Gruppo Italiano Multidisciplinare per lo Studio della Sincope

SINCOPE 2023
11° Convegno Nazionale GIMSI

Novità nei meccanismi della sincope riflessa: un fenomeno emodinamico

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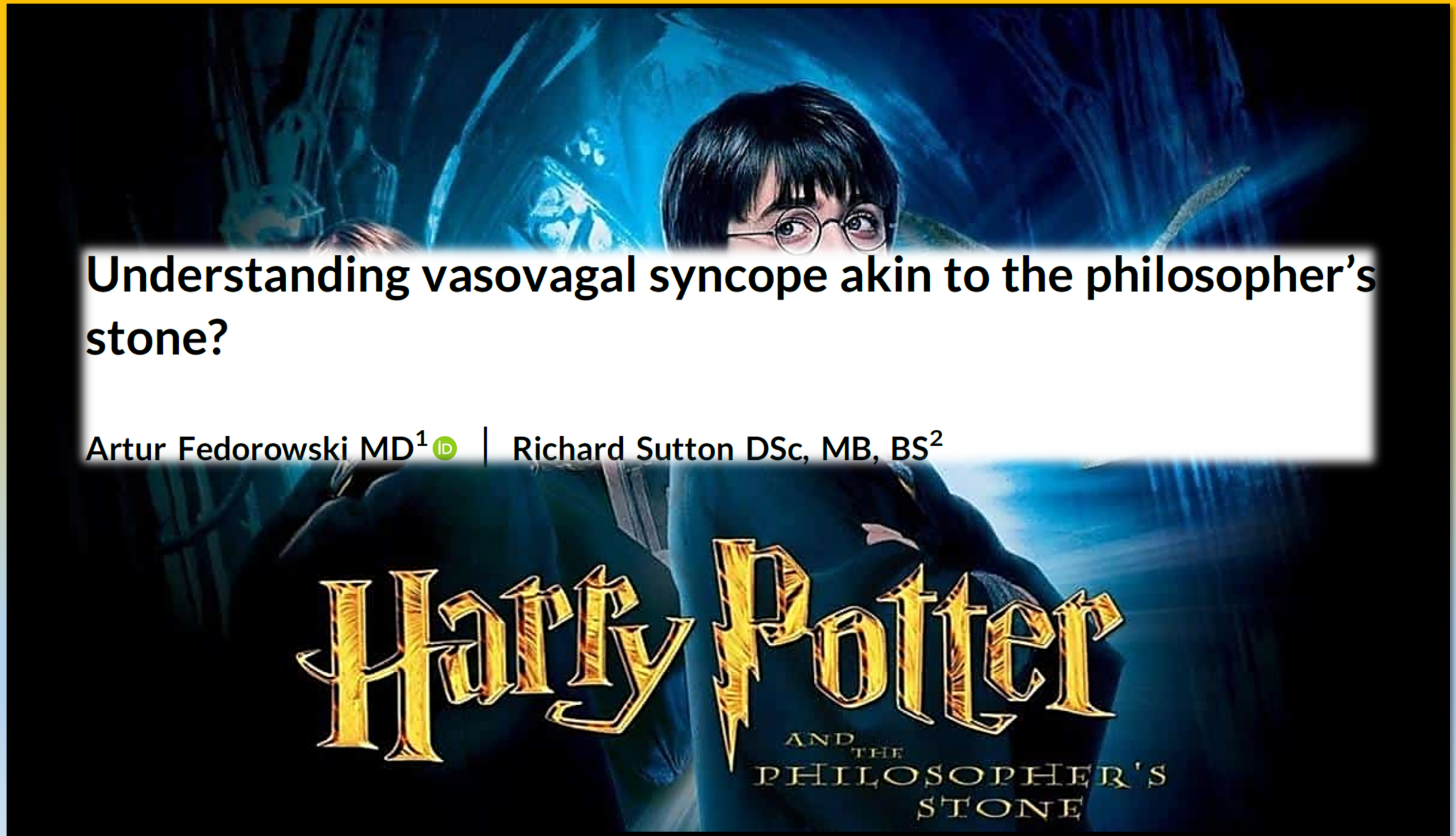


Understanding vasovagal syncope akin to the philosopher's stone?

Artur Fedorowski MD[1] | Richard Sutton DSc, MB, BS[2]

- ***PIETRA FILOSOFALE***

…Che cosa propriamente fosse, è arduo dire, soprattutto perché l'interpretazione del linguaggio alchemico segue vie divergenti:

per gli uni, i più, la pietra filosofale è una fantasiosa composizione chimica, invano cercata dagli alchimisti, la quale avrebbe dovuto possedere straordinarie virtù, come quella di trasformare qualsiasi metallo vile in oro.

Altri, però, non sono di questo parere, e notano come in molti testi alchemici si affermi esplicitamente che l'opus magnum non è opera materiale. Da essi il detto di Basilio Valentino…che il «trovare la pietra nascosta»…corrisponda simbolicamente a un'esperienza interiore, cercata e vissuta per fini di sviluppo spirituale.

Understanding vasovagal syncope akin to the philosopher's stone?

