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ORIGINAL RESEARCH

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

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RATIONALE: Assessing the relative contributions of cardioinhibition and vasodepression to the blood pressure (BP) decrease in tilt-induced vasovagal syncope requires methods that reflect BP physiology accurately.

OBJECTIVE: To assess the relative contributions of cardioinhibition and vasodepression to tilt-induced vasovagal syncope using novel methods.

METHODS AND RESULTS: We studied the parameters determining BP, that is, stroke volume (SV), heart rate (HR), and total peripheral resistance (TPR), in 163 patients with tilt-induced vasovagal syncope documented by continuous ECG and video EEG monitoring. We defined the beginning of cardioinhibition as the start of an HR decrease (HR) before syncope and used logarithms of SV, HR, and TPR ratios to quantify the multiplicative relation BP=SV·HR·TPR. We defined 3 stages before syncope and 2 after it based on direction changes of these parameters. The earliest BP decrease occurred 9 minutes before syncope. Cardioinhibition was observed in 91% of patients at a median time of 58 seconds before syncope. At that time, SV had a strong negative effect on BP, TPR a lesser negative effect, while HR had increased (all $P<0.001$). At the onset of cardioinhibition, the median HR was at 98 bpm higher than baseline. Cardioinhibition thus initially only represented a reduction of the corrective HR increase but was nonetheless accompanied by an immediate acceleration of the ongoing BP decrease. At syncope, SV and HR contributed similarly to the BP decrease ($P<0.001$), while TPR did not affect BP.

CONCLUSIONS: The novel methods allowed the relative effects of SV, HR, and TPR on BP to be assessed separately, although all act together. The 2 major factors lowering BP in tilt-induced vasovagal syncope were reduced SV and cardioinhibition. We suggest that the term vasodepression in reflex syncope should not be limited to reduced arterial vasoconstriction, reflected in TPR, but should also encompass venous pooling, reflected in SV.

GRAPHICAL ABSTRACT: A graphical abstract is available for this article.

Key Words: autonomic nervous system ■ blood pressure ■ heart rate ■ hemodynamics ■ syncope

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Vasovagal syncope (VVS) affects about one-third of the population and is classically provoked by fear, pain, or prolonged upright posture.[1] The diagnosis rests primarily on history taking and can in many cases be confirmed with a tilt table test (TTT). Tilt-evoked VVS (T-VVS) serves as a clinically useful model of VVS induced by standing.[2]

Early views of the drop of blood pressure (BP) associated with T-VVS held that it was due to cardioinhibition, vasodepression, or both. Cardioinhibition in the T-VVS context is usually limited to a strong vagal decrease of heart rate (HR) including asystole, although vagal influences can also decrease contractility. Vasodepression has widely been interpreted as a decrease of

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Novelty and Significance

What Is Known?

- In vasovagal syncope (VVS), the decrease in blood pressure (BP) has been attributed to cardioinhibition (vagal bradycardia), vasodepression (usually defined as reduced blood vessel vasoconstriction), and venous pooling; all to varying degrees.
- Conventional analysis techniques were unable to determine the amount each component contributed to VVS.
- Current evidence in regard to the relative contribution to VVS, including heart rate (HR), stroke volume (SV), and total peripheral resistance (TPR), was conflicting.

What New Information Does This Article Contribute?

- Expressing changes over time for BP, HR, SV, and TPR as logarithms of ratios allowed their relative effects to be quantified and compared with one another, over time, and between groups.
- The early decrease of BP in 163 cases of VVS during tilt table test was due to low SV and incompletely compensated for by an increase of HR. A minor decrease of TPR contributed little to the BP decrease.
- Cardioinhibition occurred in 91% of cases, began 1 minute before syncope, accelerated the BP decrease, and had a final total effect on BP as large as that of low SV.

The pathophysiology of VVS, affecting one-third of all people, is incompletely understood. The tendency of VVS to occur during prolonged standing is exploited with tilt table testing. Recording BP continuously allows hemodynamic analysis of events through Modelflow analysis. VVS is traditionally blamed on vasodepression, a reduction of sympathetic arteriolar vasoconstriction (apparent as low TPR), and on cardioinhibition, vagal bradycardia (apparent as low HR). However, various studies showed a decrease of SV before VVS, with conflicting roles for TPR and HR. This study of people with complete VVS used 2 novel methods: First, changes of BP, SV, HR, and TPR over time were expressed as logarithms of ratios, quantifying the relative effects of SV, HR, and TPR on BP. Second, both the time of onset and magnitude of cardioinhibition were quantified. We found that reduced SV was the first factor lowering BP. SV started to decrease up to 9 minutes before syncope, probably due to venous pooling. Cardioinhibition started one minute before syncope and had a final effect as large as that of SV. These findings greatly clarify vasodepression in reflex syncope to encompass both reduced arteriolar vasoconstriction (decreased TPR), as well as venous pooling (decreased SV).

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CO	cardiac output
HR	heart rate
MAP	mean arterial pressure
sMAP	smoothed mean arterial pressure
SV	stroke volume
T-VVS	tilt-induced vasovagal syncope
TPR	total peripheral resistance
TTT	tilt table test
VVS	vasovagal syncope

sympathetic arteriolar vasoconstriction, apparent as a decrease of total peripheral resistance (TPR).[3] However, hemodynamic changes in T-VVS have proved to be more complex than mere decreases of HR and TPR.

First, TPR results were variable: before syncope, decreases, but also some increases, were reported.[4,5] However, during syncope, TPR was increased[6–8] as well as during prolonged near syncope.[9] Second, HR during syncope may remain unaltered or show cardioinhibition, that is, vagal bradycardia/asystole. Both the magnitude and timing of cardioinhibition affect loss of consciousness in T-VVS: while early asystole likely contributes to syncope, late asystole need not do so, as patients may already be unconscious due to vasodepression.[10] Third, stroke volume (SV) consistently decreased in presyncope,[4,6,11–14] usually attributed to a decrease of venous return due to venous pooling in the lower limbs, abdomen, or pelvis.[4,6,14,15]

Differences between studies may reside in the composition of study groups and in a limitation to presyncope: only 3 studies assessed actual syncope, with TPR results differing from presyncope.[6–8] Finally, the methods used to compare the contributions of SV, HR, and TPR to low BP may not have reflected their multiplicative nature: the hemodynamic parameters governing changes of BP during T-VVS[16] can be analyzed using the beat-to-beat arterial pressure waveform.[17,18] Inasmuch as BP is the product of cardiac output (CO) and TPR, and CO is the product of SV and HR, BP is the product of HR, SV, and TPR.

Herein, we present 2 novel methods. The first defined the onset of cardioinhibition as the start of the presyncopal HR decrease; the second involves logarithmic transformation of ratios of SV, HR, and TPR to quantify their relative effects and thus of cardioinhibition and vasodepression. The findings may enhance knowledge of the pathophysiology of T-VVS, in particular regarding the contribution of cardioinhibition.

We studied T-VVS before, during, and after syncope with a temporal resolution of 1 second in 163 cases.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients and TTT Protocol

TTT data were gathered from the Syncope Unit of the Leiden University Medical Centre. The clinical inclusion criterion was probable VVS based on clinical features, including a combination of prodromal nausea, pallor, or sweating with the triggers, including pain, fear, or standing.[1] Most patients were seen clinically by J.G. van Dijk or R.D. Thijs.[19,20]

We used a modified Italian protocol with 10 minutes of supine rest, 20 minutes of head-up tilt, administration of 0.4 mg nitroglycerin sublingually, and 20 minutes of tilt[19] (Figure 1). When syncope seemed imminent, the test was prolonged. Patients were tilted back before the allotted time when syncope, asystole, or EEG slowing occurred. Our TTT protocol concerns recording of continuous finger BP (Finapres Nova or BMEye Nexfin), at least one ECG channel, EEG and video. All signals were stored at 200 Hz on the EEG machine (Nihon Kohden Neurofax EEG-1200).

The TTT inclusion criterion was syncope:

1. BP showed an accelerating decrease with either no HR change or a decrease at syncope.
2. The EEG showed a slow or slow-flat-slow pattern.
3. Clinical findings, judged from direct observation and video, were compatible with loss of consciousness. If the clinical onset of syncope could not be judged, cases were excluded.
4. Recognition of symptoms by the patient and eyewitnesses was required.

Exclusion criteria were presyncope only, additional orthostatic hypotension, psychogenic pseudosyncope, postural orthostatic tachycardia syndrome, apparent pacemaker activity, and excessive artifacts or loss of data.

According to Dutch law, the use of anonymous data gathered exclusively for patient care, as was the case here, did not require individual informed consent. The medical ethics committee of the Leiden University Medical Center declared that there were no objections to carrying out the study.

Clinical Parameters

TTT records were reviewed to note the times of events in seconds, relative to onset of syncope.[19] EEG data were not used in the present study.

