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CLINICAL ELECTROPHYSIOLOGY - SYNCOPE

Influence of Age on Magnitude and Timing of Vasodepression and Cardioinhibition in Tilt-Induced Vasovagal Syncope

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ABSTRACT

BACKGROUND Cardioinhibition may diminish with age, but the changing balance of cardioinhibition and vasodepression with age has not been quantified, leaving the mechanism of vasovagal syncope (VVS) in old age unclear.

OBJECTIVES This study sought to quantify age-related changes of vasodepression and cardioinhibition in tilt-induced VVS.

METHODS We studied 163 cases of tilt-induced VVS, evoked using the Italian protocol with blood pressure, heart rate, and video-electroencephalographic monitoring. Presyncope was excluded. Cardioinhibition was defined as the heart rate decrease before syncope; asystolic pauses (≥3 seconds) were divided into early and late asystole, ie, beginning early enough to or too late to be the major cause of loss of consciousness. The log-ratio method was used to quantify contributions of cardioinhibition and vasodepression, assessed in 2 10-second periods before the onset of cardioinhibition and before syncope.

RESULTS With increasing age, cardioinhibition decreased, ie, heart rate decreased less and more slowly near syncope ($P < 0.0001$), while vasodepression increased. Asystolic pauses were less frequent in the older one-half of the group than the younger one-half (26% vs 57%; $P < 0.00001$), but when it did, late asystole occurred more often (58% vs 15%; $P < 0.001$).

CONCLUSIONS The shift toward less cardioinhibition and more vasodepression with increased age probably reflects a physiological shift in circulatory control. The weakening of cardioinhibition with age may detract from the efficacy of pacing in older patients with VVS. Cardioinhibition-vasodepression balance should be considered in pacing decisions in older subjects with VVS. (J Am Coll Cardiol EP 2022;8:997-1009) © 2022 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure

HR = heart rate

LOC = loss of consciousness

LR = log-ratio

NTG = nitroglycerin

SV = stroke volume

TPR = total peripheral resistance

t-VVS = tilt-induced vasovagal syncope

VVS = vasovagal syncope

Loss of consciousness (LOC) in vasovagal syncope (VVS) is caused by low arterial blood pressure (BP), itself the result of a variable combination of vasodepression and cardioinhibition. We define vasodepression as all mechanisms in reflex syncope that decrease BP independent of heart rate (HR).[1,2] Vasodepression in tilt-induced vasovagal syncope (t-VVS) consists of a decrease in stroke volume (SV), probably caused by venous pooling, and a later and less important decrease of total peripheral resistance (TPR), which is the result of reduced arteriolar vasoconstriction.[1] We defined cardioinhibition as the sustained decrease of HR starting about 1 minute before syncope and ending at syncope and "asystolic pauses" as lasting ≥3 seconds.[1]

TABLE 1 Group Characteristics According to Age

	All (N = 163)	Younger (≤45 Years) (n = 82)	Older (>45 Years) (n = 81)	*P* Value
Age, y	45 (25-62)	25.5 (18.0-36.5)	62 (54.5-68.0)	Not tested
Male:female	75:88	29:53	46:35	0.006
Number of current spells	3 (1-8)	4 (1.25-13.75)	3 (1-5)	0.085
Weeks since last syncope	12 (4-20)	10 (3-18)	12 (4.0-22.5)	0.25
Syncope before 35 y				
Yes	99	70	29	<0.00001[a]
No	39	2	37	
Unknown	25	10	15	
Age at first syncope, y	16 (12.00-46.25)	13 (12-18)	46 (12-57)	<0.001
Reason for TTT				
VVS	134	71	63	
Not-VVS	20	7	13	0.133[b]
Other reflex syncope	6	0	6	
iOH or cOH	7	3	4	
Cardiac syncope	1	0	1	
Epilepsy	4	2	2	
PPS	2	2	0	
Other/not noted	9	4	5	
Drug use				
None	48	30	18	0.0022[a]
Antihypertensive	22	3	19	
May cause hypotension	8	4	4	
Other	57	29	28	
Unknown	28	16	12	
History				
None	42	30	12	0.00015[a]
Cardiac	14	4	10	
Hypertension	17	2	15	
Other	71	35	36	
Unknown	19	11	8	

Values are median (IQR) or n. *P* values represent the Mann-Whitney *U* test or the chi-square test.These results concern the 163 cases included in the study, divided in 2 age groups by the median age of 45 years. "Current spells" describes the number of syncopal spells in the period for which the patient sought medical attention. The "reason for TTT" states the first mentioned condition on the TTT referral form. [a]Chi-square test with exclusion of "unknown" category. [b]Chi-square test comparing VVS to not-VVS.

cOH = classical orthostatic hypotension; iOH = initial orthostatic hypotension; PPS = psychogenic pseudosyncope; TTT = tilt table test; VVS = vasovagal syncope.

The balance of vasodepression and cardioinhibition varies not only between syncopal events, as reflected by the Vasovagal Syncope International Study VVS classification,[3,4] but also within events. For instance, in our previous report[1] on the pathophysiology of VVS, vasodepression and cardioinhibition had similar effects on BP at the time of syncope, but this had taken vasodepression up to 9 minutes and cardioinhibition only about 1 minute. The variable balance between cardioinhibition and vasodepression was also apparent in the timing of asystolic pauses: "late asystole," ie, an asystolic pause starting 3 seconds before the onset of LOC or later, occurred in one-third of all subjects with asystolic pauses.[2] Late asystole could not be the major cause of LOC, suggesting that pacing in cases with late asystole might not prevent syncope.

The effects of age on the vasodepression-cardioinhibition balance are largely unknown, although fewer asystolic pauses with increasing age have been described in t-VVS.[5-9] Such assessments may be unreliable if patients were tilted back at presyncope, because that may abort cardioinhibition.[1] The presence of asystolic pauses in VVS is relevant because they predicted pacing success in patients older than 40 years of age.[10,11] It is unknown whether the occurrence of late asystole depends on age. Because present guidelines restrict pacing for VVS to older subjects,[12,13] both the incidence of asystole and of late asystole may be pertinent in older patients.

The goals of the present study were, first, to evaluate effects of age on cardioinhibition in t-VVS, including whether the occurrence of asystolic pauses and of late asystole depended on age and, second, to quantify the contributions of vasodepression and cardioinhibition to decreasing BP in t-VVS using the new log-ratio method.

METHODS

DATA AVAILABILITY. The data supporting the findings of this study are available from the corresponding author on reasonable request.