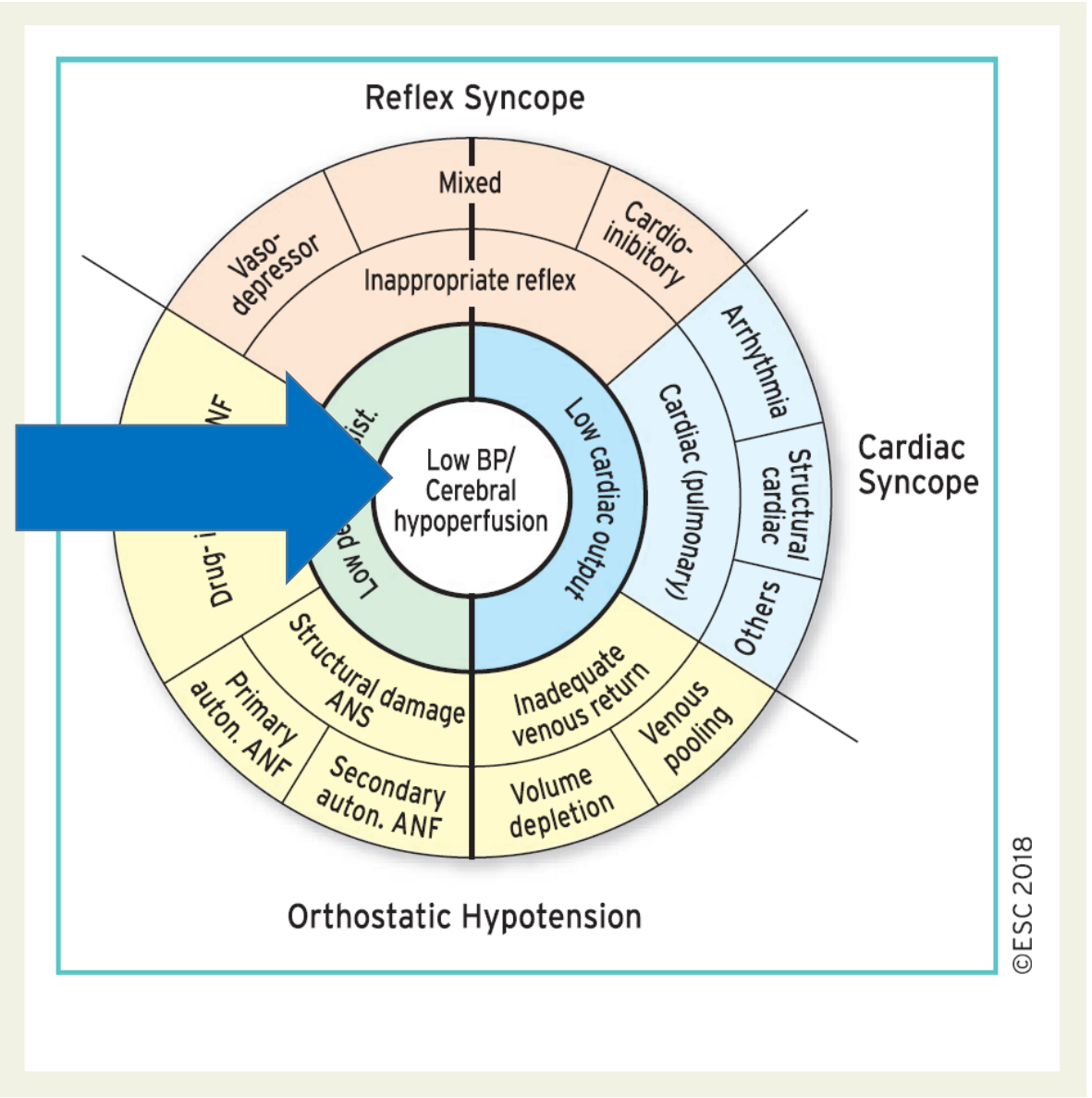
Artur Fedorowski MD[1] | Richard Sutton DSc, MB, BS[2]

Vasovagal syncope (VVS), the most common form of transient loss of consciousness, still awaits a complete understanding of its role in human physiology. It has long been a scientific puzzle why VVS occurs in approximately one-third of the population with an apparently benign long-term prognosis.[1]

J Cardiovasc Electrophysiol. 2019;30:297–298.

2018 ESC Guidelines for the diagnosis and management of syncope

ESC European Society of Cardiology



European Heart Journal (2018) **00**, 1–69

Cardiac output and vasodilation in the vasovagal response: An analysis of the classic papers

Wouter Wieling, MD, PhD[*], David L. Jardine, MD, PhD[†], Frederik J. de Lange, MD, PhD[‡], Michele Brignole, MD[§], Henning B. Nielsen, MD, DMSci[||], Julian Stewart, MD, PhD[¶], and Richard Sutton, MB BS, DSc, FHRS[#]

During VVS, the fall in BP is mediated initially by decreased CO with or without vasodilation.

The decrease in CO is secondary to SV reduction.

There has been much debate as to whether decreased CO or vasodilation is the dominant hypotensive mechanism preceding vasovagal syncope.

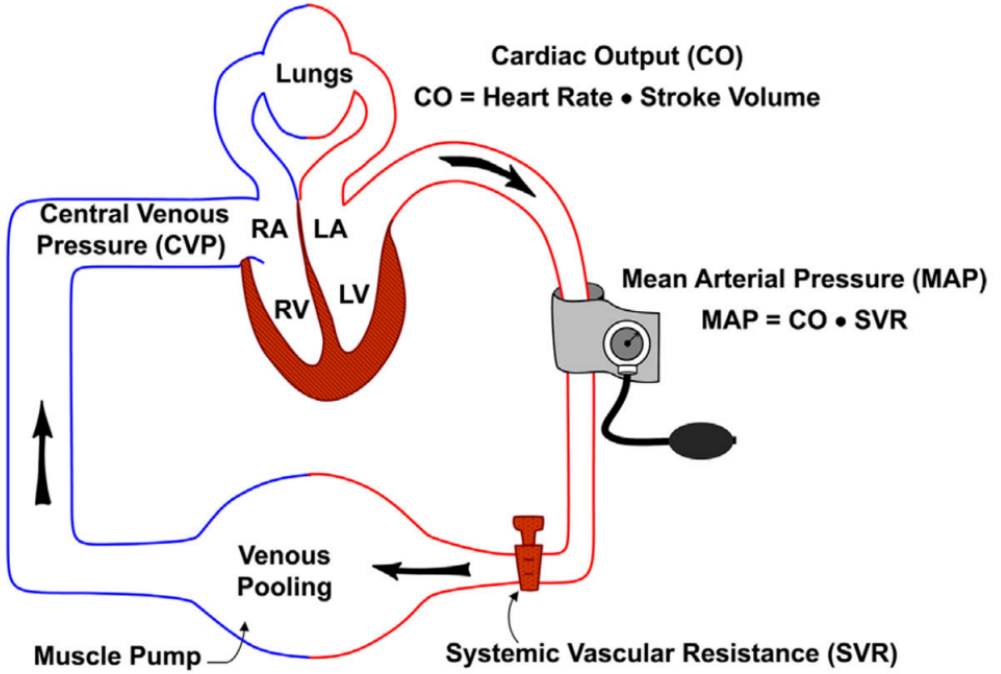


Figure 1.
Ohm's law: Mean arterial pressure = Cardiac output (CO) × Systemic Vascular Resistance (SVR). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; Venous pooling = accumulation of blood in the venous system.

Heart Rhythm. 2016 March ; 13(3): 798–805.