- Video was used to record the onset of syncope (loss of facial, jaw or neck tone, involuntary eye opening, or a lack of response).
- The times of tilting upwards, tilting back, and of nitroglycerin use were noted.
- Syncope latency was defined as the time to syncope onset from either head-up tilt, when patients fainted without nitroglycerin, or from nitroglycerin administration when syncope occurred after nitroglycerin.
- Onset and duration of the first asystole period were noted, defined as an RR interval of at least 3 seconds. The duration of bradycardia was defined as that of contiguous RR intervals of at least 2 seconds duration.

Syncope and Tilt Periods

We extracted ECG and BP signals to form the syncope period, starting up to 10 minutes before syncope and ending 2 minutes after syncope (Figure 1). Note that the period before syncope lasted <10 minutes if patients developed syncope within 10 minutes after head-up tilt or after nitroglycerin administration. We also extracted the tilt period, from 4 minutes before to 4 minutes after tilting up, to illustrate basic autonomic reactivity.

Hemodynamic Analysis

To quantify BP, we used the individual smoothed mean arterial pressure (sMAP), in which each sample in a 200 Hz signal represents the average of all samples from 1 second before to 1 second after the sample.

Continuous BP data were used to calculate SV, TPR, and CO using Modelflow (Finapres Medical Systems, Enschede, The Netherlands). The calculations start with measured values of BP and HR. SV is derived from the shape of the arterial pressure curve per heartbeat. SV and HR together yield CO, and BP and CO then yield TPR. The TPR calculations rely on preceding heart beats and are susceptible to preceding calibration periods and artifacts, so more TPR data were omitted than was the case for the other parameters. We expressed BP as mm Hg; SV as L; HR as min^{-1} and TPR as mm Hg·min·L^{-1}. Beats missed by the software were added and erroneously recognized beats deleted. Periods with movement artifacts, premature ventricular complexes, or BP calibrations were inspected: when such periods lasted a few seconds and were preceded and followed by stable periods of the same magnitude, BP or HR was linearly interpolated. Longer stretches or omissions flanked by changing BP were treated as missing data. Interpolation or omission of BP was also performed on the corresponding periods of systolic and diastolic BP, SV, TPR, and CO. All data were resampled at one value per second. Please see the Major Resources Table in the Data Supplement.

Distinguishing Stages

We averaged the 1 second time series across subjects to reveal common patterns, using the onset of syncope to temporally align data. We divided the syncope period into stages to allow analysis on a group level, not to classify individual records. We based the stages on changes of direction of sMAP, HR, SV, and TPR. These concern the start or end of an increase of a decrease. For instance, if HR is first stable, then increases, and finally decreases, then both the start of the increase and of the decrease constitute changes of direction. Stages were periods between such changes of direction. To help visual identification of these points, we calculated the slope of a line of best fit, using least-squares linear regression, of an 80 seconds period around each sample of the averages for sMAP, SV, HR, and TPR. The slope was used to assess the presence of increases

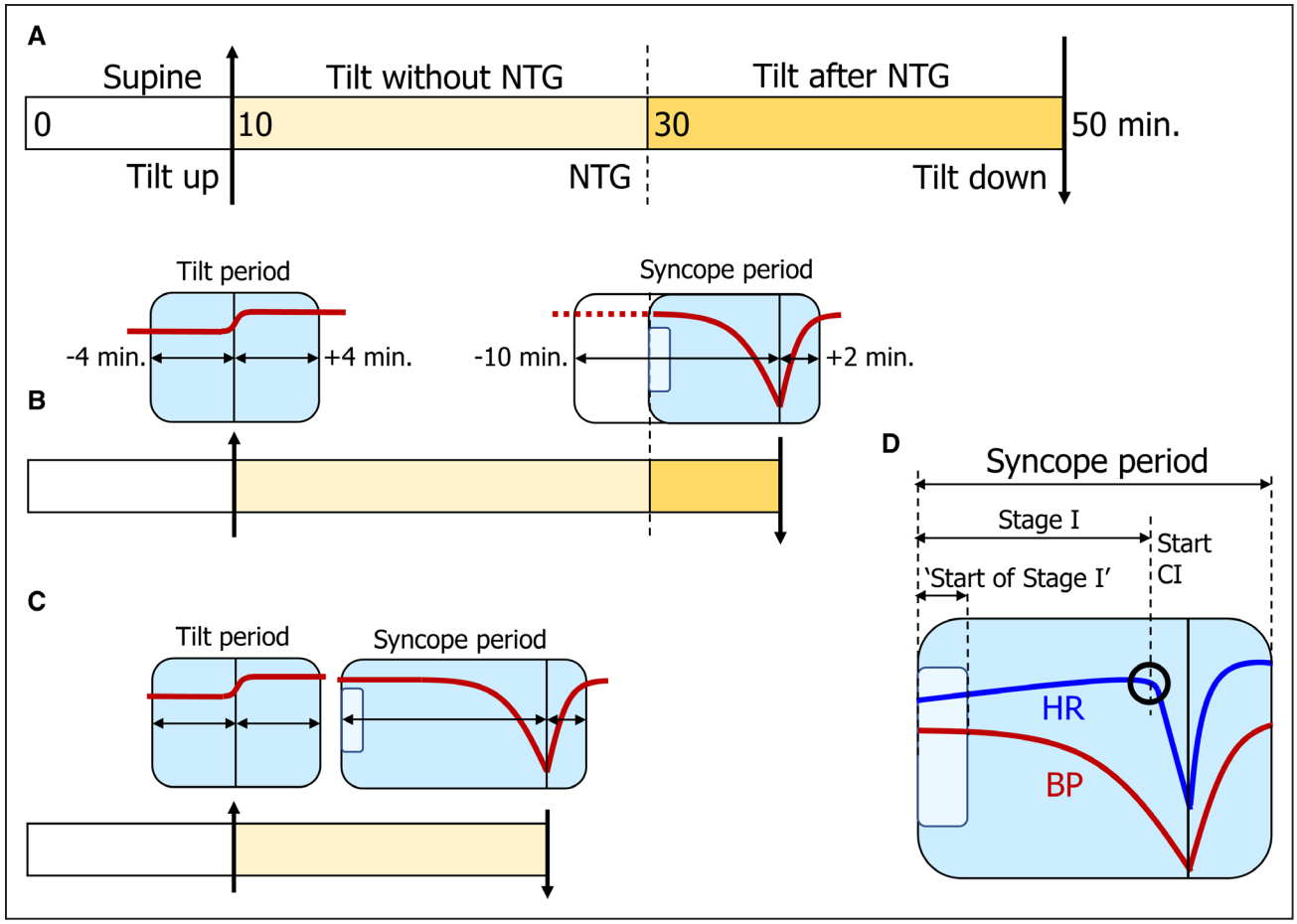

Figure 1. Formation of study periods.
A, The tilt table test (TTT) protocol: 10 min of supine rest, followed by 20 min of head-up tilt, administration of nitroglycerin (NTG), and another 20 min of head-up tilt. The tilt period ran from 4 min before tilt up to 4 min afterwards. The syncope period consisted of a maximum of 10 min before syncope and 2 min after syncope. **B**, Syncope occurred about seven minutes after NTG. To avoid mixing the conditions with and without NTG, the syncope period contained 7 min from NTG application to syncope plus 2 min after syncope. **C**, Syncope occurred >10 min after head-up tilt, so 10 min before syncope were extracted. **D**, The syncope period of **B** in detail: stage I ran from the start of the syncope period to either the start of cardioinhibition (CI) or 30 s before syncope. The start of stage I represents a 1 min period at the beginning of the syncope period, indicated in **B**, **C**, and **D**; this acted as the baseline for comparison with other stages. BP indicates blood pressure; and HR, heart rate.

and decreases objectively, for which we used a difference from zero at $P<0.05$ (t-statistic).

We used short periods, epochs, to quantify sMAP, HR, TPR, and SV within stages. The start and end points of these epochs were based on whether the epochs occurred well before syncope or close to it: events occurring >30 seconds before syncope were determined individually, and later epochs were described with fixed times relative to syncope onset.

Other Analysis Techniques

We defined cardioinhibition as an abruptly starting decrease of HR, starting on average about one minute before syncope and ending at syncope. Whether cardioinhibition occurred and when it started in individual patients was determined through a consensus procedure (J.G. van Dijk, I.A. van Rossum, F. Kerkhof, and M. Ghariq), using plots of individual HR, smoothed HR, and a plot of the change of HR, without recourse to sMAP or clinical data. The onset of cardioinhibition was defined as the time when HR started a decrease towards minimal values at syncope. Minimum HR was measured between 15 seconds before syncope to 15 seconds after it. The magnitude of cardioinhibition was the difference between HR at the onset of cardioinhibition and the minimum HR near syncope. The speed of cardioinhibition was the magnitude divided by the time difference between onset of cardioinhibition and syncope. To evaluate effects of the start of cardioinhibition on BP, we aligned the hemodynamic data according to the time of onset of cardioinhibition and again created averages. To compare results with the VASIS classification (Vasovagal Syncope International Study), we also counted cases fitting the VASIS 2A criteria of cardioinhibition,[21] that is, HR below 40 bpm for at least 10 seconds without asystole.