PATIENT AND TILT TABLE TEST DATA. Data acquisition and processing details have been published.[1] In short, data of 163 of 2,189 successive tilt tests from the Syncope Unit of Leiden University Medical Centre were analyzed retrospectively.[1,14] A modified Italian protocol consisted of 10 minutes of supine rest, 20 minutes of head-up tilt, 0.4 mg nitroglycerin

TABLE 2 LOC and Asystole According to Groups by Age

	Younger vs Older				Early vs Late Asystole			
	All (N = 163)	Younger (n = 82)	Older (n = 81)	*P* Value	All (N = 68)	Early (n = 44)	Late (n = 24)	*P* Value
Age, y	45 (25-62)	25.5 (18.0-36.5)	62 (54.5-68.0)	Not tested	35 (20-51)	25 (19-41)	55 (40-62)	<0.0001
Duration LOC, s	19 (14-27)	19 (13-24)	19 (15-30)	0.17	25 (17-32)	21 (16-29)	28 (23-36)	<0.05
Asystole, with:without	68:95 (42:58)	47:35 (57:43)	21:60 (26:74)	<0.00001	68:0 (100:0)	44:0 (100:0)	24:0 (100:0)	Not tested
Latency of LOC, s	519 (322-775)	490 (289-720)	548 (364-850)	0.077	519 (322-775)	467 (273-698)	546 (461-815)	0.084
Interval asystole to LOC, s	−5 (−7 to −0.5)	−6 (−8 to −4)	0 (−5.3 to 4.3)	<0.0001	−5 (−7 to −0.5)	−6.5 (−8 to −54)	2.5 (−1 to 4)	<0.0001

Values are median (IQR) or n (%). *P* values represent the Mann-Whitney *U* test or chi-square test. Statistical tests were not performed when a characteristic was used as definition for a group. The "all (n = 163)" portion shows group characteristics of the entire study group and of the 2 subgroups obtained by dividing the group into younger and older subgroups along the median age. The "all (n = 68)" portion shows a subgroup of those with asystole, divided into a group with early and with late asystole. Those in whom asystole started 3 seconds before the onset of LOC were classified as having "late asystole;" those in whom asystole started before that had "early asystole."

LOC = loss of consciousness.

(NTG) sublingually, and a further 20 minutes of tilt, unless syncope intervened. Measurements in all cases comprised continuous BP, electrocardiography, and video-electroencephalography. Additional clinical data focused on VVS, drug use, and medical history.

The clinical inclusion criterion was probable VVS, based on prodromal nausea, pallor or sweating, with triggers including pain, fear, or standing. The 4 tilt inclusion criteria were an accelerating decrease of BP, syncopal electroencephalographic changes, clinical LOC through video, and recognition by patients or eyewitnesses.[1,15] Exclusion criteria were presyncope without syncope, abnormal tilt responses other than VVS, pacemaker activity, and artifacts. BP and HR were measured and beat-to-beat estimates of SV and TPR were derived using Modelflow (Finapres Medical Systems, the Netherlands). Further numerical analyses were performed with MATLAB (MathWorks). BP, HR, SV, and TPR were resampled at 1 second, resulting in a continuous time series. The start and end of asystole was measured from the electrocardiograph, and LOC was assessed using video recording.[1] Their times were expressed in seconds relative to the start of LOC.

Individual informed consent was not required by Dutch law at the time, provided the data were obtained in the context of patient care, which was the case. The study was approved by the medical ethics committee of the Leiden University Medical Centre.

EFFECTS OF AGE ON VARIOUS EXPRESSIONS OF CARDIOINHIBITION. To illustrate hemodynamic changes over time, we formed averages of mean arterial pressure, HR, SV, and TPR,[1] separately for younger and older patients, divided by median age.

As in our previous report,[1] we defined the onset of cardioinhibition for each individual patient as the time when HR started to decrease toward syncope. We reviewed (J.G.v.D., I.A.v.R.) the end of cardioinhibition as the "minimum HR" around syncope to negate some artifacts. The HR difference between onset and end of cardioinhibition was the "magnitude of cardioinhibition" in beats/min, and the time between the 2 events was the "duration of cardioinhibition" in seconds. Dividing magnitude by duration yielded the "rate of HR decrease," in beats/min/s.

We counted patients with asystolic pauses (≥3 seconds). The onset and duration of asystolic pauses and of LOC were expressed as whole seconds. "Late asystole" was defined as asystole starting 3 seconds before the onset of LOC or later.[2] All other asystolic pauses were labeled "early asystole." The correlation between the onset of asystole and of LOC was studied, and individual results were plotted to count cases of early and late asystole in relation to age. In this regard we considered inclusion of NTG cases. In a previous study on the relative time of asystole and LOC,[2] tests in which NTG had been used were excluded. A later study[1] found that NTG acted for a short period, suggesting that NTG might not affect cardioinhibition, which is a relatively late occurrence. Because NTG did not affect cardioinhibition parameters (see the Supplemental Appendix), we included NTG cases.

RELATIVE CONTRIBUTIONS OF CARDIOINHIBITION AND VASODEPRESSION. We used the "log-ratio method" to quantify cardioinhibition and vasodepression, as explained previously.[1] We first calculated baseline values of BP, HR, SV, and TPR for each patient as the mean of a 1-minute period after head-up tilt. Later values were expressed as ratios of the baseline. These ratios reflect the physiological relation $BP = HR \times SV \times TPR$.[1] Their log-ratio ($_{LR}$) are additive: $BP_{LR} = HR_{LR} + SV_{LR} + TPR_{LR}$, meaning that BP_{LR} at any point in time is the sum of the other 3 log-ratios. We regarded vasodepression as the BP-decreasing effect of SV_{LR} and TPR_{LR}; SV decreases

TABLE 3 Hemodynamic Data

	Younger vs Older					
	Period 1			Period 2		
	Younger	Older	*P* Value	Younger	Older	*P* Value
BP	−0.061 (n = 82) (−0.086 to −0.035)	−0.097 (n = 67) (−0.145 to −0.058)	<0.0001	0.412 (n = 79) (−0.458 to −0.35)	−0.413 (n = 81) (−0.494 to −0.331)	0.84
Vasomotor BP component (includes vasodepression)	−0.108 (n = 82) (−0.165 to −0.062)	−0.131 (n = 67) (−0.193 to −0.085)	0.046	−0.129 (n = 77) (−0.209 to −0.018)	−0.23 (n = 81) (−0.37 to −0.117)	<0.0001
Chronotropic BP component (includes cardioinhibition)	0.048 (n = 82) (0.01 to 0.092)	0.039 (n = 67) (−0.005 to 0.082)	0.28	−0.268 (n = 80) (−0.391 to −0.188)	−0.177 (n = 81) (−0.28 to −0.05)	<0.0001
SV	−0.089 (n = 80) (−0.186 to −0.027)	−0.085 (n = 65) (−0.152 to −0.036)	0.70	−0.21 (n = 41) (−0.301 to −0.144)	−0.176 (n = 64) (−0.287 to −0.122)	0.35
TPR	−0.02 (n = 80) (−0.068 to 0.024)	−0.058 (n = 65) (−0.103 to −0.015)	<0.01	0.007 (n = 34) (−0.119 to 0.064)	−0.077 (n = 47) (−0.146 to 0.008)	<0.05