VASOVAGAL SYNCOPE AND THE CAROTID SINUS MECHANISM

SIR THOMAS LEWIS, M.D., F.R.C.P., F.R.S.
(From the Department of Clinical Research, University College Hospital Medical School)

the cause of syncope is mainly vasomotor and not vagal ;* but the vagus adds impressively to the clinical picture by inducing conspicuous slowing of the heart and gastric manifestations. The combination of vagal and vasomotor effects, while fully justifying the term "vasovagal," brings me to the consideration of a discovery which is possibly very relevant to the pathology of the attacks now discussed.

Cardiovascular Dynamics During Orthostasis and the Influence of Intravascular Instrumentation*

Paul M. Stevens, M.D.

In the pre-syncopal period, the cardiac index of both early and late fainters fell by a mean of 39 per cent of baseline, in contrast to non-fainters, whose cardiac index decreased by only 19 per cent of baseline at the end of 20 min. of orthostasis (< 0.001).

All fainters showed a marked fall in systolic, diastolic and pulse pressure at the time of presyncopal symptoms.

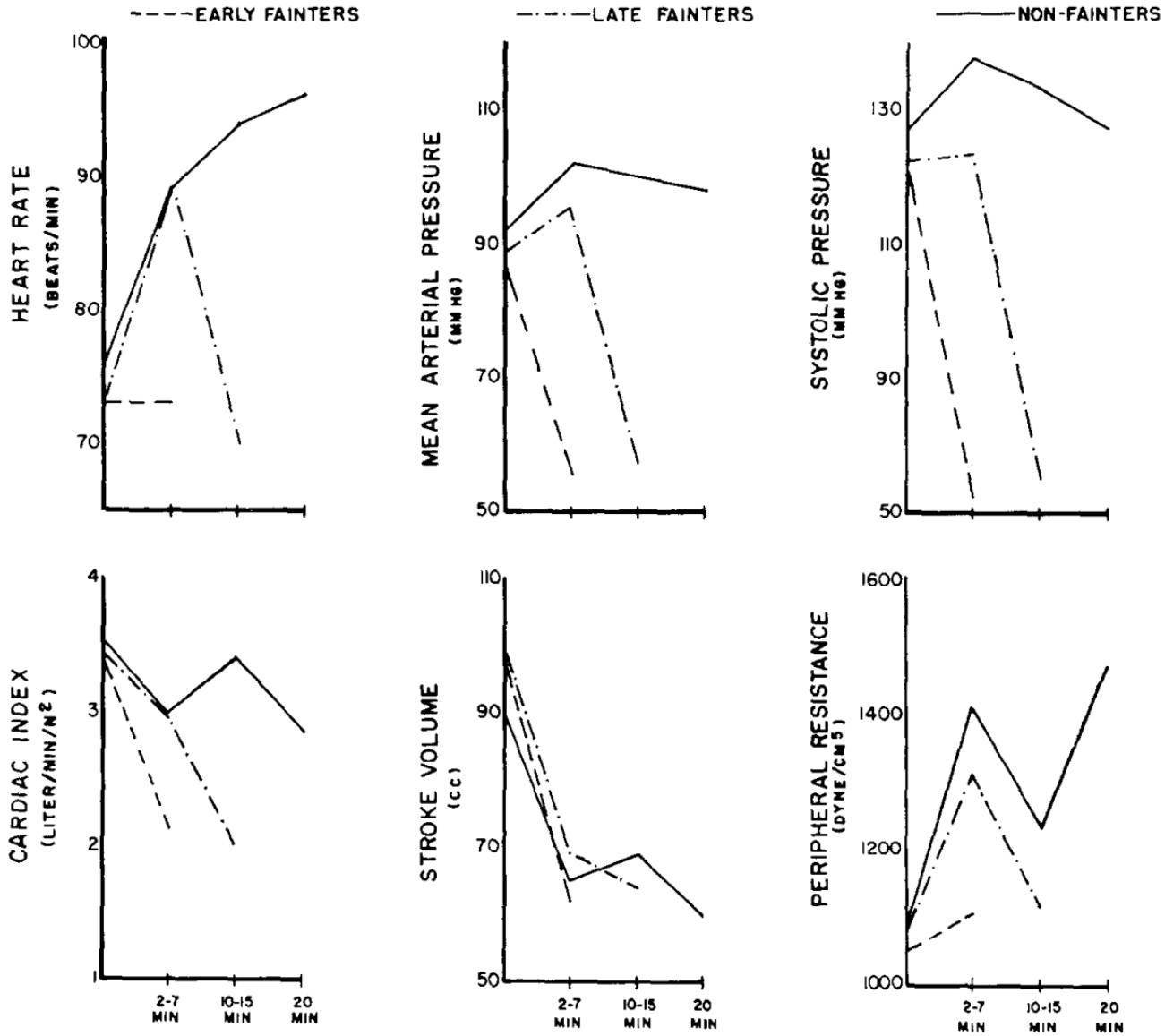
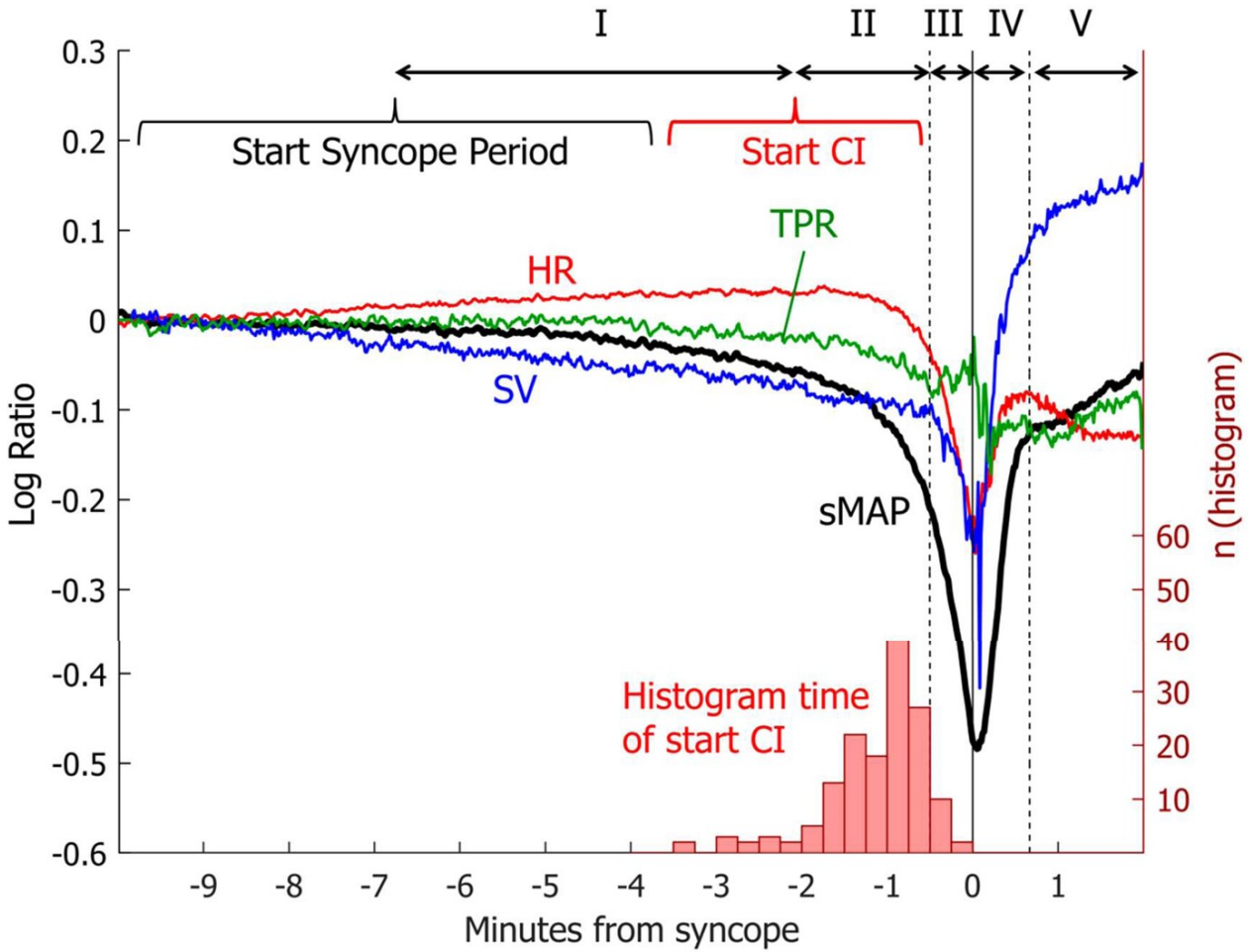


