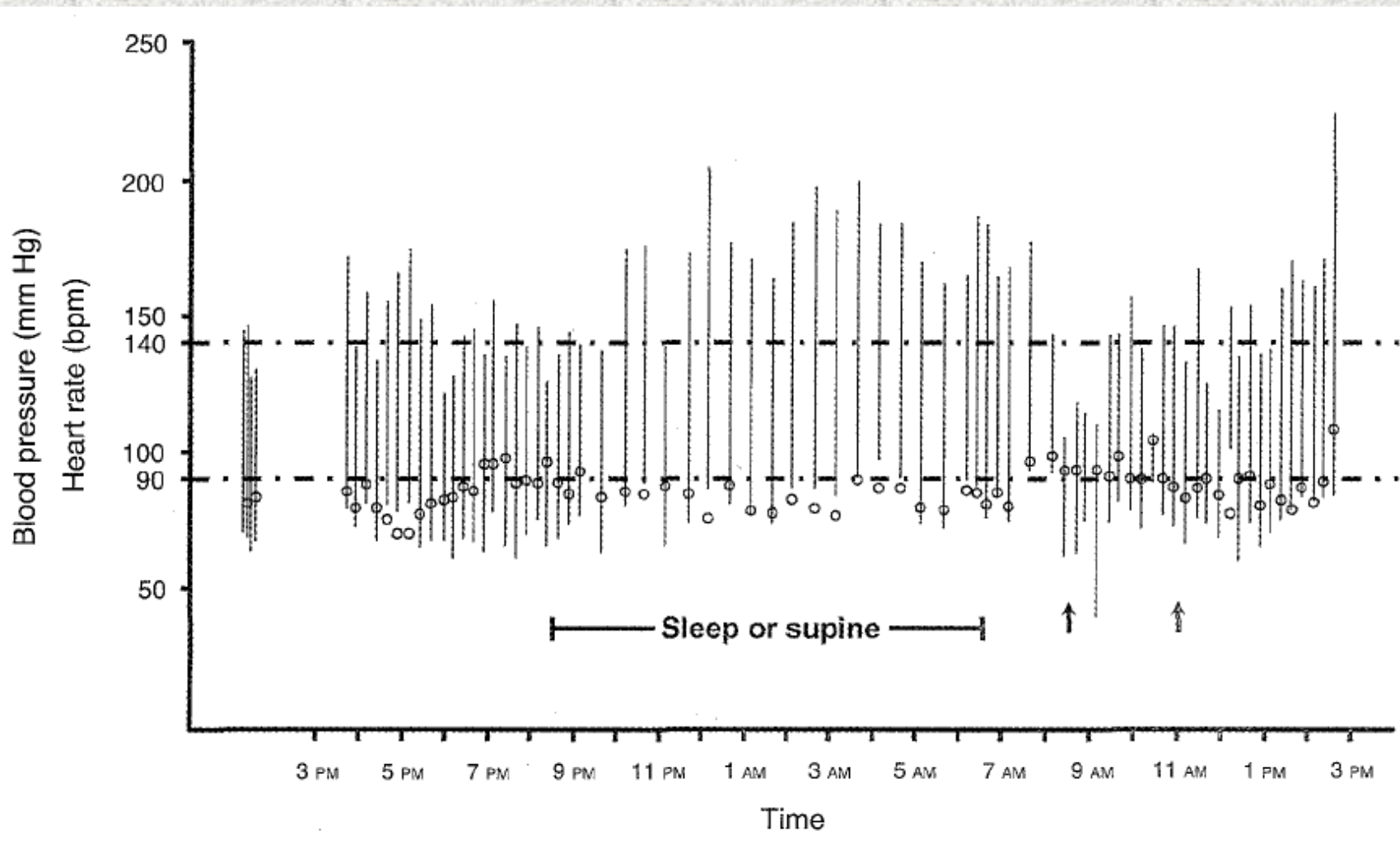


TABLE 4. Final Diagnosis or Condition Associated With Orthostatic Hypotension

Diagnosis or condition	Percentage of patients (N= 100)
Neurologic	
Multiple system atrophy	16
Pure autonomic failure	11
Parkinson disease	7
Idiopathic peripheral neuropathy	5
Baroreflex failure	2
Lewy body disease	2
Sympathetic autonomic neuropathy	1
Polyradiculopathy	1
Nonneurologic	
Cancer	13
Carotid endarterectomy	5
Autonomic dysfunction	7
Diabetes mellitus	4
Amyloidosis	2
Multiple myeloma	2
Head and neck surgery	3
Polymyalgia rheumatica	1
Uncertain	18

The role of adrenomedullin and galanin in recurrent vasovagal syncope: a case control study.