TABLE 3 Continued

	Early vs Late Asystole					
	Period 1			Period 2		
	Early	Late	*P* Value	Early	Late	*P* Value
BP	−0.051 (n = 44) (−0.079 to −0.033)	0.105 (n = 24) (−0.136 to −0.047)	<0.01	−0.419 (n = 44) (−0.483 to −0.371)	−0.419 (n = 24) (−0.512 to −0.343)	0.69
Vasomotor BP component (includes vasodepression)	−0.09 (n = 44) (−0.141 to −0.05)	−0.129 (n = 24) (−0.192 to −0.076)	0.06	−0.02 (n = 40) (−0.135 to 0.082)	−0.169 (n = 24) (−0.231 to −0.07)	<0.005
Chronotropic BP component (includes cardioinhibition)	0.044 (n = 44) (0.008 to 0.074)	0.033 (n = 24) (0.002 to 0.093)	0.76	−0.337 (n = 42) (−0.462 to −0.278)	−0.224 (n = 24) (−0.339 to −0.169)	<0.0005
SV	−0.062 (n = 44) (−0.116 to −0.011)	−0.111 (n = 24) (−0.184 to −0.019)	0.12	−0.1 (n = 19) (0.211 to 0.022)	−0.173 (n = 10) (−0.31 to −0.129)	0.10
TPR	−0.034 (n = 44) (−0.075 to 0.015)	−0.032 (n = 24) (−0.07 to 0.001)	0.89	−0.002 (n = 17) (−0.119 to 0.096)	−0.024 (n = 13) (−0.132 to 0.02)	0.43

Values are median (IQR) of log-ratios. *P* values refer to the Mann-Whitney *U* test. Numbers of valid observations are stated.Comparisons are made between older and younger patients and between early and late asystole. See Table 1 or the main text for group definitions. Period 1 represents the 10 seconds before the individual onset of cardioinhibition, and period 2 the 10 seconds before syncope. Period 1 could not be defined for 14 patients in the older group because they were lacking a recognizable onset of cardioinhibition.For period 1, the age comparison showed that in the older group BP was lower, that chronotropic and vasomotor components did not differ, and that TPR was lower. In period 2, BP did not differ between groups, but the chronotropic component was weaker in the older group while their vasomotor component was stronger, because of lower TPR. The early versus late asystole comparison for period 1 showed that only BP differed, with a lower value for the late asystole group. In period 2, BP did not differ, but the vasomotor component was lower in the late asystole group, while the chronotropic component was lower in the early asystole group.

BP = blood pressure; SV = stroke volume; TPR = total peripheral resistance.

represented venous pooling, and TPR decreases indicated arterial vasoconstriction status: $VD_{LR} = SV_{LR} + TPR_{LR}$. Hence, $BP_{LR} = HR_{LR} + VD_{LR}$; this equation describes BP decreases as the sum of vasodepression and cardioinhibition. Because many values for SV_{LR} or TPR_{LR} were missing close to syncope, we also calculated VD_{LR} by subtracting HR_{LR} from BP_{LR}: $VD_{LR} = BP_{LR} - HR_{LR}$.

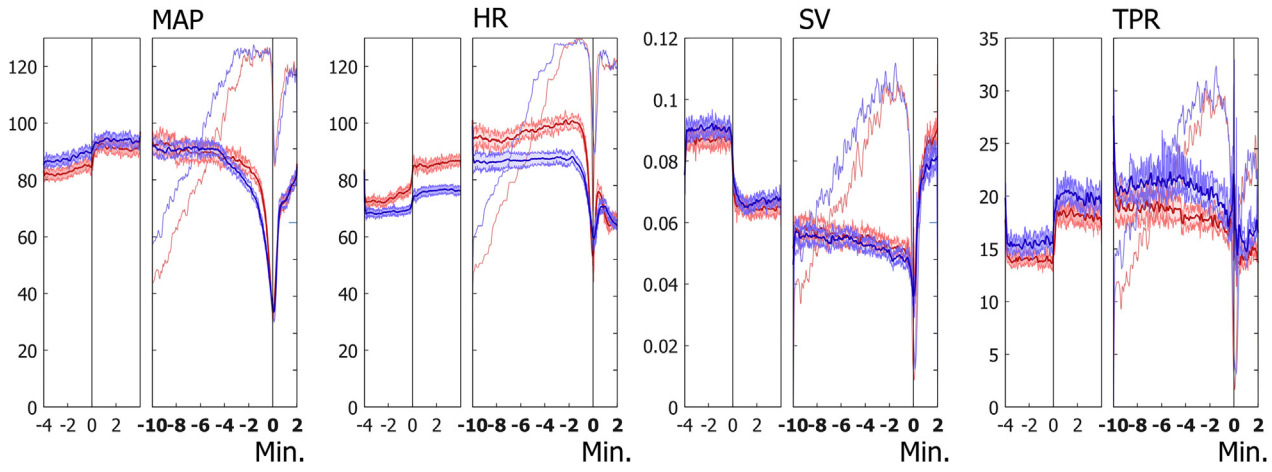
These equations describe BP increases as well as decreases, whereas the terms "vasodepression" and "cardioinhibition" only imply BP decreases. To include BP increases and decreases, we use "vasomotor BP component" for SV_{LR} and TPR_{LR}, and "chronotropic BP component" for HR_{LR}.

To quantify changes of these components, we chose 2 10-second periods and calculated mean values per parameter per patient per period. The first ended at the individual start of cardioinhibition to represent the state in which BP had decreased because of vasodepression, with partial correction by increased HR.[1]

Because the start of cardioinhibition could not be identified in 14 patients,[1] we could not define a first period (period 1) in these patients. The second period (period 2) ended at syncope and represents both vasodepression and cardioinhibition.