Main Parameter Analysis

The parameters systolic BP, diastolic BP, and CO will only be shown for illustrative purposes. We limited the quantitative analysis to sMAP, SV, HR, and TPR. BP at a time A (BP_A) is the product of SV_A, HR_A, and TPR_A; at a later time B, $BP_B = SV_B \cdot HR_B \cdot TPR_B$. The alteration over the time between A and B can be expressed as the ratio BP_B/BP_A:

$$\frac{BP_B}{BP_A} = \frac{SV_B \cdot HR_B \cdot TPR_B}{SV_A \cdot HR_A \cdot TPR_A} = \frac{SV_B}{SV_A} \cdot \frac{HR_B}{HR_A} \cdot \frac{TPR_B}{TPR_A}$$

Hence, calculating ratios per parameter (BP_R=BP_B/BP_A; similar for SV_R, HR_R, and TPR_R) quantifies alterations of the 3 parameters affecting BP. We averaged data of the first minute of the syncope period to obtain values for A and expressed all subsequent measurements as ratios relative to this. As ratios are dimensionless, they allow a comparison between variables. Within one subject multiplication of the 3 ratios yields their combined effect on BP. For example, suppose SV_R=0.5, HR_R=1.2, and TPR_R=1.0. SV_R will by itself decrease BP to 50%; HR_R will increase it to 120%, and TPR_R will not change it. Together they alter BP by a factor 0.5·1.2·1.0=0.6.

Unfortunately, summarizing ratios across subjects yields errors if there are decreases as well as increases. For example, for one person SV_R=0.5, HR_R=2.0, and TPR_R=1.0. Their product is 1.0 and shows that BP does not change. For another person, SV_R=2.0, HR_R=0.5, and TPR_R=1.0; again, the product of 1.0 means that BP does not change. However, the means across the 2 persons are 1.25 for SV_R, 1.25 for HR_R, and 1.0 for TPR_R, suggesting an incorrect overall increase of BP. In truth, the doubling effect of one parameter canceled the halving effect of another within each subject. Logarithms solve this problem: the logarithm (base 10) of 0.5 is −0.3010, the logarithm of 2.0 is +0.3010, and the logarithm of 1.0 is 0.0. A multiplicative relation between parameters becomes an additive one for their logarithms, as $log(ab) = log(a) + log(b)$. Thus, the log ratio of BP, BP_{LR}, is SV_{LR}+HR_{LR}+TPR_{LR}. The utility of this log-ratio method becomes apparent by calculating mean log ratios per parameter across the 2 persons: for SV, HR, and TPR, they are 0, correctly showing nil effect on BP. Thus, the absolute value of the log ratios reflects effect magnitude, while their sign indicates effect direction, that is, a decrease or increase.

This use of log ratios does justice to the physiological multiplicative effects of SV, HR, and TPR on BP while allowing quantitative comparisons between variables, periods, and groups.

Statistical Analysis

The χ^2 test was used test group differences for count data. Although most log ratios were normally distributed, as assessed with the Kolmogorov-Smirnov test, we used nonparametric analyses throughout, at a slight cost in power but with increased robustness and a consistent presentation. We used the Friedman test with post hoc tests based on the χ-distributions to compare parameters per stage, and tested whether variables had an effect on BP by testing whether the median of each variable differed from zero with the sign test. We used Matlab (Version R2018b, The Mathworks) for numerical and statistical analysis. A Bonferroni correction for multiple testing for the 35 comparisons in the Table yielded a corrected value of 0.0014; we used a threshold of 0.001.

RESULTS

Patients

The results of inclusion and exclusion and the characteristics of the 163 included patients are shown in the Data Supplement.[19,22–25] Asystole was observed in 68 cases (42%) with a median duration of 6 seconds (range 3–37 seconds). Another 14 cases (8.6%) fulfilled the VASIS 2A criterion of cardioinhibition without asystole. Bradycardia occurred in 71 patients with a median duration of 12 seconds (range 2–155 seconds). Tilting back to the horizontal position took 12 seconds and the horizontal position was reached 13.6±4.2 seconds after the onset of syncope (range 2–30 seconds).

T-VVS occurred in 53 (33%) patients without nitroglycerin, with a median syncope latency after head-up tilt of 709 seconds (range 97–1686 seconds). T-VVS was evoked with nitroglycerin in 110 patients (67%), with a median syncope latency of 466 seconds after nitroglycerin application (range 85–1558 seconds).

Effects of Tilting

Figure 2 shows averaged data for tilt-up periods. Tilting-up caused increases of sMAP, diastolic BP, HR, and TPR, decreases of SV and CO (*t* test, all $P<0.001$), and no change in systolic BP.

Recognition of Stages

Figure 2 shows averages and numbers of valid measurements. Note that data >5 minutes before syncope only reflect patients who fainted at least 5 minutes after the start of their respective condition (head-up tilt or nitroglycerin application), while data closer to syncope also reflect those who fainted earlier. Figure 3 shows which sections of the averaged sMAP, SV, HR, and TPR exhibited increases, decreases, or no change. The changes of direction are indicated. Figure 4 shows averaged log ratios. As holds for Figure 2, data just before syncope represent more patients than data longer before syncope. Also, note that aligning data according to the onset of syncope has a smoothing effect on events that occur at different times respective to syncope between persons. This is the case for the start of cardioinhibition, as illustrated by the histogram (see below for an analysis according to the onset of cardioinhibition). Figures 2 through 4 suggest the following events up to syncope:

- sMAP started to decrease as early as 9 minutes before syncope; this accelerated about 5 minutes before syncope.
- SV decreased consistently from about 9 minutes before syncope; this accelerated 30 seconds before syncope.
- HR started to increase about 9 minutes before syncope and started to decrease 90 to 30 seconds before syncope.
- TPR changes were limited to a slight increase until 300 seconds before syncope, a slight decrease ending about 30 seconds before syncope, when there is an abrupt spike.

The very gradual start of the early changes of SV, sMAP, and HR meant they could not be reliably measured

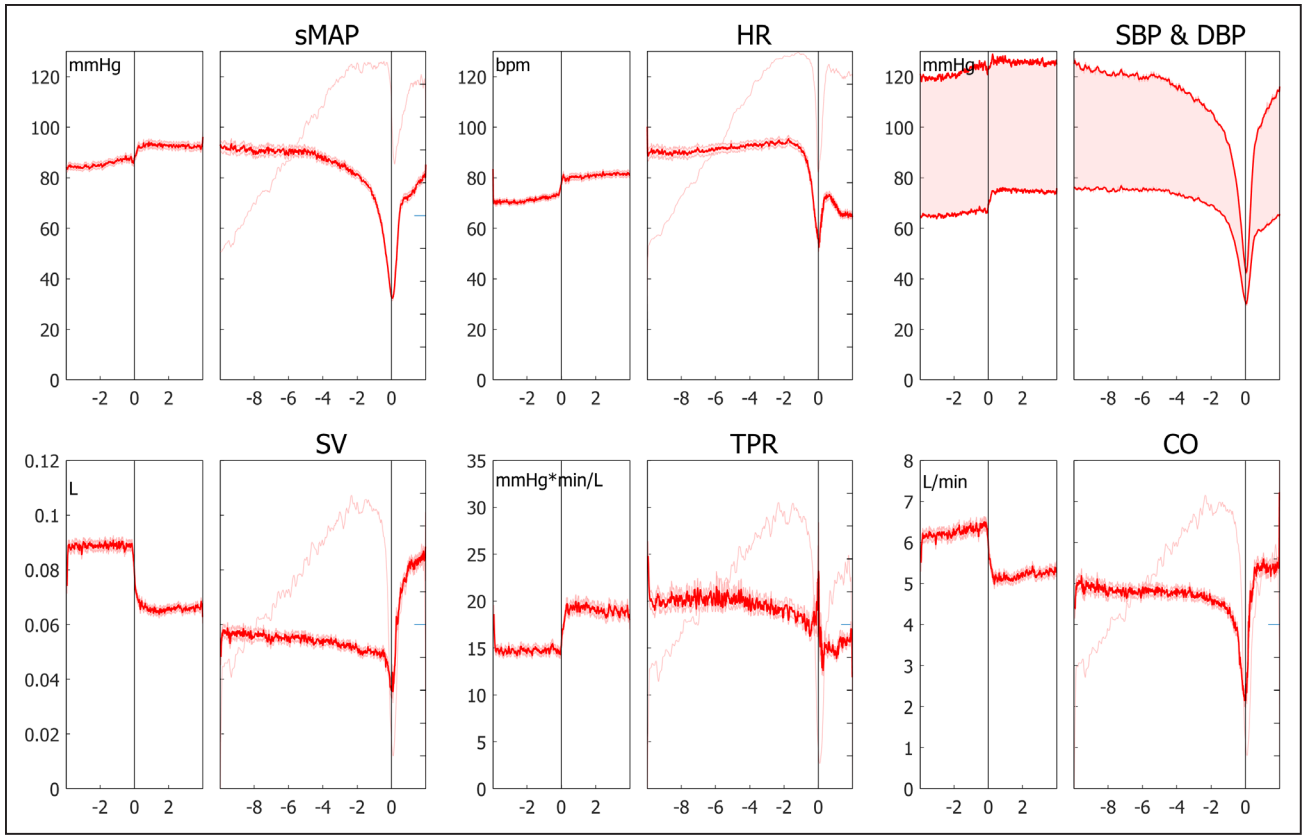

Figure 2. Main results.
The panels represent group averages and standard errors for syncope cases (n=163). The **left** represents the tilt period, and the **right** the syncope period as explained in Figure 1. The **right** also shows the number of valid measurements as light-colored lines, as a percentage of each group. The left-hand side axes show the units of measurement for the parameters, and the right-hand ones a scale of 0%–100% for the number of valid measurements. CO indicates cardiac output; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; sMAP, smoothed mean arterial pressure; SV, stroke volume; and TPR, total peripheral resistance.

