

Hemodynamic mechanisms underlying prolonged post-faint hypotension

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Abstract

Objective During hypotension induced by tilt-table testing, low presyncopal blood pressure (BP) usually recovers within 1 min after tilt back. However, in some patients prolonged post faint hypotension (PPFH) is observed. We assessed the hemodynamics underlying PPFH in a retrospective study.

Methods Seven patients (2 females, aged 31–72 years) experiencing PPFH were studied. PPFH was defined as a systolic BP below 85 mmHg for at least 2 min after tilt back. In 6 out of 7 presyncope was provoked by 0.4 mg sublingual NTG, administered in the 60° head-up tilt position following head-up tilt for 20 min. Continuous BP was monitored and stroke volume (SV) was computed from pressure pulsations. Cardiac output (CO) was calculated

from $SV \times \text{heart rate (HR)}$; and total peripheral resistance (TPR) from mean BP/CO. Left ventricular contractility was estimated by dP/dt_{\max} of finger pressure pulse.

Results Systolic BP (SYS), diastolic BP (DIAS) and HR during PPFH were lower compared to baseline: SYS 75 ± 14 versus 121 ± 18 mmHg, DIAS 49 ± 9 versus 71 ± 9 mmHg and HR 52 ± 14 versus 67 ± 12 beats/min ($p < 0.05$). Marked hypotension was associated with a 47% fall in CO 3.1 ± 0.6 versus 5.9 ± 1.3 L/min ($p < 0.05$) and decreases in dP/dt , 277 ± 77 versus 759 ± 160 mmHg/s ($p < 0.05$). The difference in TPR was not significant 1.1 ± 0.3 versus 1.0 ± 0.3 MU ($p = 0.229$). In four patients, we attempted to treat PPFH by 30° head-down tilt. This intervention increased SYS only slightly (to 89 ± 12 mmHg).

Interpretation PPFH seems to be mediated by severe cardiac depression.

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Abbreviations

BP	Blood pressure
CO	Cardiac output
DIAS	Diastolic blood pressure
HR	Heart rate
HUT	Head-up tilt testing
LV	Left ventricle
MAP	Mean arterial pressure
PP	Pulse pressure
PPFH	Prolonged post faint hypotension
SV	Stroke volume
SYS	Systolic blood pressure
TPR	Total Peripheral Resistance.

Introduction

After tilt-induced syncope, moving the patient back to the horizontal position rapidly restores central blood volume and hypotension is usually corrected within 1 min [7, 15, 31, 44, 48]. However, in some patients, vasovagal reactions may be complicated by prolonged post faint hypotension (PPFH), i.e., persistent-marked hypotension associated with symptoms of malaise, severe weakness, light-headedness and nausea [10, 35, 49]. Early clinical investigations documented a major increase in forearm blood flow at the time of severe vasovagal syncope [1, 2] suggesting that pronounced systemic vasodilatation is the main driver of the hypotension. This was supported by micro-neurographic studies demonstrating MSNA withdrawal during syncope [22, 43]

We, therefore, hypothesized in this study that PPFH is mediated by prolonged vasodilatation. We tested this hypothesis retrospectively by computing the hemodynamics underlying PPFH. Finger arterial blood pressure (BP) was monitored continuously and cardiac variables were computed from the pressure pulsations. Hemodynamics during PPFH were compared to baseline (supine) values prior to head up tilt.

Methods

Study population and protocol

Out of 391 patients that visited our syncope unit for routine clinical testing in the period August 2007 to April 2009, the data of 7 consecutive patients with a clinical history of vasovagal fainting, and PPFH during head-up tilt testing (HUT) were analyzed retrospectively. All tilt-table tests were performed by the same clinician (WW).

A positive tilt test was defined as a progressive fall in blood pressure and symptoms and signs of impending syncope. PPFH was defined as a systolic BP persistently below 85 mmHg for at least 2 min after tilt back to the horizontal.

HUT was performed between 9:00 a.m. and 1:00 p.m. in a temperature-controlled room (23°C) according to the Italian protocol [30]. Nitro-glycerine (0.4 mg) was administered sublingually after a period of 20 min passive HUT (60°). HUT was then maintained until impending syncope. When progressive fall in blood pressure occurred, associated with prodromal symptoms, subjects were tilted back to the horizontal. The tilt back maneuver was accomplished in 2–3 s.

The study was approved by the Medical Ethical Committee of the Academic Medical Center, University of Amsterdam, The Netherlands.

Data acquisition and analysis

Non-invasive beat-to-beat blood pressure was measured at the finger. (Finometer Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, the Netherlands) [18] $n = 4$ patients or its successor, a Nexfin device (BMEYE, Amsterdam, the Netherlands) $n = 3$ [11, 43]. From both devices, the brachial artery pressure values reconstructed from finger arterial pressures, were used. Values from devices are interchangeable.