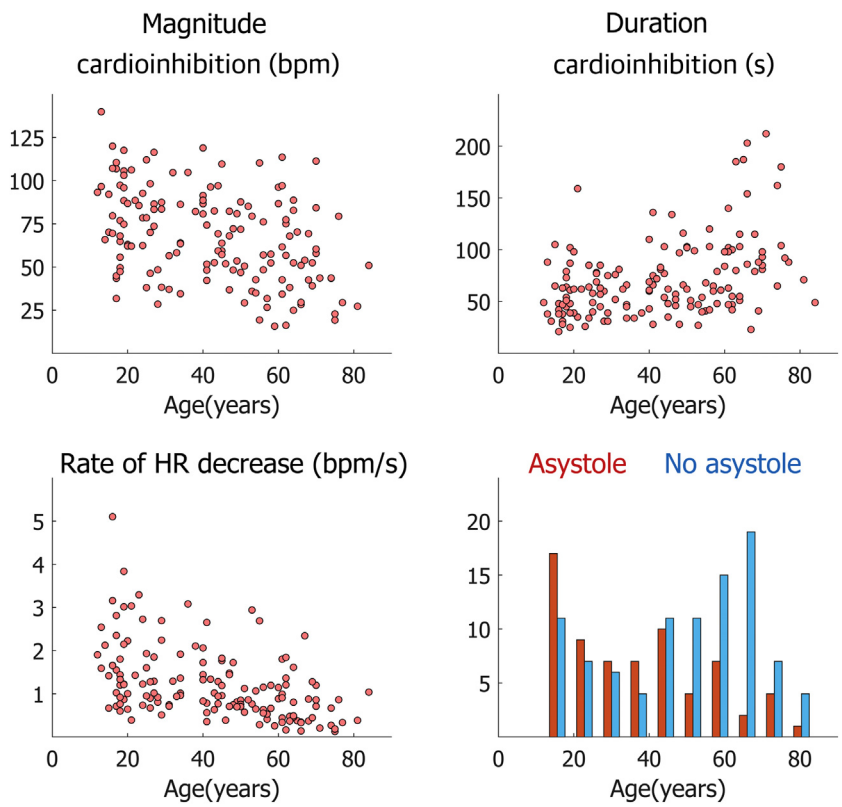
The effect of age on these changes was assessed, first, through correlation of cardioinhibition and vasodepression with age and, second, by assessing differences between the younger one-half and older one-half of the study group, divided by the median age. The time course of cardioinhibition and vasodepression for younger and older groups was illustrated by showing group means of cardioinhibition and vasodepression per second. The same was done for groups of early and late asystole.

FIGURE 1 **Hemodynamics and Age**



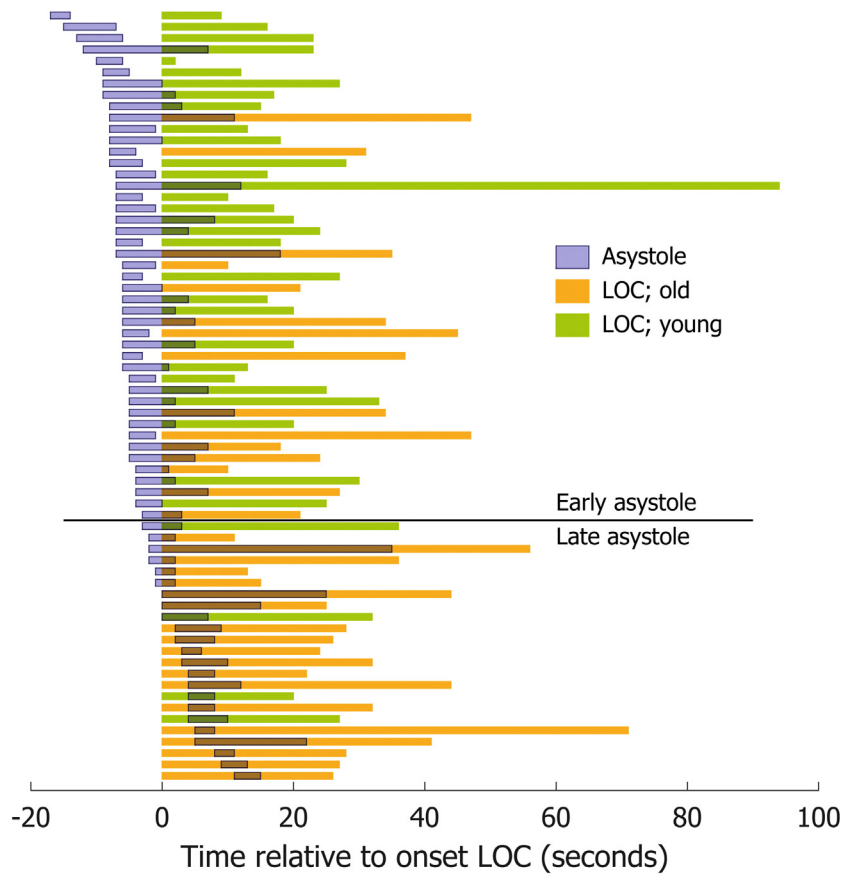
Average values and 1 SE are shown for mean arterial blood pressure (MAP), heart rate (HR), stroke volume (SV), and total peripheral resistance (TPR), for younger **(red)** and older **(blue)** halves of the group. **Left panels** show an 8-minute period, with time 0 indicating head-up tilt. **Right panels** show 10 minutes before and 2 minutes after syncope. Time 0 here denotes the start of loss of consciousness. Units are mm Hg for MAP, beats/min for HR, liters for SV, and mm Hg · min · L^{-1} for TPR. **Thin lines** indicate percentages of valid measurements, with 100% at the top of the right axis. Before head-up tilt, blood pressure and SV were higher and HR was lower in older subjects. Just before syncope, HR decreased faster and further in younger patients.

FIGURE 2 **Relations of Cardioinhibition With Age**



The magnitude of cardioinhibition ($\rho = -0.40$; $P < 0.0001$) **(upper left)** and the rate of heart rate (HR) decrease ($\rho = 0.40$; $P < 0.0001$) **(lower left)** both decline with age, while duration increases ($\rho = 0.40$; $P < 0.0001$) **(upper right).** A histogram of age versus presence or absence of asystole **(lower right)** shows that patients with asystolic pauses were generally younger than those without. beats/min = beats/min.

FIGURE 3 **Onsets of Asystole and of LOC**



Each set of **horizontal bars** represents 1 patient. The **green or orange bars** represent the duration of loss of consciousness (LOC) for younger and older patients. **Blue bars** denote asystolic pauses. Results were sorted by the difference between the onsets of asystole and of LOC. The **horizontal line** distinguishes early and late asystolic pauses.

STATISTICAL ANALYSIS. We used nonparametric methods because some distributions were skewed or not homoscedastic and to promote consistency. Differences were investigated using the Mann-Whitney *U* test for quantitative data and the chi-square test for count data. Spearman rank correlation was used to assess correlations. Statistical tests were performed using MATLAB. A Bonferroni correction, based on testing and relations with age in Tables 1 to 3, yielded a corrected value of 0.0014. *P* values greater than that threshold but <0.01 are reported as trends.