individually, but the more abrupt onset of cardioinhibition could be measured. We recognized 3 stages before syncope: stage I ran from the start of the individual's syncope period, meaning it started 10 minutes before syncope or less if syncope occurred within 10 minutes after head-up tilt or after nitroglycerin administration. Stage I ended with either the onset of cardioinhibition or 30 seconds before syncope, if cardioinhibition was absent. Stage II started with the onset of cardioinhibition, if present, and ended 30 seconds before syncope. Stage III started 30 seconds before syncope and ended at syncope.

Events after syncope were divided into stages IV and V. Their distinction rested on events 40 seconds after syncope when the sharp HR rise stopped, SV increased slower, and the TPR spike ended.

Comparison of SV, HR, and TPR Across Stages

Six epochs characterized the stages:

1. The start of stage I was the first minute of valid measurements of the syncope period; data from other epochs were compared with this one.
2. The end of stage I was defined as a one minute period ending at the start of cardioinhibition, if present, or 30 seconds before syncope if not.
3. The end of stage II was only defined if cardioinhibition was present, as a period of one minute ending 30 seconds before syncope, or from the start of cardioinhibition to 30 seconds before syncope, if cardioinhibition started later than 50 seconds before syncope.
4. The syncope epoch lasted 15 seconds and ended when the horizontal position was reached at tilting back, meaning it included the start of syncope but excluded data in the horizontal position.
5. The end of stage IV ran from 20 to 40 seconds after syncope, ending at a direction change for sMAP, HR, and TPR, as explained above.
6. The end of stage V comprised the last 20 seconds of the record, from 100 to 120 seconds after syncope.

For all epochs, absolute values, ratios, and log ratios are summarized in the Table and Figure 5. SV_{LR}, HR_{LR}, and TPR_{LR} differed within every stage, meaning the 3 parameters exerted different effects on BP.

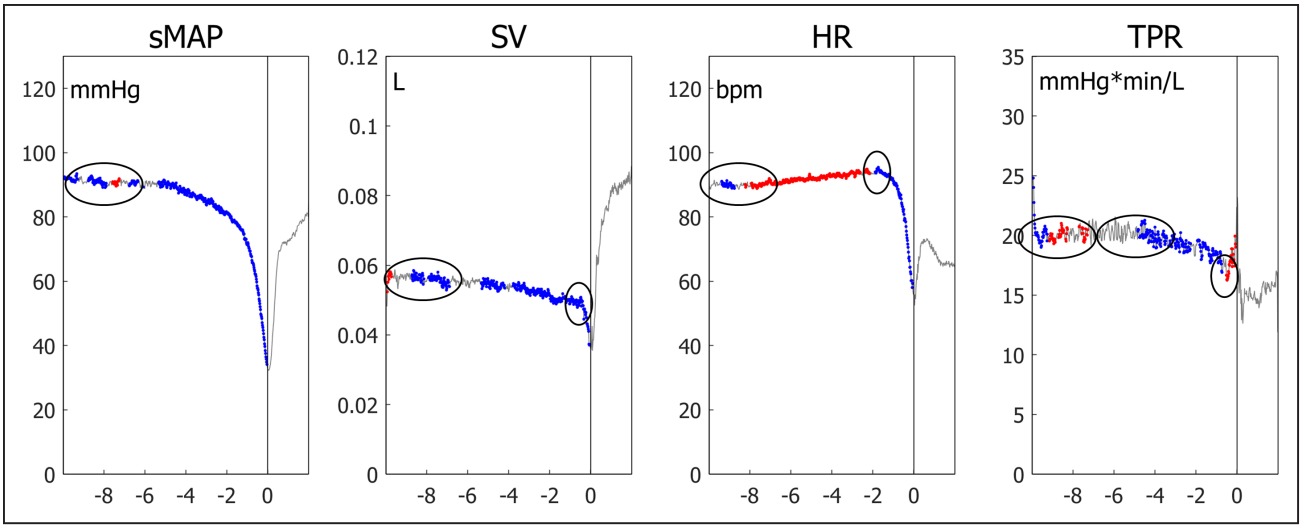

Figure 3. Direction changes to help distinguish stages.
The averaged data of Figure 2 are shown. Lines of best fit were calculated for each sample up to syncope at 600 s, representing data from 40 s before each sample to 40 s after it. Points after syncope were not included. Points at which slopes differed significantly from zero at $P<0.05$ are indicated with red for increases and blue for decreases. Direction changes are indicated with ellipses for periods before syncope. Smoothed mean arterial pressure (sMAP), stroke volume (SV), heart rate (HR), and total peripheral resistance (TPR) all show gradual changes as early as 9 min before syncope. TPR shows a slight decrease around 5 min before syncope. HR shows a decrease 1 to 2 min before syncope, and SV decreases and TPR increases simultaneously 30 seconds before syncope.

At the end of stage I, post hoc tests between the 3 pairs of variables (SV-HR, SV-TPR, and HR-TPR) showed differences for all 3 pairs. All 3 also differed significantly from zero, meaning they all had an effect on BP. SV_{LR} and TPR_{LR} lowered BP, while HR_{LR} increased it. Their relative magnitude is reflected by the median log-ratio values. For SV_{LR}, HR_{LR}, and TPR_{LR}, these were −0.077, 0.035, and −0.022. Note that the value for BP_{LR} of −0.059 was close to the sum of SV, HR, and TPR of −0.064 (the addition is not exact due to missing values). SV_{LR} was over 3 times larger than TPR_{LR}, while HR_{LR}, acting in the opposite direction of SV_{LR} and TPR_{LR}, was only about one-fifth of their sum of −0.99.

The end of stage II showed similar effects, except for HR_{LR}, that did not differ significantly from zero at the end of stage II, so SV_{LR} and TPR_{LR} remained as negative influences on BP. Compared with the end of stage I, the effects of SV_{LR} and TPR_{LR} were larger but more so for TPR_{LR} than for SV_{LR}. This phase shows a transition of HR_{LR} from increasing BP to lowering it.

In the syncope epoch, the number of valid observations dropped sharply because of loss of data. The log ratios SV_{LR} and HR_{LR} were at their lowest. As they did not differ from one another, they strongly decreased BP to a similar degree. TPR_{LR} did not differ from zero, so it had no effect on BP_{LR} in this stage.

At the end of stages IV and V, SV_{LR} differed from HR_{LR} and TPR_{LR}, but HR_{LR} did not differ from TPR_{LR}. All 3 differed from zero; so, after syncope SV_{LR} increased beyond initial tilted values, while HR_{LR} and TPR_{LR} remained lower.

Effects of Nitroglycerin

The effects of nitroglycerin are described in the Data Supplement.[11,12,26–28] In short, SV_{LR} was lower in stages I and II in those who used nitroglycerin than in those who did not. In those who did not use nitroglycerin, SV_{LR} was also lower than baseline, showing that the SV effects were augmented but not caused by nitroglycerin.

The Start and Magnitude of Cardioinhibition

We introduced a novel pragmatic definition of the time course and magnitude of cardioinhibition as pertaining to HR. Cardioinhibition was recognized in 149 (91.4%) of patients. In some remaining cases, HR also decreased, but with such a gradual onset that it could not be measured reliably. The histogram (Figure 4) of the start of HR decrease shows its variability. The median time of cardioinhibition onset was 58.1 seconds before syncope, with a range of 199.6 to 12.1 seconds. At the start of cardioinhibition, median HR was 98 bpm (range 54–146 bpm). Minimum HR around syncope showed a median value of 33 bpm (range 3–90 bpm). The median magnitude from the start of cardioinhibition to minimum HR was 65 bpm (range 16–139 bpm). The median speed of cardioinhibition was 0.99 bpm/s (range 0.13–4.9).