Fig. 1. Cardiovascular responses of fainters and nonfainters to orthostasis.

Novel Methods for Quantification of Vasodepression and Cardioinhibition During Tilt-Induced Vasovagal Syncope

J. Gert van Dijk, Maryam Ghariq, Fabian I. Kerkhof, Robert Reijntjes, Marc J. van Houwelingen, Ineke A. van Rossum, Dirk P. Saal, Erik W. van Zwet, Johannes J. van Lieshout, Roland D. Thijs, David G. Benditt

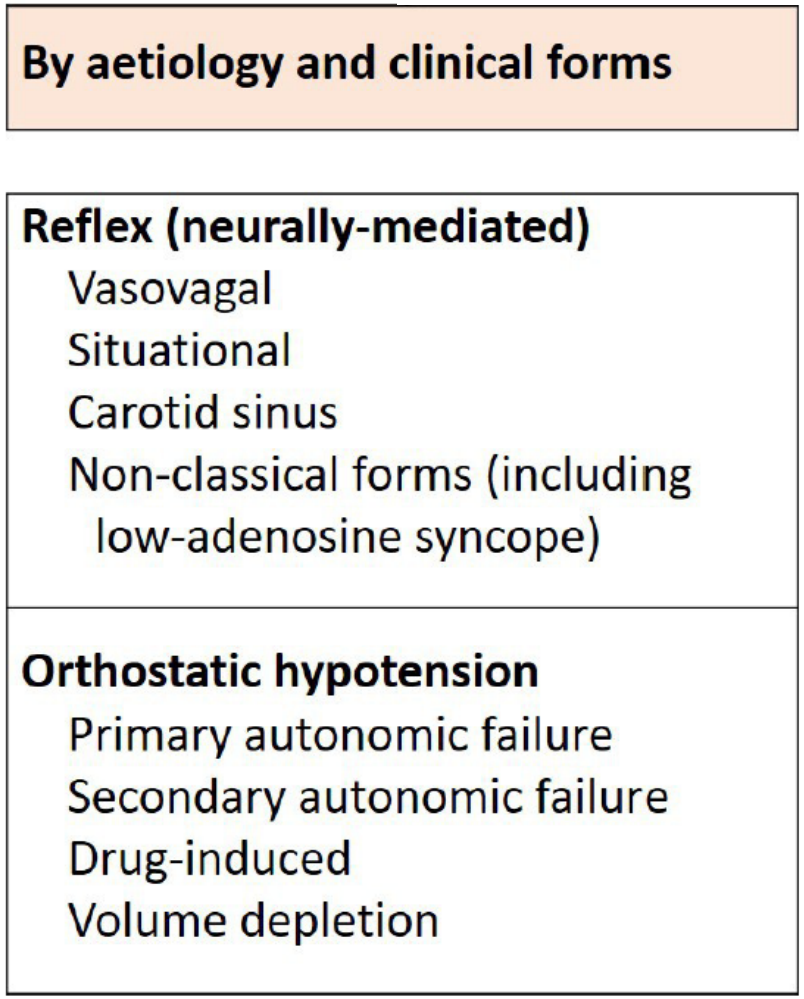


BP = SV x HR x SVR

The two major factors lowering BP in T-VVS were **reduced SV** and **cardioinhibition**.

Circulation Research 2020

New insights in diagnostics and therapies in syncope: a novel approach to non-cardiac syncope



Traditionally, reflex syncope and orthostatic hypotension are classified by their aetiology and clinical presentation

Figure 3 Classification of non-cardiac syncope according its aetiology (left panel) and mechanism (right panel). AV, atrioventricular; BP, blood pressure.

Brignole M, Rivasi G. *Heart* 2021;**107**:864–873.