RESULTS

The study group comprised 163 patients (median age 45 years; 75 men [46%]) (Table 1). There was a trend toward more men in the older group (57% vs 35% in the younger group). VVS started at an older age and less often before 35 years of age in the older group (Table 1). The older group tended to use antihypertensive drugs or drugs with hypotension as a possible side effect more often (Table 1). The medical history revealed more frequent cardiac disease and hypertension in the older group. Figure 1 shows averaged hemodynamic parameters: qualitatively, the older group had relatively high BP and SV, but low HR and TPR, in the baseline supine condition.

EFFECTS OF AGE ON PARAMETERS OF CARDIOINHIBITION. Cardioinhibition was noted in 149 patients (91.4%). All 14 patients in whom cardioinhibition could not be determined (median age 64.5 years) belonged to the older one-half of the

cohort. The median cardioinhibition magnitude was 67.9 beats/min (IQR: 48.0-86.7 beats/min). Median cardioinhibition duration was 62 seconds (IQR: 46.8-87.3 seconds). The median rate of HR decrease was 0.99 beats/min/s (IQR: 0.67-1.61 beats/min/s).

All 3 descriptive cardioinhibition parameters were related to age (Figure 2): duration increased, but the rate of HR decrease and cardioinhibition magnitude decreased (all $P < 0.0001$).

Asystolic pauses occurred in 68 cases (41.7%). The older one-half of the patient population exhibited fewer asystolic pauses (26%) than the younger one-half (57%) did.

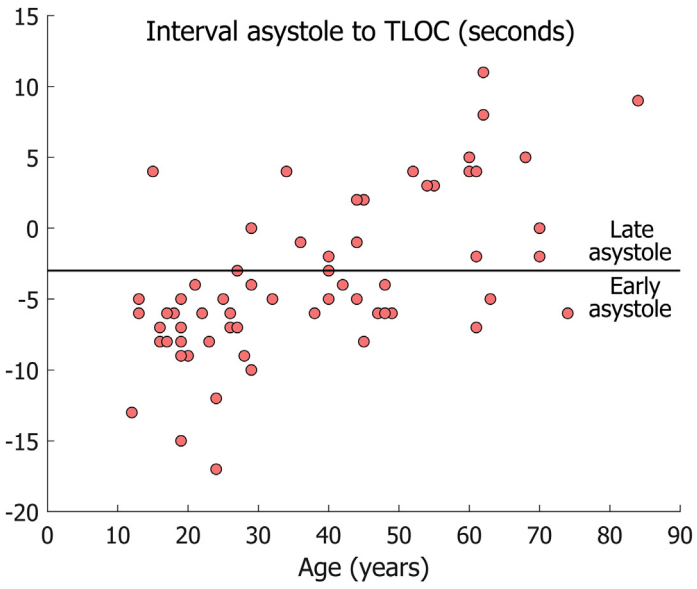
Figure 3 shows the distribution of the duration between the times of onset of asystolic pauses and of LOC. There were 24 patients with late asystole (35.3%) and 44 with early asystole (64.7%). Younger cases clustered at the top, indicating early asystole, and older cases at the bottom, indicating late asystole. The interval between the onsets of asystole and of LOC was related to age ($P < 0.0001$) (Figure 4), meaning that asystolic pauses started later with increasing age. To summarize this another way, of 82 younger patients, 47 had asystole (57.3%), divided into 37 (45.1%) with early and 10 (12.2%) with late asystole (Central Illustration). Of the 81 older cases, 21 had asystole (25.9%), divided into 7 (8.6%) with early and 14 (17.3%) with late asystole (Central Illustration). The proportions of early and late asystole differed between age groups ($P < 0.001$).

In brief, increasing age was associated with a less profound and slower HR decrease, fewer asystolic pauses, and a higher proportion of late asystole among those with asystolic pauses.

RELATIVE IMPACT OF CARDIOINHIBITION AND VASODEPRESSION. The time course of cardioinhibition and vasodepression for the younger and older age groups is shown in Figure 5 and Table 2. Just before the start of cardioinhibition (period 1), BP had decreased more in the older than in the younger one-half of the cohort. This was caused by vasodepression in both groups, which is apparent from negative vasomotor components. Vasodepression and SV did not differ between the older and younger groups, but TPR tended to be lower in the older group. The chronotropic component showed positive values, ie, a probably corrective HR increase that did not differ between age groups. In short, just before the onset of cardioinhibition, the older group had a lower BP, with a trend toward a greater decrease of TPR.

Just before syncope (period 2), BP was very low but not different between groups. The chronotropic component was negative in both groups, indicating cardioinhibition. Cardioinhibition was stronger in the younger than in the older group, whereas the reverse was true for vasodepression. TPR tended to decrease more in older patients.

FIGURE 4 Age and Difference Between Onsets of Asystole and TLOC



Age was related strongly and highly significantly to the interval ($\rho = 0.60$; $P < 0.0001$). Those with late asystole **(top)** had a higher age than those with early asystole **(bottom).** TLOC = transient loss of consciousness.

Figure 6 shows relations of age with BP, cardioinhibition, and vasodepression for period 2. BP was not related to age ($P = 0.99$), but cardioinhibition and vasodepression were ($P < 0.0001$). The changes occur across the entire age spectrum.

Results of those with early and late asystole are shown in Tables 1 and 2 and Figure 7. Those with early asystole had a younger age and tended to have a shorter duration of LOC. Just before the start of cardioinhibition (period 1), only BP differed between the groups, with lower BP in the late asystole group. Just before syncope (period 2), BP was low but not different between early and late asystole groups. The chronotropic and vasomotor components were negative in both groups: cardioinhibition was stronger in the early asystole group, and vasodepression tended to be stronger in the late asystole group.