The VASIS 2A criteria of cardioinhibition without asystole were met in 14 cases (8.6%) and the VASIS 2B criteria of asystole >3 seconds in 68; together, these constitute 50.3% of patients. Note that the VASIS criteria only reflect the magnitude of cardioinhibition to

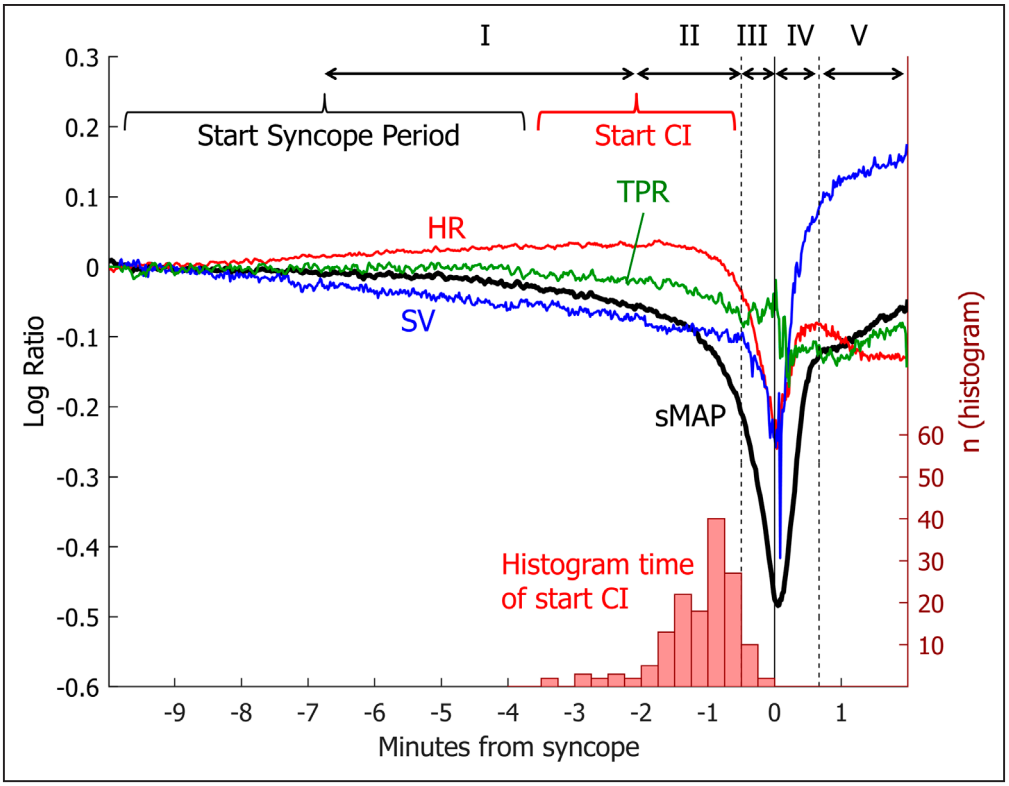

Figure 4. Main parameters as log ratios.
For each variable and individual the mean of the first valid minute of the syncope period was set to a value of 1. Group averages are shown for smoothed mean arterial pressure (sMAP; black), stroke volume (SV; blue), heart rate (HR; red), and total peripheral resistance (TPR; green). At each point in time the logarithm of the sMAP ratio is the sum of the logarithms of the ratios of SV, HR, and TPR, so the SV, HR, and TPR data can be summed to obtain sMAP. However, missing data for TPR around syncope mean that the sum may, however, be lower than the measured sMAP. Stage I started at the onset of the syncope period and ended either at the onset of cardioinhibition or 30 s before syncope. Stage II was present if there was cardioinhibition and started at the onset of cardioinhibition, ending 30 s before syncope. Stage III started 30 s before syncope and ended at syncope; stages IV started at syncope and ended 40 s after it. Stage V ran from 40 s after syncope to the end of the recording 2 min after syncope. The red histogram shows the individually determined start of HR decrease, defining the start of cardioinhibition and of stage II. Stage III started 30 s. before syncope, where SV started a steep decline while TPR started to increase. At syncope, virtually simultaneous with tilt back, all variables change sign, starting stage IV. Stage V starts where the increases of HR and blood pressure (BP) stopped or slowed down. See the text for an interpretation.

classify T-VVS results, whereas we also studied timing of cardioinhibition.

To illustrate the consequences of cardioinhibition, we used its start time as the alignment point to average data across subjects (Figure 6). The resulting averaged HR illustrates how abruptly cardioinhibition started. The decrease of BP accelerated sharply at the start of cardioinhibition, and more so for those with a high than a low speed of cardioinhibition.

We did not investigate whether contractility was affected as a possible other expression of cardioinhibition. A vagal decrease of contractility might cause an additional decrease in BP through a decrease in SV.

Stages IV and V

Tilting back initiated a rapid rise of SV (Figure 2). The increase of SV was not finished at the end of the record, where it approached the initial supine levels. The TPR spike ended abruptly, making way for a stable value similar to the supine level. In stage IV, HR increased at first, until the increase stopped and made way for a limited decrease and stabilization. sMAP showed an early quick partial recovery in stage IV followed by a slower partial recovery in stage V.

DISCUSSION

The novel definition of the onset of cardioinhibition and the logarithm ratio method to assess the determinants of BP changes allowed quantification of the hemodynamic evolution of T-VVS. Most importantly, a gradual decrease in SV was the initial abnormality, starting as early as 9 minutes before syncope in some subjects. While SV fell, HR rose, but not sufficient to prevent a slow decrease of BP. Mean TPR also decreased, but, compared with SV, the TPR decrease started later, had a much smaller effect on BP, and ended earlier, that is, well before the onset of syncope. Cardioinhibition started at a median

Table. Relative effects of SV, HR, and TPR on BP

	Start Record	End-Stage I	End-Stage II	Syncope	End-Stage IV	End-Stage V
Original						
sMAP, mm Hg, median (50th–75th); n	90.2 (82.3 to 101.3); 163	76.8 (67.7 to 85.2); 163	68.2 (60.1 to 78.8); 136	33.2 (25.0 to 40.4); 152	64.6 (55.1 to 74.0); 140	78.7 (68.9 to 90.0); 162
SV, L, median (50th–75th); n	0.060 (0.049 to 0.069); 162	0.047 (0.038 to 0.060); 162	0.048 (0.039 to 0.062); 135	0.034 (0.028 to 0.047); 58	0.068 (0.055 to 0.084); 132	0.083 (0.070 to 0.098); 160
HR, n/min. median (50th–75th); n	85.7 (75.8 to 96.3); 163	95.2 (80.7 to 109.1); 163	90.1 (74.1 to 104.7); 136	47.3 (37.0 to 63.9); 159	70.8 (58.8 to 81.4); 163	61.2 (56.4 to 69.8); 160
TPR, mm Hg, min/L median (50th–75th); n	19.3 (15.0 to 23.1); 162	17.2 (14.5 to 21.7); 162	16.5 (13.6 to 20.5); 135	16.4 (13.3 to 21.4); 49	13.8 (11.6 to 18.2); 130	14.6 (12.5 to 19.7); 160
Ratios						
sMAP	1	0.87 (0.80 to 0.93)	0.77 (0.69 to 0.86)	0.35 (0.28 to 0.44)	0.71 (0.59 to 0.81)	0.87 (0.76 to 0.97)
SV	1	0.84 (0.71 to 0.94)	0.83 (0.71 to 0.96)	0.58 (0.45 to 0.69)	1.13 (0.99 to 1.37)	1.43 (1.23 to 1.60)
HR	1	1.09 (1.00 to 1.18)	1.02 (0.93 to 1.14)	0.57 (0.40 to 0.78)	0.83 (0.71 to 0.95)	0.75 (0.65 to 0.84)
TPR	1	0.95 (0.87 to 1.05)	0.92 (0.81 to 1.01)	0.91 (0.70 to 1.12)	0.78 (0.64 to 0.89)	0.83 (0.70 to 0.99)
Logarithms						
sMAP	0	−0.059 (−0.100 to −0.034)	−0.116 (−0.164 to −0.069)	−0.455 (−0.554 to −0.365)	−0.150 (−0.231 to −0.096)	−0.060 (−0.119 to −0.013)
SV	0	−0.077 (−0.150 to −0.029)	−0.082 (−0.156 to −0.022)	−0.242 (−0.349 to −0.164)	0.051 (−0.011 to 0.135)	0.154 (0.088 to 0.203)
HR	0	0.035 (0.001 to 0.073)	0.006 (−0.033 to 0.056)	−0.257 (−0.42 to −0.124)	−0.082 (−0.161 to −0.022)	−0.127 (−0.189 to −0.076)
TPR	0	−0.021 (−0.064 to 0.021)	−0.039 (−0.095 to 0.001)	−0.040 (−0.161 to 0.049)	−0.109 (−0.193 to −0.049)	−0.080 (−0.158 to −0.008)
Friedman (*P*)	…	<0.0001	<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001
Post hoc	…	SV:HR *P*<0.0001	SV:HR *P*<0.0001	SV:HR 0.90*	SV: HR <0.0001	SV:HR <0.0001
		SV:TPR <0.0001	SV: TPR 0.007*	SV:TPR <0.0001	SV:TPR <0.0001	SV:TPR <0.0001
		HR:TPR <0.0001	HR:TPR <0.0001	HR:TPR <0.0001	HR:TPR 0.02*	HR:TPR 0.93*
Difference from zero (sign test)	…	SV <0.0001	SV <0.0001	SV <0.0001	SV <0.0001	SV <0.0001
		HR <0.0001	HR 0.55*	HR <0.0001	HR <0.0001	HR <0.0001
		TPR <0.001	TPR <0.0001	TPR 0.33*	TPR <0.0001	TPR <0.0001

For each of the 6 epochs that characterize the stages of VVS data are presented for the main parameters sMAP, SV, HR, and TPR. These are presented first as absolute measurements, then as ratios, relative to the first minute of the tilted syncope period, and finally as logarithms of these rations. All are represented as the median value and the 25th and 75th percentile values. Finally, the statistical analysis is presented. The Friedman test data concern whether there are differences between the log ratios of SV, HR, and TPR within an epoch, and the post hoc tests show which pairs of parameters show significant differences. The differences from zero show whether a parameter exerted a statistically significant effect on BP. BP indicates blood pressure; HR, heart rate; sMAP, smoothed mean arterial pressure; SV, stroke volume; TPR, total peripheral resistance; and VVS, vasovagal syncope.