Plasek J et al

Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic.
157(2):162-7, 2013 Jun.

There is a different galanin secretion pattern during orthostatic provocation in patients with recurrent vasovagal syncope than healthy individuals.

For adrenomedullin, no significant difference was found.

Neuropeptides in Evaluation of Causes of Syncope

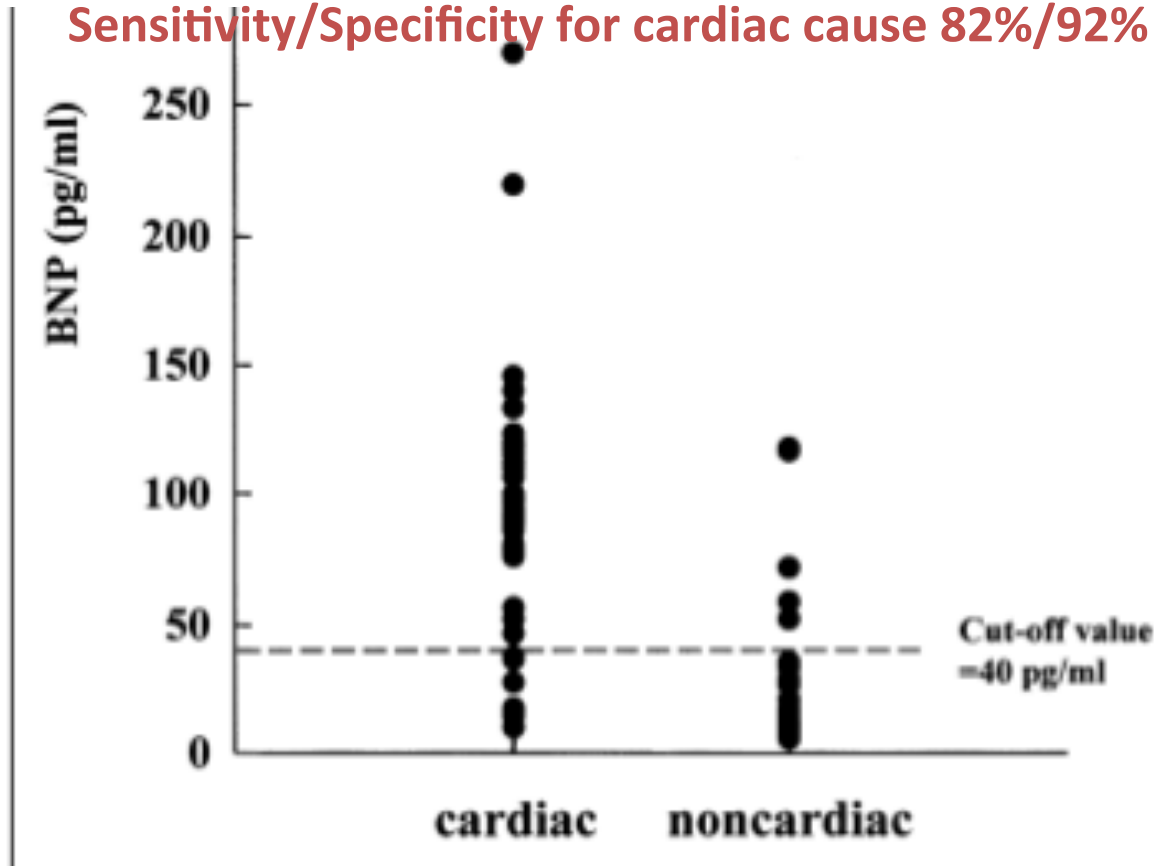
NT-proBNP in Syncope

- **Reported to aid differentiating cardiac and non-cardiac causes**
- **Physiologic impact not studied**
- **Utility criticized**
 - **inpatients**
 - **older than controls**

Usefulness of Brain Natriuretic Peptide as a Marker for Separating Cardiac and Noncardiac Causes of Syncope

Kojiro Tanimoto, MD, Kazushi Yukiiri, MD, Katsufumi Mizushige, MD, Yuichiro Takagi, MD, Hisashi Masugata, MD, Kaori Shinomiya, MD, Naohisa Hosomi, MD, Tsutomu Takahashi, MD, Koji Ohmori, MD, and Masakazu Kohno, MD

Sensitivity/Specificity for cardiac cause 82%/92%



NT-pro-BNP for diagnostic and prognostic evaluation in patients hospitalized for syncope

Roman Pfister^{a,*}, Jens Hagemeister^a, Susanne Esser^a, Martin Hellmich^b,
Erland Erdmann^a, Christian A. Schneider^a