DISCUSSION

This study provides 3 main findings regarding the impact of age on cardioinhibition and vasodepression in t-VVS. First, cardioinhibition weakened with age; this is evidenced by a decrease in magnitude plus a

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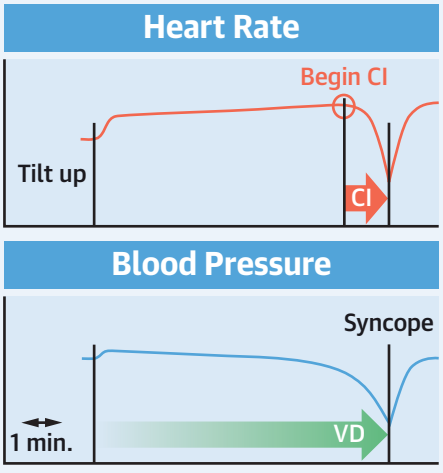
CENTRAL ILLUSTRATION Vasovagal Syncope in Older Patients



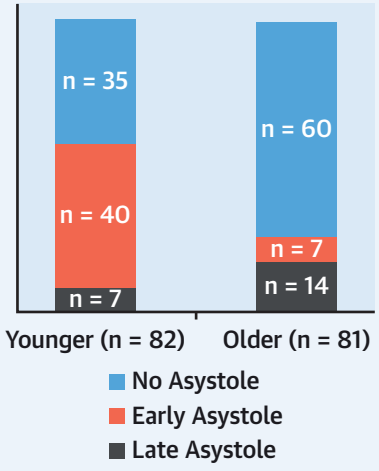
Decrease of blood pressure in vasovagal syncope

Blood pressure decreases in vasovagal syncope because of:

- Cardioinhibition (CI)
- Vasodepression (VD)

Effects of age on CI and VD were quantified with the log-ratio method in 163 patients with complete syncope during a tilt table test

- CI weakened with age
- VD strengthened with age



Effects of age on asystole

- Asystole occurred less often in older patients
- Asystole occurred more often as 'late asystole' (ie, too late to cause unconsciousness)

Vasovagal syncope in older patients

- Mostly due to vasodepression
- Asystole less frequent
- If asystole occurs, it is more often 'late asystole'

These effects may decrease the chance of successful pacing in older patients with vasovagal syncope.

van Dijk JG, et al. J Am Coll Cardiol EP. 2022;8(8):997-1009.

The **top panel** compares the time course of late, abrupt and quick cardioinhibition with that of early, slow and gradual vasodepression. The **bottom panel** shows the influence of age on the pattern of asystole. VD = vasodepression.

longer duration and therefore a slower HR decrease and by fewer asystolic pauses. The percentage of patients with asystole in the group of older patients was less than one-half that in the younger group (26% vs 57%). Second, with increasing age asystolic pauses started later relative to LOC: late asystole occurred in 12% of the younger one-half of all cases (ie, 21% of those with asystolic pauses in that group). Late

asystole formed 17% of all older cases (67% of those with asystole in that group). In short, asystole occurred less often with increased age, but when it did, it more often took the form of late asystole. Both effects mean that asystole was less likely to contribute to syncope in older than in younger patients.

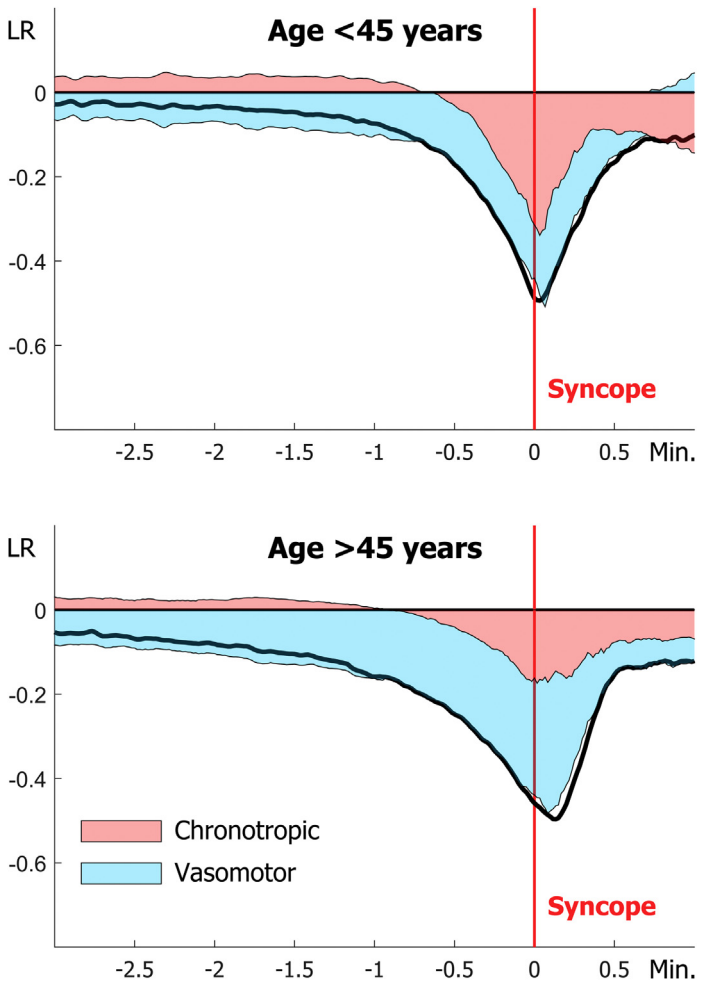
Finally, the log-ratio method showed that vasodepression tended to be stronger in older than in younger patients just before the onset of cardioinhibition, and it was markedly stronger in the period just before syncope. Cardioinhibition, present in both groups, was stronger in younger than in older patients.

EFFECTS OF AGE ON CARDIOINHIBITION AND VASODEPRESSION. While cardioinhibition weakened with age, vasodepression concomitantly strengthened. This is in line with a recent study.[9] The opposite changes of cardioinhibition and vasodepression are probably explained by changes in how age affects parasympathetic and sympathetic circulatory control: parasympathetic control decreases with age, and there is a shift toward more sympathetic control.[16-21] The reduced parasympathetic drive is thought to compensate for a lower intrinsic heart rate.[17,22] Such age effects directly influence physiological autonomic responses: in younger people, normal responses to standing rely heavily on increases of HR, whereas increases in TPR are more important for older people.[19] These results fit well with our findings, so we suggest that the simultaneous cardioinhibition weakening and vasodepression strengthening in t-VVS with age reflects physiological differential sympathetic and parasympathetic aging.

THE PROPORTION OF ASYSTOLIC PAUSES. The decrease in proportion of patients with asystolic pauses with age resembled other studies qualitatively, but not quantitatively.[5-9] One study reported asystolic pauses in 5.3% of patients over 65 years,[5] which is similar to the 6% in our subgroup of 27 patients of the same age category. But other estimates were 0% of patients aged 66 ± 1 year,[6] and 15.2% of patients aged 6-22 years;[8] an asystolic VASIS type 2B response was seen in 2.1% of young and 0% of elderly patients.[7] We suspect that such low proportions of asystolic pauses may be the result of tilting back early, ie, at presyncope, because this aborts later t-VVS events, including cardioinhibition. Hence, the proportion of cases with asystolic pauses in t-VVS cannot be assessed reliably if presyncope is the test end point.