*As most effects were highly significant, *P* value larger than 0.001 are shown.

time of 58 seconds before syncope. At syncope, low SV, and low HR contributed similarly to the very low BP.

The novel methods and the high temporal resolution, large number of subjects and use of averaging as an illustration technique allowed recognition of stages and of as yet underestimated phenomena. Major ones were the abrupt effect of the start of cardioinhibition on BP, the final perisyncopal decrease of SV, and the abrupt and short-lived TPR spike around the time of syncope.

Effects of Tilting Up

The changes of SV, HR, and TPR after tilt-up conformed to expectation, meaning a reduction of venous return is the likely explanation for the fall in SV.

Recognizing Stages

Beginnings and ends of stages were based on changes of direction of sMAP, SV, HR, or TPR. The stages were defined to study events on a group level, not for individual analysis. Individual variability was large, so some persons may have early TPR increases, while others have decreases.

These stages differ from the 4 phases described earlier,[4] using other underlying principles and meant for individual analysis. The most important difference is that we emphasize the start of cardioinhibition as a fundamental as well as a literal turning point. Its profound effects on BP warrant labeling cardioinhibition as the second major pathophysiological event in T-VVS, next to the fall of SV.

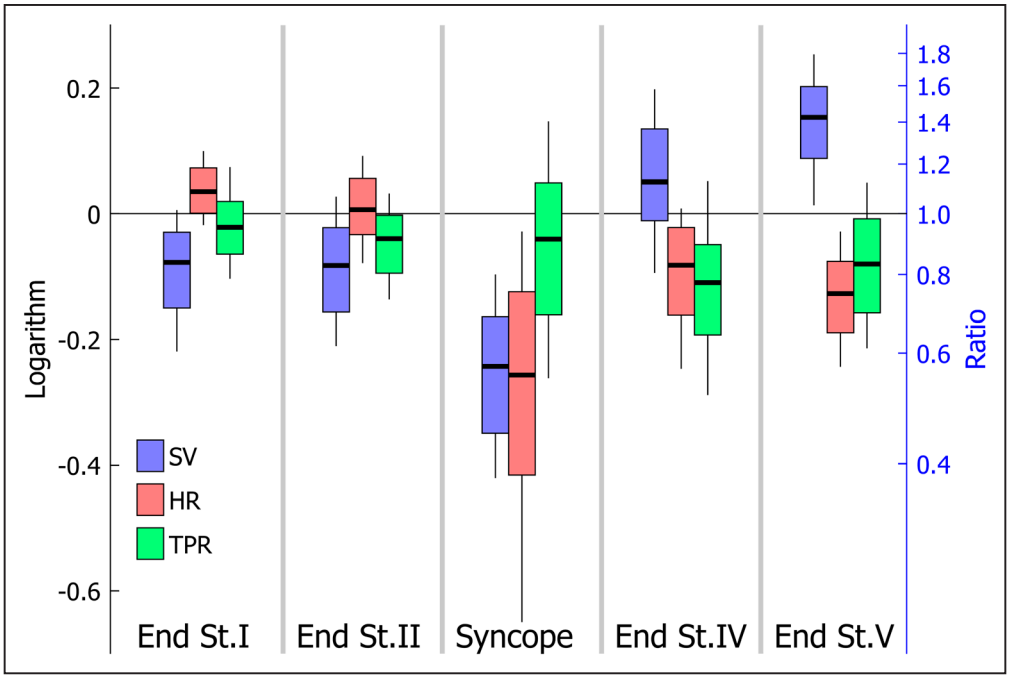

Figure 5. Hemodynamic variables at specific times.
The log ratios of stroke volume (SV), heart rate (HR), and total peripheral resistance (TPR) are shown as box plots for 5 epochs. The vertical line down the middle of each box plot reaches from the 10th to the 90th percentile, while the colored patches denote the 25th, 50th, and 75th percentiles. For the initial period (not shown), log ratios were zero. The dots represent data from individual patients. Corresponding ratios are shown at the right-hand axis. Statistical differences are shown in the Table and discussed in the main text.

From Falling SV to Cardioinhibition

Low SV in T-VVS has been attributed to venous pooling in the abdomen, pelvis, or skeletal muscles.[4,6,14,15] Cardioinhibition, here restricted to a decrease of HR, was present in 91% of subjects. This seemingly high percentage is the result of the chosen definition, but probably also reflects the inclusion criterion of full syncope, as late cardioinhibition may be missed when the test is stopped at presyncope. From its onset, cardioinhibition took only one minute to lower BP as much as SV had done over a much longer time. At the onset of cardioinhibition, the median HR was 98 bpm, which was higher than baseline HR. Hence, cardioinhibition

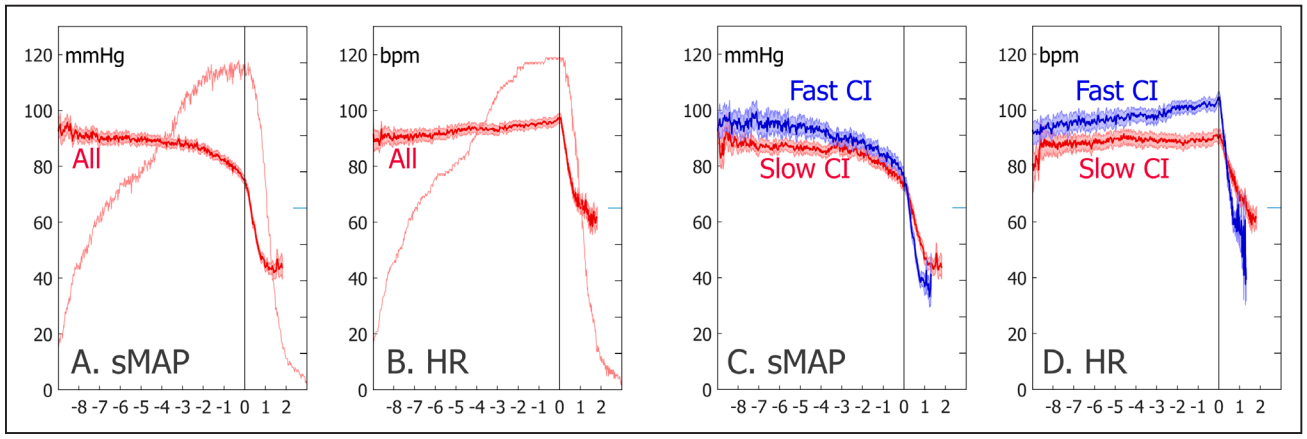

Figure 6. The start of cardioinhibition (CI).
The data of all subjects with syncope and recognized CI (n=149) were shifted in time to align the time of start of CI to zero on the time axis, resulting in averaged smoothed mean arterial pressure (sMAP) in **A** and heart rate (HR) in **B**. As before, the thin line represents the number of valid observations over time. Data after tilting back to the horizontal position were omitted because they represented a different condition than the head-up tilt position in which syncope occurred. This data censure explains the sharp decrease in the number of valid observations shortly after the start of CI. Note the abrupt onset of CI in the HR (**B**) and the kink in sMAP in **A**, where CI accelerated the decrease of blood pressure (BP). This acceleration was explored further by using the speed of CI (ie, the magnitude of HR divided by the time between the start of CI and the onset of syncope). Two groups were made according to the median of the speed of CI: fast CI (blue) and slow CI (red). **C**, Data for sMAP, **D** for HR. The difference in speed of CI is obvious in **D**. **C**, The rate of decrease of BP was very similar for both groups in the 4 min before the start of CI, and both groups then showed an acceleration of BP decrease at the start of CI. This was more pronounced for those with fast CI than with slow CI, illustrating effects on HR on BP.

started as a mere weakening of the initial corrective influence of HR, but even this modest HR decrease was associated with an immediate acceleration of the decrease of BP (Figure 6). About 10 seconds after the onset of cardioinhibition, HR decreased below values just after head-up tilt, so from then on cardioinhibition decreased HR below levels needed for the upright body position.