New insights in diagnostics and therapies in syncope: a novel approach to non-cardiac syncope

The dominant mechanism of syncope should be carefully assessed and assigned to hypotensive or to bradycardic phenotype, the choice of therapy (counteracting hypotension or bradycardia) depending on the given phenotype…

The efficacy of therapy is largely determined by the mechanism of syncope rather than its aetiology or clinical presentation

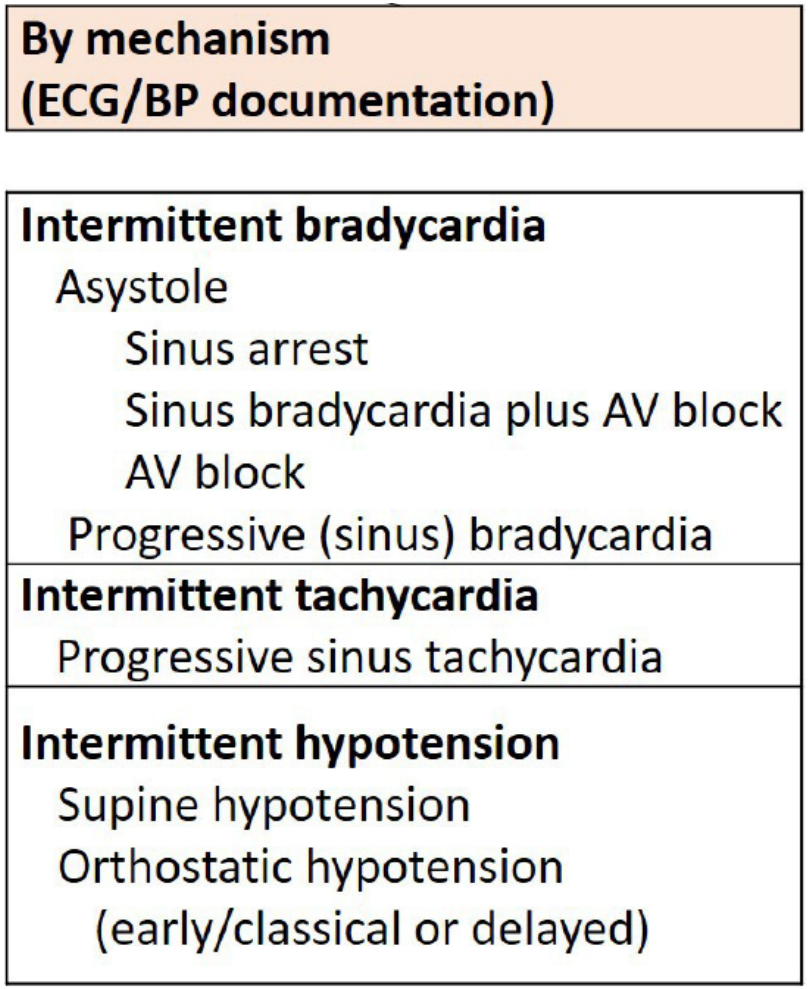


Figure 3 Classification of non-cardiac syncope according its aetiology (left panel) and mechanism (right panel). AV, atrioventricular; BP, blood pressure.

Brignole M, Rivasi G. *Heart* 2021;**107**:864–873.

Mechanisms of non-cardiac syncope

Non-cardiac syncope	
Hypotensive phenotype	**Bradycardic phenotype**
Vasodepressor or mixed reflex syncope during TT	Cardioinhibitory response to TT
Vasodepressor or mixed carotid sinus syndrome	Cardioinhibitory carotid sinus syndrome
Blood pressure falls detected on 24h-ambulatory blood pressure monitoring	Syncopal reflex asystole (>3 sec) or non-syncopal reflex asystole (>6 sec) detected by ILR
	Low adenosine syncope

Abbreviations: ILR, implantable loop recorder; TT, Tilt Testing

Non-cardiac syncope due to bradycardic phenotype is likely when syncope occurs at the time of an asystolic pause >3 s recorded during a spontaneous event or induced by carotid sinus massage or by tilt testing.

Rivasi G et al. Kardiol Pol 2021

Mechanisms of non-cardiac syncope

Non-cardiac syncope	
Hypotensive phenotype	**Bradycardic phenotype**
Vasodepressor or mixed reflex syncope during TT	Cardioinhibitory response to TT
Vasodepressor or mixed carotid sinus syndrome	Cardioinhibitory carotid sinus syndrome
Blood pressure falls detected on 24h-ambulatory blood pressure monitoring	Syncopal reflex asystole (>3 sec) or non-syncopal reflex asystole (>6 sec)

Abbreviations: ILR, implantable loop recorder; TT, Tilt Testing

Non-cardiac syncope due to hypotensive phenotype is likely when syncope occurs in patients who have constitutional or drug-related persistent hypotension, or inappropriately low blood pressure during ambulatory blood pressure monitoring, or have hypotensive symptoms induced by tilt testing

Rivasi G et al. Kardiol Pol 2021

2018 ESC Guidelines for the diagnosis and management of syncope

The patients with persistent low BP and those who show a hypotensive susceptibility on tilt testing seem to satisfy the criteria for low BP phenotype.

Being only a concept, the guidelines were unable to define more precisely low-BP phenotype.

Brignole M et al. J Hypertension 2021

Tilt testing

Recommendations	Class[a]	Level[b]
Indications		
Tilt testing should be considered in patients with suspected reflex syncope, OH, POTS, or PPS.[23,24,105–109,111–117]	IIa	B
Tilt testing may be considered to educate patients to recognize symptoms and learn physical manoeuvres.[119–121]	IIb	B
Diagnostic criteria		
Reflex syncope, OH, POTS, or PPS should be considered likely if tilt testing reproduces symptoms along with the characteristic circulatory pattern of these conditions.[23,24,105–109,111–117]	IIa	B