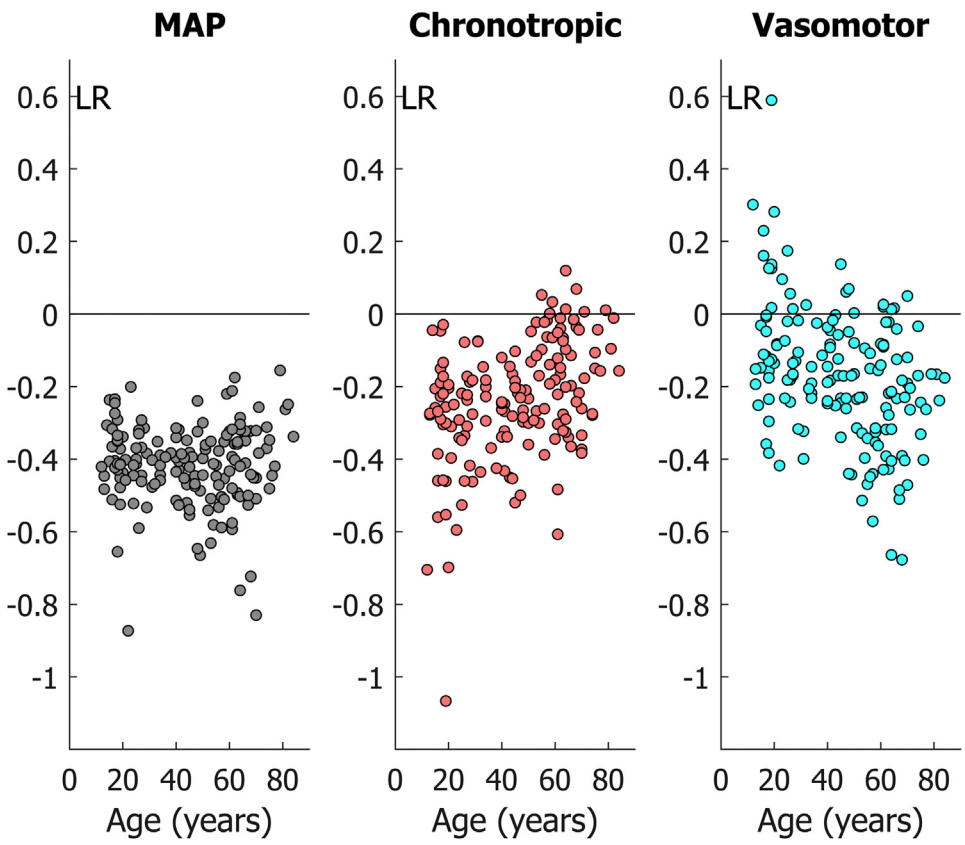
Rivasi et al[9] reported effects of age on tilt positivity using the Italian protocol, which does stipulate syncope as the end point. Calculating the proportion of those with asystole resulted in 27% for their patients aged 10-39 years and 11% for those aged 50-89 years. These groups conform to our younger and older groups, who, however, developed asystolic pauses about twice as often, at 57% and 26%. The duration of tilting back was not the likely explanation: it was 12 seconds in our study, similar to the shortest of the 3 times in a study proving that a shorter duration was associated with fewer cardioinhibition responses.[23] Perhaps our stringent syncope criteria, demanding

FIGURE 5 Time Course of Chronotropic and Vasomotor Effects by Age



The Figure shows cumulative log-ratios (LRs) of chronotropic HR **(pink)** and vasomotor **(blue)** effects on BP **(bold black line).** Values represent means per second. Positive log-ratio (LR) values indicate values higher than baseline, increasing BP, and negative ones the reverse. The vertical line at time 0 indicates the onset of syncope. The negative vasomotor component (vasodepression) initially outweighs the positive HR effect. Close to syncope, chronotropic and vasomotor components both decrease BP, ie, they represent cardioinhibition and vasodepression. The major cause of the BP decrease at syncope is cardioinhibition in the younger one-half of the group **(top)** and vasodepression in the older one-half of the group **(bottom).** Abbreviations as in Figure 1.

FIGURE 6 Effect of Age on Chronotropic and Vasomotor Influences Just Before Syncope



LR values of the 10-second period just before syncope (period 2, see text) are shown for BP, cardioinhibition, and VD. Negative values indicate values lower than baseline, which for cardioinhibition and VD mean a BP-decreasing effect. The decrease of BP was not affected by age ($\rho = 0.00$; $P = 0.99$), but chronotropic influences were most negative (strongest cardioinhibition) at low age (rho: 0.36; $P < 0.0001$) and vasomotor effects were most negative (VD) at high age ($\rho = -0.36$; $P < 0.0001$). Abbreviations as in Figures 1 and 5.

circulatory, behavioral as well as electroencephalographic alterations, excluded cases of presyncope that might otherwise be passed as "syncope."

It may be impossible to negate all effects of tilt-back decisions. The end of cardioinhibition occurred at the time of minimum HR around syncope. In that period patients are tilted down, and it is likely that the resulting quick increase of venous return helps end cardioinhibition. This strongly suggests that cardioinhibition, once started, is maintained by an unidentified hemodynamic factor until 1 of 2 conditions is fulfilled. The first is that the triggering hemodynamic factor is no longer present, because patients either fall or are tilted back. The second is that the dorsal nucleus of the vagal nerve will sooner or later cease to function because of hypoperfusion, ending cardioinhibition and allowing the intrinsic cardiac rhythm to resume.

The apparently great dependence of the proportion of asystolic pauses on the tilt protocol suggests that patients without such pauses may well evolve pauses with a different tilt-back protocol. We speculate that the fact that this detection predicted pacing success[11] does not depend on the absolute proportion of asystolic pauses, but on the relative strength of cardioinhibition compared with that of vasodepression: those in whom cardioinhibition starts at a relatively high BP, ie, with a limited degree of vasodepression, may well have most to gain from pacing.