We hypothesize that cardioinhibition was not directly triggered by gravity but was secondarily evoked by an as yet unidentified hemodynamic consequence of venous pooling.

Given its effects on BP, perhaps preventing the fall of HR at the start of cardioinhibition by pacing might slow the BP decrease, perhaps allowing patients the time to prevent syncope. There is evidence that early pacing could indeed be beneficial.[29,30]

The Final SV Fall and TPR Spike

The final SV fall and TPR spike occur at stages III and IV, when BP is low and changes quickly. We discussed the validity of Modelflow under such conditions in the Data Supplement. We concluded that, as Modelflow in the present study was not calibrated using a reference method, the use of relative values is superior to that of absolute values. The reliability of CO, SV, and hence TPR is unknown when BP is below 60 to 70 mm Hg and when large SV changes occur within 5 seconds. This holds for the period near syncope, that is, stages III and IV.

The abrupt final fall of SV starting 30 seconds before syncope was as unexpected as the simultaneous spike of TPR. Still, the 3 papers we found using Modelflow during actual syncope all recorded a rise in TPR at syncope.[6–8] A TPR increase was also present in patients with a vasovagal response with a stable very low BP[9] and can also be seen in Figure 4 of a review.[4] Hence, the TPR spike is not limited to our study. There is no obvious pathophysiological explanation for the SV fall or the TPR spike. This may be the result of reduced reliability of Modelflow.

The TPR spike suggests a sudden increase in peripheral resistance, contradicting findings of muscle nerve sympathetic activity that point to a cessation of vasoconstrictor impulses in muscles during syncope.[31,32] However, this cessation does not occur in all cases.[33,34] Resolving the discrepancy may require simultaneous assessment of clinical events, Modelflow and nerve traffic in T-VVS, as suggested previously.[33]

Vasodepression and Cardioinhibition

Vasodepression has been used as a descriptive term without a specified mechanism in the VASIS criteria for TTT.[21,35] A narrow interpretation of the term may limit it to a loss of sympathetically mediated arteriolar vasoconstriction, apparent as a decrease of TPR. However, in view of the strong effect of SV, we propose to redefine vasodepression in the context of T-VVS as all BP-lowering mechanisms that are independent from HR. This leaves the VASIS classification intact. This wider concept of vasodepression has been used before.[10] Vasodepression then comprises venous vasodepression, meaning venous pooling apparent as a SV decrease, as well as arterial vasodepression, that is, decreased arteriolar vasoconstriction apparent as a TPR decrease. In pathophysiological calculations, vasodepression can be presented as the product of SV and TPR, just as CO is the product of HR and SV.

The relative importance of the 3 factors cardioinhibition, venous, and arterial vasodepression may well differ in other forms of reflex syncope. For instance, the combination of cardioinhibition with arterial vasodepression would reflect a more classical reflex concept, which may occur in forms with a very short latency after being triggered, such as carotid sinus syncope.

Limitations

The first limitation is that the events of T-VVS depend on the protocol: for instance, the duration of tilting back is known to affect the incidence and duration of asystole.[36] We do not know the extent to which our findings depended on the protocol. Second, the log-ratio method ignores the absolute value of the baseline parameters. Third, doubts may be raised about Modelflow accuracy at the extreme conditions during syncope. We discussed Modelflow limitations in the Data Supplement. [18,37–50] Fourth, we did not assess individual variability nor effects of factors that may affect the patterns described here, such as sex or age. As for nitroglycerin, the similarity of events with and without nitroglycerin has been stressed.[11,12] Fifth, we did not attempt to quantify changes of ventricular contractile state during the course of T-VVS. Finally, we refrained from trying to assign the changes to autonomic or humoral influences.[51]

Conclusions

T-VVS is the result of 3 overlapping processes. The first is a gradual fall of SV, likely due to venous pooling. The second and least important process is a decrease of TPR, the likely result of diminished arteriolar vasoconstriction. The third and final process was cardioinhibition, starting late but gaining strength so quickly that its effect on BP at syncope was similar in size to that of the fall of SV. Before the onset of cardioinhibition, HR had increased, tending to correct the developing hypotension. However, once cardioinhibition was triggered,

HR declined precipitously, causing BP to decline steeply, ending with syncope.

ARTICLE INFORMATION

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Disclosures

D.G. Benditt has been a consultant for Medtronic Inc, and Zoll Corp. M.J. van Houwelingen also acts as a Finapres representative. The other authors report no conflicts.

Supplemental Material

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REFERENCES

1. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martín A, et al; ESC Scientific Document Group. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39:1883–1948. doi: 10.1093/eurheartj/ehy037ssE
2. Sutton R, Brignole M. Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. *Eur Heart J*. 2014;35:2211–2212. doi: 10.1093/eurheartj/ehu255
3. Wieling W, Jardine DL, de Lange FJ, Brignole M, Nielsen HB, Stewart J, Sutton R. Cardiac output and vasodilation in the vasovagal response: an analysis of the classic papers. *Heart Rhythm*. 2016;13:798–805. doi: 10.1016/j.hrthm.2015.11.023
4. Jardine DL, Wieling W, Brignole M, Lenders JWM, Sutton R, Stewart J. The pathophysiology of the vasovagal response. *Heart Rhythm*. 2018;15:921–929. doi: 10.1016/j.hrthm.2017.12.013
5. Stewart JM, Medow MS, Sutton R, Visintainer P, Jardine DL, Wieling W. Mechanisms of vasovagal syncope in the young: reduced systemic vascular resistance versus reduced cardiac output. *J Am Heart Assoc*. 2017;6:e004417. doi: 10.1161/JAHA.116.004417
6. Fucà G, Dinelli M, Suzzani P, Scarfò S, Tassinari F, Alboni P. The venous system is the main determinant of hypotension in patients with vasovagal syncope. *Europace*. 2006;8:839–845. doi: 10.1093/europace/eul095
7. Nigro G, Russo V, Rago A, Iovino M, Arena G, Golino P, Russo MG, Calabrò R. The main determinant of hypotension in nitroglycerine tilt-induced vasovagal syncope. *Pacing Clin Electrophysiol*. 2012;35:739–748. doi: 10.1111/j.1540-8159.2012.03388.x
8. Li H, Liao Y, Han Z, Wang Y, Liu P, Zhang C, Tang C, Du J, Jin H. Head-up tilt test provokes dynamic alterations in total peripheral resistance and cardiac output in children with vasovagal syncope. *Acta Paediatr*. 2018;107:1786–1791. doi: 10.1111/apa.14342
9. Heyer GL. Clinical features of prolonged tilt-induced hypotension with an apparent vasovagal mechanism, but without syncope. *Auton Neurosci*. 2019;218:87–93. doi: 10.1016/j.autneu.2019.03.001
10. Saal DP, Thijs RD, van Zwet EW, Bootsma M, Brignole M, Benditt DG, van Dijk JG. Temporal relationship of asystole to onset of transient loss of consciousness in tilt-induced reflex syncope. *JACC Clin Electrophysiol*. 2017;3:1592–1598. doi: 10.1016/j.jacep.2017.07.006
11. Gisolf J, Westerhof BE, van Dijk N, Wesseling KH, Wieling W, Karemaker JM. Sublingual nitroglycerin used in routine tilt testing provokes a cardiac output-mediated vasovagal response. *J Am Coll Cardiol*. 2004;44:588–593. doi: 10.1016/j.jacc.2004.04.038
12. Verheyden B, Liu J, van Dijk N, Westerhof BE, Reybrouck T, Aubert AE, Wieling W. Steep fall in cardiac output is main determinant of hypotension during drug-free and nitroglycerine-induced orthostatic vasovagal syncope. *Heart Rhythm*. 2008;5:1695–1701. doi: 10.1016/j.hrthm.2008.09.003
13. Fu Q, Verheyden B, Wieling W, Levine BD. Cardiac output and sympathetic vasoconstrictor responses during upright tilt to presyncope in healthy humans. *J Physiol*. 2012;590:1839–1848. doi: 10.1113/jphysiol.2011.224998
14. Jardine DL. Vasovagal syncope: new physiologic insights. *Cardiol Clin*. 2013;31:75–87. doi: 10.1016/j.ccl.2012.10.010
15. Stewart JM, McLeod KJ, Sanyal S, Herzberg G, Montgomery LD. Relation of postural vasovagal syncope to splanchnic hypervolemia in adolescents. *Circulation*. 2004;110:2575–2581. doi: 10.1161/01.CIR.0000145543.88293.21
16. van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. *Clin Sci (Lond)*. 1991;81:575–586. doi: 10.1042/cs0810575
17. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol (1985)*. 1993;74:2566–2573. doi: 10.1152/jappl.1993.74.5.2566
18. Jellema WT, Wesseling KH, Groeneveld AB, Stoutenbeek CP, Thijs LG, van Lieshout JJ. Continuous cardiac output in septic shock by simulating a model of the aortic input impedance: a comparison with bolus injection thermodilution. *Anesthesiology*. 1999;90:1317–1328. doi: 10.1097/00000542-199905000-00016
19. van Dijk JG, Thijs RD, van Zwet E, Tannemaat MR, van Niekerk J, Benditt DG, Wieling W. The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes. *Brain*. 2014;137:576–585. doi: 10.1093/brain/awt332
20. Shmuely S, Bauer PR, van Zwet EW, van Dijk JG, Thijs RD. Differentiating motor phenomena in tilt-induced syncope and convulsive seizures. *Neurology*. 2018;90:e1339–e1346. doi: 10.1212/WNL.0000000000005301
21. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, Bartoli P, Sutton R. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study. *Europace*. 2000;2:66–76. doi: 10.1053/eupc.1999.0064
22. Sahota IS, Maxey C, Pournazari P, Sheldon RS. Clusters, gaps, and randomness: vasovagal syncope recurrence patterns. *JACC Clin Electrophysiol*. 2017;3:1046–1053. doi: 10.1016/j.jacep.2017.02.008
23. Sheldon R, Hersi A, Ritchie D, Koshman ML, Rose S. Syncope and structural heart disease: historical criteria for vasovagal syncope and ventricular tachycardia. *J Cardiovasc Electrophysiol*. 2010;21:1358–1364. doi: 10.1111/j.1540-8167.2010.01835.x
24. Sheldon RS, Sheldon AG, Connolly SJ, Morillo CA, Klingenheben T, Krahn AD, Koshman ML, Ritchie D; Investigators of the Syncope Symptom Study and the Prevention of Syncope Trial. Age of first faint in patients with vasovagal syncope. *J Cardiovasc Electrophysiol*. 2006;17:49–54. doi: 10.1111/j.1540-8167.2005.00267.x
25. Sumner GL, Rose MS, Koshman ML, Ritchie D, Sheldon RS; Prevention of Syncope Trial Investigators. Recent history of vasovagal syncope in a young, referral-based population is a stronger predictor of recurrent syncope than lifetime syncope burden. *J Cardiovasc Electrophysiol*. 2010;21:1375–1380. doi: 10.1111/j.1540-8167.2010.01848.x
26. Divakaran S, Loscalzo J. The role of nitroglycerin and other nitrogen oxides in cardiovascular therapeutics. *J Am Coll Cardiol*. 2017;70:2393–2410. doi: 10.1016/j.jacc.2017.09.1064