Additional advice and clinical perspectives

- A negative tilt table response does not exclude a diagnosis of reflex syncope.
- While sensitivity and specificity are at acceptable levels when measured in patients with VVS and healthy controls, in usual clinical settings of syncope of uncertain origin tilt testing suggests the presence of a *hypotensive susceptibility*, which may exist not only in reflex syncope but also with other causes of syncope including some forms of cardiac syncope. The concept of hypotensive susceptibility rather than diagnosis has important practical utility, because the presence or absence of hypotensive susceptibility plays a major role in guiding pacemaker therapy in patients affected by reflex syncope and in the management of hypotensive therapies, which are frequently present in the elderly with syncope (see sections 5.1 and 5.2).
- A positive cardioinhibitory response to tilt testing predicts, with high probability, asystolic spontaneous syncope; this finding is relevant for therapeutic implications when cardiac pacing is considered (see section 5.2.6). Conversely, the presence of a positive vasodepressor, a mixed response, or even a negative response does not exclude the presence of asystole during spontaneous syncope.[122,123]
- Tilt testing may be helpful in separating syncope with abnormal movements from epilepsy.[137]
- Tilt testing may have value in distinguishing syncope from falls.[23]
- Tilt testing may be helpful in separating syncope from PPS. In suspected PPS, the tilt test should preferably be performed together with EEG monitoring; a normal EEG helps to confirm the diagnosis.[116,117] In the absence of an EEG, a video recording will be helpful in confirming the diagnosis.
- Tilt testing should not be used to assess the efficacy of a drug treatment.[118]

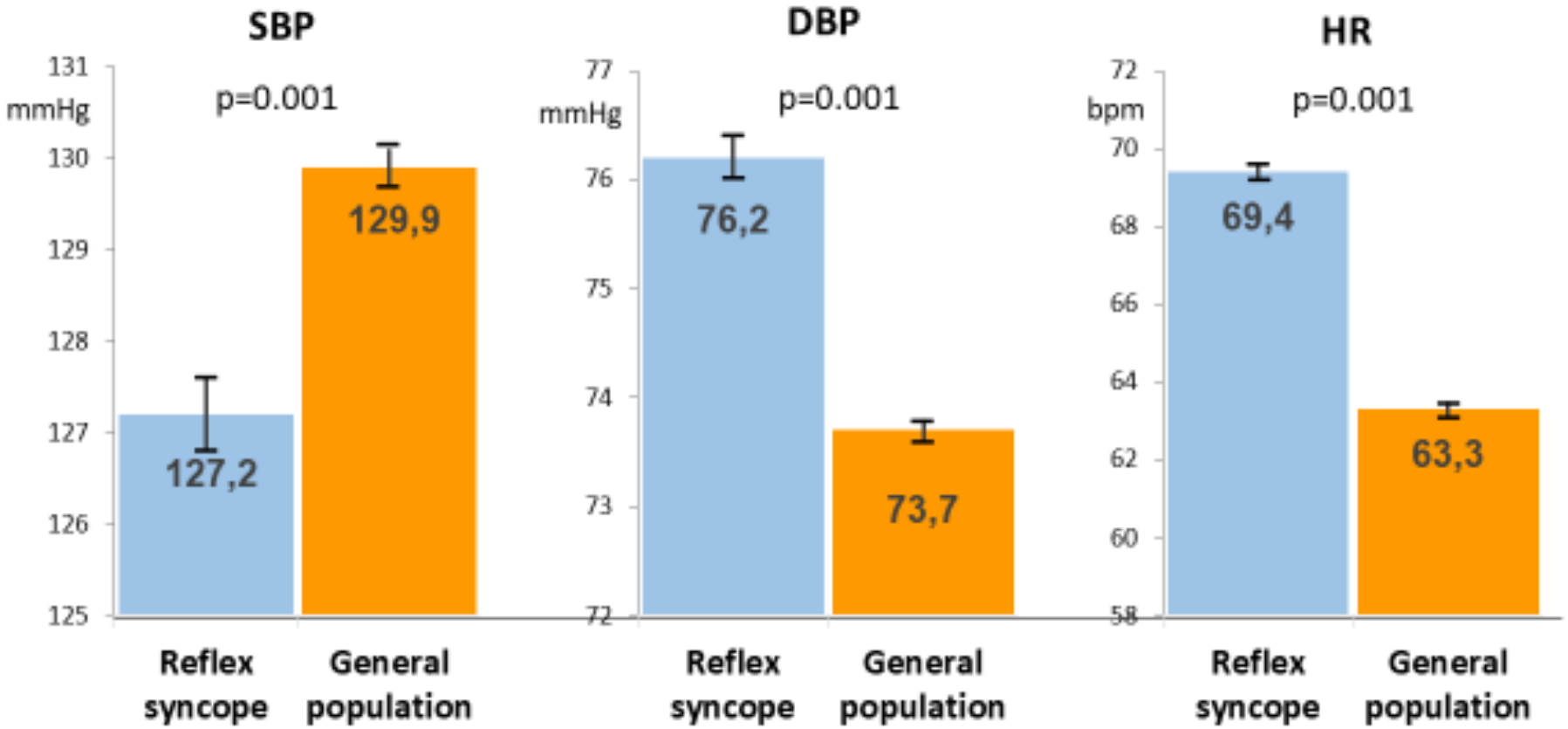
ESC European Society of Cardiology

Low-blood pressure phenotype underpins the tendency to reflex syncope

	Reflex syncope (6 studies)	General population (6 studies)
Total patients	**6.516**	**64.968**
Mean age	**54±19**	**50±21**
Females	**56%**	**55%**