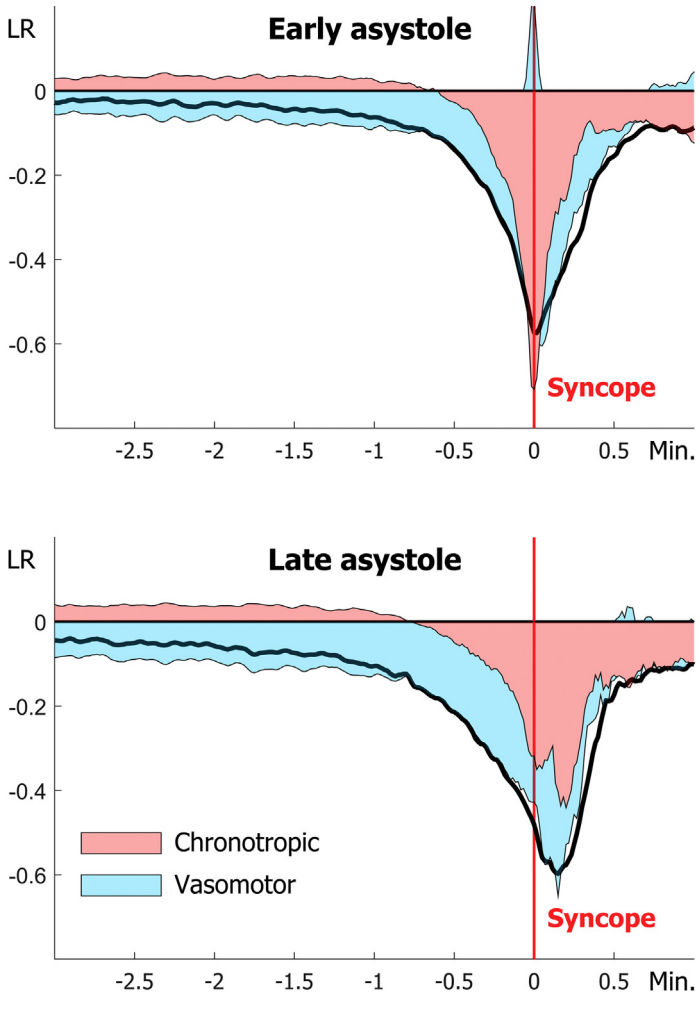
ASYSTOLIC PAUSES AND LOC. In a previous study[2] on the timing of the onsets of asystolic pauses and LOC, we argued that asystole starting 3 seconds before the onset of LOC or later was unlikely to have been the major cause of syncope. That interval was chosen because it is just shorter than the shortest described interval of 4 seconds in studies in which asystolic pauses were considered the major cause of

LOC.[24,25] We chose that interval to increase confidence that the resulting "late asystole" was not the major cause of syncope. However, we do not think that a sudden asystolic pause will cause LOC after 3 or 4 seconds, if BP and cardiac output were normal until then; 7-10 seconds is a more likely interval.[24,25] In t-VVS, asystolic pauses start when BP and cardiac output are already compromised, shortening the time to LOC. **Figure 4** shows that intervals of 5-8 seconds accounted for 32 of the 68 patients with asystole (47%), with 6 seconds being the most prevalent interval (n = 10). We suggest that LOC is likely to follow the onset of asystole after about 6 seconds in typical t-VVS.

STUDY LIMITATIONS. First, tilt data cannot be translated precisely to spontaneous syncope. Available evidence suggests that bradycardia is more prominent clinically than on tilt. Should this be correct at all ages, bradycardia/asystole may be more important in older patients than tilt results indicate.[26] Second, the conservative 3-second threshold for "late asystole" may underestimate the impact of cardioinhibition. Third, a short vasodepression spike was recorded at syncope in **Figure 3** and was discussed earlier.[1] This may involve an incorrect estimate of SV by Modelflow when SV decreases very quickly.[27] Fourth, the decision when to tilt back may have influenced the end of cardioinhibition and in turn various aspects of cardioinhibition. Fifth, effects of age can in part be caused by age-related comorbidity, such as hypertension and the use of drugs. We have not tried to disentangle primary effects of age from such secondary indirect age effects.

Finally, the descriptive parameters of cardioinhibition treated cardioinhibition as a linear process. This was justified in view of the apparent linear decrease of HR after the onset of cardioinhibition (see **Figure 6** in Van Dijk et al[1]), the time course of cardioinhibition deserves more detailed study.

FIGURE 7 Time Course of Chronotropic and Vasomotor Effects by Time of Onset of Asystole



Those with early asystole (n = 44) **(top)** and late asystole (n = 24) **(bottom)** are shown. In the early asystole group, cardioinhibition was strong and peaked early, whereas it was weaker and peaked later in the late asystole group. LR = log-ratio.

CLINICAL IMPLICATIONS. The present findings indicate that vasodepression becomes more important with age and cardioinhibition less so. This suggests that basing pacing decisions on asystole only may not be ideal in the elderly: the low proportion of asystolic pauses means there will be fewer candidates, and the high proportion of late asystole means that hysteresis pacing to counter bradycardia may not prevent syncope.

We previously reinterpreted cardioinhibition as the entire HR decrease toward syncope, paving the way for the realization that the start of the HR decrease already had a strong impact on blood pressure.[1] That realization may give rise to testable hypotheses regarding pacing in VVS. For instance, early pacing, ie, before or at the start of cardioinhibition, may be better than late pacing, that is waiting for extreme bradycardia. Tailoring pacing parameters, such as pacing at the high HR before cardioinhibition starts, might be useful. Pacing modes such as closed loop pacing may prove useful, as might triggering pacing based not on bradycardia, but on other information such as ventricular impedance.[10]

Finally, studies on pacing in elderly patients should take the relative strengths of vasodepression and cardioinhibition into account, assuming that those with early strong cardioinhibition and weak vasodepression may benefit most. In fact, the

efficacy of the BioSync trial[11] may have rested on such patients. A first study could assess this balance in tilt tests, using the log-ratio method and syncope as the tilt-back criterion, followed by noninvasive tests in patients who are ambulatory; although challenging, this appears feasible with new devices.[28] Meanwhile, implantable electrocardiographic monitors, if equipped with position sensors, could identify significant cardioinhibition occurring after a syncopal fall, suggesting that pacing is unlikely to be useful.

CONCLUSIONS

With advancing age, both vasodepression and cardioinhibition change in t-VVS: while vasodepression becomes stronger with age, the contribution of cardioinhibition weakens. These effects may represent a shift from parasympathetic toward sympathetic control with increasing age. The results may have an impact on pacing utility in older patients with VVS. Whereas asystolic pauses occurred less often with advancing age, the proportion of late asystole increased. Both findings may detract from the efficacy of bradycardia-based pacing.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Low blood pressure in VVS is the result of cardioinhibition, ie, a decrease in HR, and factors not related to HR: vasodepression. Using a new method to measure their relative strength, cardioinhibition was shown to become less important, but vasodepression more so, with advancing age.

TRANSLATIONAL OUTLOOK: Relying on HR information only is likely to overestimate the role of bradycardia in VVS. Assessing the relative roles of vasodepression and cardioinhibition may help avoid over-reliance on bradycardia detection while also improving the efficacy of pacing in VVS, through a reappraisal of required hemodynamic effects.

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KEY WORDS aging, autonomic nervous system, hemodynamics, pathophysiology, syncope

APPENDIX For supplemental methods, results, and references, please see the online version of this paper.