27. Parker JO, West RO, Di Giorgi S. The effect of nitroglycerin on coronary blood flow and the hemodynamic response to exercise in coronary artery disease. *Am J Cardiol*. 1971;27:59–65. doi: 10.1016/0002-9149(71)90083-x
28. Ghariq M, Thijs RD, Bek LM, van Zwet EW, Benditt DG, van Dijk JG. A higher proportion of men than of women fainted in the phase without nitroglycerin in tilt-induced vasovagal syncope [published online January 18, 2020]. *Clin Auton Res*. doi: 10.1007/s10286-020-00666-5
29. Baron-Esquivias G, Morillo CA, Moya-Mitjans A, Martinez-Alday J, Ruiz-Granell R, Lacunza-Ruiz J, Garcia-Civera R, Gutierrez-Carretero E, Romero-Garrido R. Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope: the SPAIN study. *J Am Coll Cardiol*. 2017;70:1720–1728. doi: 10.1016/j.jacc.2017.08.026
30. Ruzieh M, Ghahramani M, Nudy M, Naccarelli GV, Mandrola J, Grubb BP, Foy AJ. The benefit of closed loop stimulation in patients with cardioinhibitory vasovagal syncope confirmed by head-up tilt table testing: a systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2019;55:105–113. doi: 10.1007/s10840-019-00531-0
31. Morillo CA, Eckberg DL, Ellenbogen KA, Beightol LA, Hoag JB, Tahvanainen KU, Kuusela TA, Diedrich AM. Vagal and sympathetic mechanisms in patients with orthostatic vasovagal syncope. *Circulation*. 1997;96:2509–2513. doi: 10.1161/01.cir.96.8.2509
32. Jardine DL, Ikram H, Frampton CM, Frethey R, Bennett SI, Crozier IG. Autonomic control of vasovagal syncope. *Am J Physiol*. 1998;274:H2110–H2115. doi: 10.1152/ajpheart.1998.274.6.H2110
33. Vaddadi G, Esler MD, Dawood T, Lambert E. Persistence of muscle sympathetic nerve activity during vasovagal syncope. *Eur Heart J*. 2010;31:2027–2033. doi: 10.1093/eurheartj/ehq071
34. Iwase S, Nishimura N, Mano T. Role of sympathetic nerve activity in the process of fainting. *Front Physiol*. 2014;5:343. doi: 10.3389/fphys.2014.00343
35. Sutton R, Petersen M, Brignole M, et al. Proposed classification for tilt induced vasovagal syncope. *Eur J Cardiac Pacing Electrophysiol*.1992;2:180–183.
36. Zyśko D, Fedorowski A, Nilsson D, Rudnicki J, Gajek J, Melander O, Sutton R. Tilt testing results are influenced by tilt protocol. *Europace*. 2016;18:1108–1112. doi: 10.1093/europace/euv262
37. Friedman DB, Jensen FB, Matzen S, Secher NH. Non-invasive blood pressure monitoring during head-up tilt using the Penaz principle. *Acta Anaesthesiol Scand*. 1990;34:519–522. doi: 10.1111/j.1399-6576.1990.tb03137.x
38. Petersen ME, Williams TR, Sutton R. A comparison of non-invasive continuous finger blood pressure measurement (Finapres) with intra-arterial pressure during prolonged head-up tilt. *Eur Heart J*. 1995;16:1641–1654.
39. Harms MP, Wesseling KH, Pott F, Jenstrup M, Van Goudoever J, Secher NH, Van Lieshout JJ. Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clin Sci (Lond)*. 1999;97:291–301.
40. Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth*. 2001;87:212–222. doi: 10.1093/bja/87.2.212
41. Lador F, Hervé P, Bringard A, Günther S, Garcia G, Savale L, Ferretti G, Soccal PM, Chemla D, Humbert M, et al. Non-invasive determination of cardiac output in pre-capillary pulmonary hypertension. *PLoS One*. 2015;10:e0134221. doi: 10.1371/journal.pone.0134221
42. de Wilde RB, Schreuder JJ, van den Berg PC, Jansen JR. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia*. 2007;62:760–768. doi: 10.1111/j.1365-2044.2007.05135.x
43. de Wilde RB, Geerts BF, Cui J, van den Berg PC, Jansen JR. Performance of three minimally invasive cardiac output monitoring systems. *Anaesthesia*. 2009;64:762–769. doi: 10.1111/j.1365-2044.2009.05934.x
44. Bogert LW, van Lieshout JJ. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Exp Physiol*. 2005;90:437–446. doi: 10.1113/expphysiol.2005.030262
45. van Lieshout JJ, Toska K, van Lieshout EJ, Eriksen M, Walløe L, Wesseling KH. Beat-to-beat noninvasive stroke volume from arterial pressure and Doppler ultrasound. *Eur J Appl Physiol*. 2003;90:131–137. doi: 10.1007/s00421-003-0901-8
46. Sugawara J, Tanabe T, Miyachi M, Yamamoto K, Takahashi K, Iemitsu M, Otsuki T, Homma S, Maeda S, Ajisaka R, et al. Non-invasive assessment of cardiac output during exercise in healthy young humans: comparison between Modelflow method and Doppler echocardiography method. *Acta Physiol Scand*. 2003;179:361–366. doi: 10.1046/j.0001-6772.2003.01211.x
47. Dyson KS, Shoemaker JK, Arbeille P, Hughson RL. Modelflow estimates of cardiac output compared with Doppler ultrasound during acute changes in vascular resistance in women. *Exp Physiol*. 2010;95:561–568. doi: 10.1113/expphysiol.2009.050815
48. Schlöglhofer T, Gilly H, Schima H. Semi-invasive measurement of cardiac output based on pulse contour: a review and analysis. *Can J Anaesth*. 2014;61:452–479. doi: 10.1007/s12630-014-0135-8
49. Critchley LA, Lee A, Ho AM. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. *Anesth Analg*. 2010;111:1180–1192. doi: 10.1213/ANE.0b013e3181f08a5b
50. Gibbons TD, Zuj KA, Peterson SD, Hughson RL. Comparison of pulse contour, aortic Doppler ultrasound and bioelectrical impedance estimates of stroke volume during rapid changes in blood pressure. *Exp Physiol*. 2019;104:368–378. doi: 10.1113/EP087240
51. Torabi P, Ricci F, Hamrefors V, Melander O, Sutton R, Benditt DG, Fedorowski A. Impact of cardiovascular neurohormones on onset of vasovagal syncope induced by head-up tilt. *J Am Heart Assoc*. 2019;8:e012559. doi: 10.1161/JAHA.119.012559