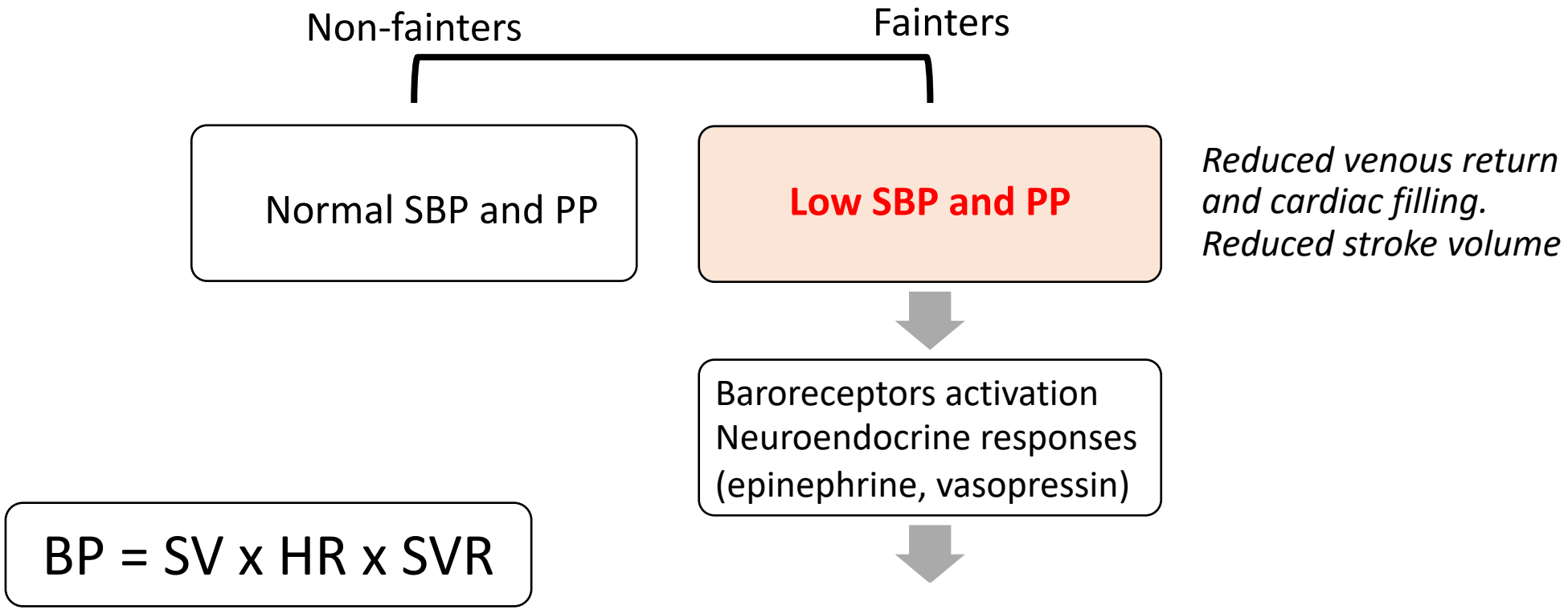
Brignole M et al., J Hypertension 2021

Patients with reflex syncope have a different cardiovascular physiology than in the general population



Brignole M et al., J Hypertension 2021

Patients with reflex syncope have a different cardiovascular physiology than in the general population *(J Hypertension 2021)*



Impact of Cardiovascular Neurohormones on Onset of Vasovagal Syncope Induced by Head-up Tilt

Parisa Torabi, MD; Fabrizio Ricci, MD, PhD; Viktor Hamrefors, MD, PhD; Olle Melander, MD, PhD; Richard Sutton, DSc, MB, BS; David G. Benditt, MD; Artur Fedorowski, MD, PhD

Table 3. Relation Between Neurohormone Level and Time to Syncope in Linear Regression Model Adjusted for Age and Sex

Neurohormone	Supine (n=161)	*P* Value	3-Minute HUT (n=151)	*P* Value	Δ Value (n=151)	*P* Value
Epinephrine	−0.71 (0.59)	0.23	−2.13 (0.59)*	<0.001*	−3.24 (0.78)*	<0.001*
Norepinephrine	0.15 (0.65)	0.82	0.97 (0.66)	0.14	2.49 (1.83)	0.18
CT-proAVP	0.46 (0.61)	0.45	−1.39 (0.68)*	0.043*	−2.07 (0.61)*	0.001*
CT-proET-1	0.96 (0.66)	0.15	0.70 (0.58)	0.23	0.57 (0.84)	0.50
MR-proANP	0.50 (0.77)	0.52	−0.14 (0.71)	0.84	−0.33 (2.25)	0.88
MR-proADM	2.31 (0.77)*	0.003*	1.76 (0.82)*	0.035*	1.83 (1.62)	0.26

Data are reported as β-coefficient and standard error per 1 SD. CT-proAVP indicates C-terminal pro–arginine vasopressin; CT-proET-1, C-terminal pro–endothelin-1; HUT, head-up tilt test; MR-proADM, midregional fragment of pro-adrenomedullin; MR-proANP, midregional fragment of pro–atrial natriuretic peptide.
*$P<0.05$.

TT positivity is associated with neuroendocrine activation characterized by excess epinephrine and vasopressin release

J Am Heart Assoc. 2019;8:e012559.

Patients with reflex syncope have a different cardiovascular physiology than in the general population *(J Hypertension 2021)*

Non-fainters

Normal SBP and PP

Fainters

Low SBP and PP

Reduced venous return and cardiac filling. Reduced stroke volume

Baroreceptors activation
Neuroendocrine responses (epinephrine, vasopressin)

Compensatory increase of DBP and HR

Increased peripheral vascular resistance

VV reflex (when compensatory mechanisms fail)

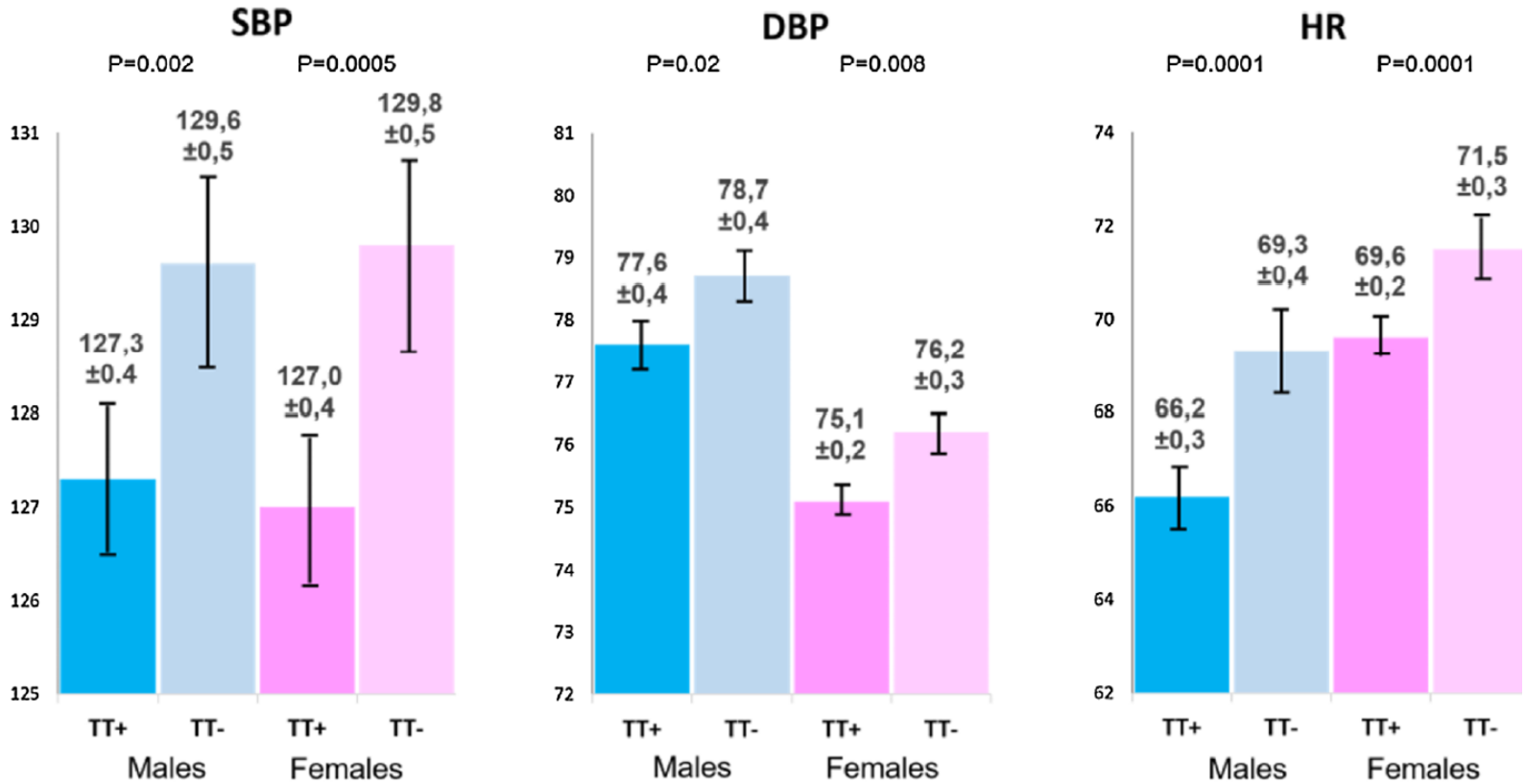
$$BP = SV \times HR \times SVR$$

Reflex syncope occurs when orthostatic stress or other typical triggers overcome the capacity of these adaptive mechanisms, leadings to a decrease in MAP and a reduced blood supply to the brain.

Underlying hemodynamic differences are associated with responses to tilt testing

5236 patients
TT induced reflex syncope in 3129 (60%) patients
and did not induce reflex syncope in 2107 (40%) patients.

to explore whether differences in resting hemodynamic parameters may be associated with tilt test results in patients with suspected reflex syncope…



Abbreviations: DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; TT-, tilt-negative; TT+, tilt-positive.

Low resting BP predisposes to positive response to TT
Hypertension protects from positive response to TT

Confirmatory analysis

Variables	Total syncope population (n = 5236) N	Tilt-positive patients (n = 3129) n (%)	Univariable analysis p value	Multivariable analysis p value
Age subgroups				
10–29 years	748	493 (66)	0.006	0.016
30–59 years	1415	848 (60)		
≥ 60 years	3073	1788 (58)		
Gender				
Males	2351	1428 (61)	0.20	0.10
Females	2885	1701 (59)		
Baseline SBP at the time of tilt testing				
> 128 mmHg	2443	1358 (56)	0.0001	0.0001
≤ 128 mmHg	2793	1771 (63)		
Baseline HR at the time of tilt testing				
> 69 bpm	2088	1176 (56)	0.0001	0.0001
≤ 69 bpm	2324	1490 (64)		
Hypertension*				
Yes	1655	864 (52)	0.0001	0.0001
No	3581	2265 (63)		

Table 1. Univariable and multivariable analysis of factors predicting tilt test positivity in patients investigated for unexplained syncope using the Italian tilt test protocol. *SBP* systolic blood pressure, *HR* heart rate.
*Adjusted for age, gender and heart rate.

Fedorowski A et al. Scientific Report 2021

Underlying hemodynamic differences are associated with responses to tilt testing

Artur Fedorowski[1,2✉], Giulia Rivasi[3], Parisa Torabi[1], Madeleine Johansson[1,2], Martina Rafanelli[3], Irene Marozzi[3], Alice Ceccofiglio[3], Niccolò Casini[3], Viktor Hamrefors[1], Andrea Ungar[3], Brian Olshansky[4], Richard Sutton[2,5], Michele Brignole[6,7] & Gianfranco Parati[6,8]

Our results suggest that patients with TT-induced reflex syncope may have increased resting vagal tone and/or lower sympathetic tone, both expressed by lower HR, and narrower hemodynamic margins in the face of orthostatic stress, expressed by lower initial BP.

Underlying hemodynamic differences are associated with responses to tilt testing

Artur Fedorowski[1,2✉], Giulia Rivasi[3], Parisa Torabi[1], Madeleine Johansson[1,2], Martina Rafanelli[3], Irene Marozzi[3], Alice Ceccofiglio[3], Niccolò Casini[3], Viktor Hamrefors[1], Andrea Ungar[3], Brian Olshansky[4], Richard Sutton[2,5], Michele Brignole[6,7] & Gianfranco Parati[6,8]

In this three-center analysis of syncope patients with high pre-test probability of reflex mechanism, we found a slightly different hemodynamic pattern among those who were tilt-test positive. Males and females who had induction of reflex syncope during TT had lower baseline SBP, DBP, and HR compared with those who did not. We propose that patients more resistant to orthostatic stress induced by TT, who have slightly higher BP and HR, may have greater hemodynamic reserve in the face of gravitational challenge.

Why some subjects develop reflex syncope and others not ?

- The patients prone to reflex syncope demonstrate a different resting cardiovascular hemodynamic profile than general population

- The different resting cardiovascular hemodynamic profile in the syncope population underpins the genesis of reflex syncope instead of being a readily dismissed neurological phenomenon.

- This finding was completely unknown before this study and provides the rationale for the *Hypotensive Phenotype*

Understanding vasovagal syncope akin to the philosopher's stone?

Artur Fedorowski MD[1] | Richard Sutton DSc, MB, BS[2]

Non è facile scoprire la Pietra Filosofale […].

Gli alchimisti trascorrevano lunghi anni nei laboratori, guardavano quel fuoco che purificava i metalli.

Fissavano il fuoco così a lungo che, a poco a poco, scomparivano dalle loro menti tutte le vanità del mondo. E un bel giorno, poi scoprivano che la purificazione dei metalli aveva infine purificato anche loro.

Paulo Coelho, L'Alchimista, 1988.

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Grazie per l'attenzione