To avoid hydrostatic pressure differences, the hand was held at heart level. The measured signal was analog to digital converted at 200 Hz, and stored on a hard-disk for off-line analysis. Systolic (SYS) and diastolic (DIAS) arterial pressures were derived from the arterial pressure waveform. Mean arterial pressure (MAP) was calculated from the integral of the arterial pressure wave over one beat divided by the corresponding beat interval. Pulse pressure (PP) was defined as the difference between systolic and diastolic pressure. Heart rate (HR) was computed as the inverse of the inter-beat interval and expressed as beats per minute. Beat-to-beat left ventricular stroke volume (SV) was estimated by modeling flow from the arterial pressure waveform (Modelflow, TNO Biomedical Instrumentation, expressed in ml [46]. Cardiac output, expressed in L/min, was the product of estimated SV and HR. Total Peripheral Resistance (TPR), expressed in mmHg s/ml, further called Medical Units or MU was computed by MAP at heart level divided by the computed CO. The Modelflow method computes aortic flow from finger arterial pressure by simulating a non-linear model of the aortic input impedance and was applied to finger pressures of Finometer as well as Nexfin [46].

This pulse wave analysis method corrects for individual differences in age, gender, height, and weight [26], permitting group average data to be examined accurately in subjects without structural or functional heart disease [8, 34]. Previous experiments during orthostatic stress have demonstrated good correlation between Modelflow and standard CO estimates such as inert gas rebreathing [39] and thermodilution [21]. With Doppler ultrasound, it was shown that Modelflow accurately tracks changes in cardiac output on a beat-to-beat basis [40]. Under the adverse circumstances of very low arterial blood pressures, Modelflow computations have also been shown to be accurate [24].

As a measure of cardiac contractility, the time derivative of peripherally measured pressure, dP/dt , was calculated. The maximal value of dP/dt is a measure of cardiac contractility when measured in the left ventricle (LV), however, values determined noninvasively from the radial artery have been shown to correlate well with Doppler estimates of LV dP/dt [3, 38].

Sampling of time intervals

For each interval, hemodynamic variables were initially averaged over 10-s periods (for plotting) and then averaged (6×10 s periods for each minute) for statistical testing. Values for all variables are expressed as mean \pm 1 standard deviation.

The following periods were analyzed:

1. Baseline: the last 3 min in the supine position before HUT.
2. Early HUT: the steady-state adjustment to orthostatic stress during the first to third minute of HUT.
3. Presyncope: the last minute before tilt-back to the horizontal position.
4. Recovery: the 5 min following tilt-back to the horizontal position.

In four of the seven patients, it was attempted to combat the severe symptomatic hypotension during PPFH by increasing venous return with 30° head down tilting. The effects of this intervention on BP recovery were analyzed separately.

Statistical analysis

Statistical analysis was performed with Sigmaplot 11.0. Variables were tested for normality using the Shapiro–Wilk test. Changes in the hemodynamic variables were tested with One Way Repeated Measures Analysis of Variance versus supine as control (multiple comparisons vs. control, Holm–Sidak method. A p value $<$ 0.05 was considered statistically significant.

Results

The data of seven patients (two females) with a mean age of 50 years (range 31–72 years) were studied. Six had a

typical history of vasovagal faints since adolescence. Six patients complained of prolonged weakness, light-headedness and nausea after fainting. In three patients, fainting was triggered by seeing blood, injection or injuries.

The upper arm blood pressure, measured via sphygmomanometer with the patients lying supine prior to the test was SYS 118 ± 12 mmHg and DIAS 77 ± 12 mmHg. At the time of impending, syncope typical symptoms and signs were observed, including light-headedness, abdominal discomfort, nausea, blurred vision, pallor, and sweating.

One patient fainted during the first 20 min of HUT and the remaining six patients after administration of nitroglycerine at 20 min HUT.

Two patients had an abrupt decrease in heart rate followed by asystole of 10–20 s and loss of consciousness (less than 30 s) during tilt back.

The analyzed periods are listed in Table 1. All patients had normal early steady-state adjustments to the upright posture.

Presyncope (last minute before tilt back)

SYS decreased rapidly during the minute prior to tilt back from values of $109/76 \pm 16/10$ – $72/48 \pm 19/11$ mmHg (Fig. 1). At the moment of tilt back, SYS fell to less than 50 mmHg in all patients.

Compared to baseline, the CO in the last minute had decreased by 36% ($p <$ 0.05). There was a simultaneous fall in dP/dt from values of 759 ± 156 – 508 ± 235 mmHg/s ($p <$ 0.05). TPR was above baseline: 0.96 ± 0.29 versus 1.27 ± 0.54 MU ($p <$ 0.05).

Recovery

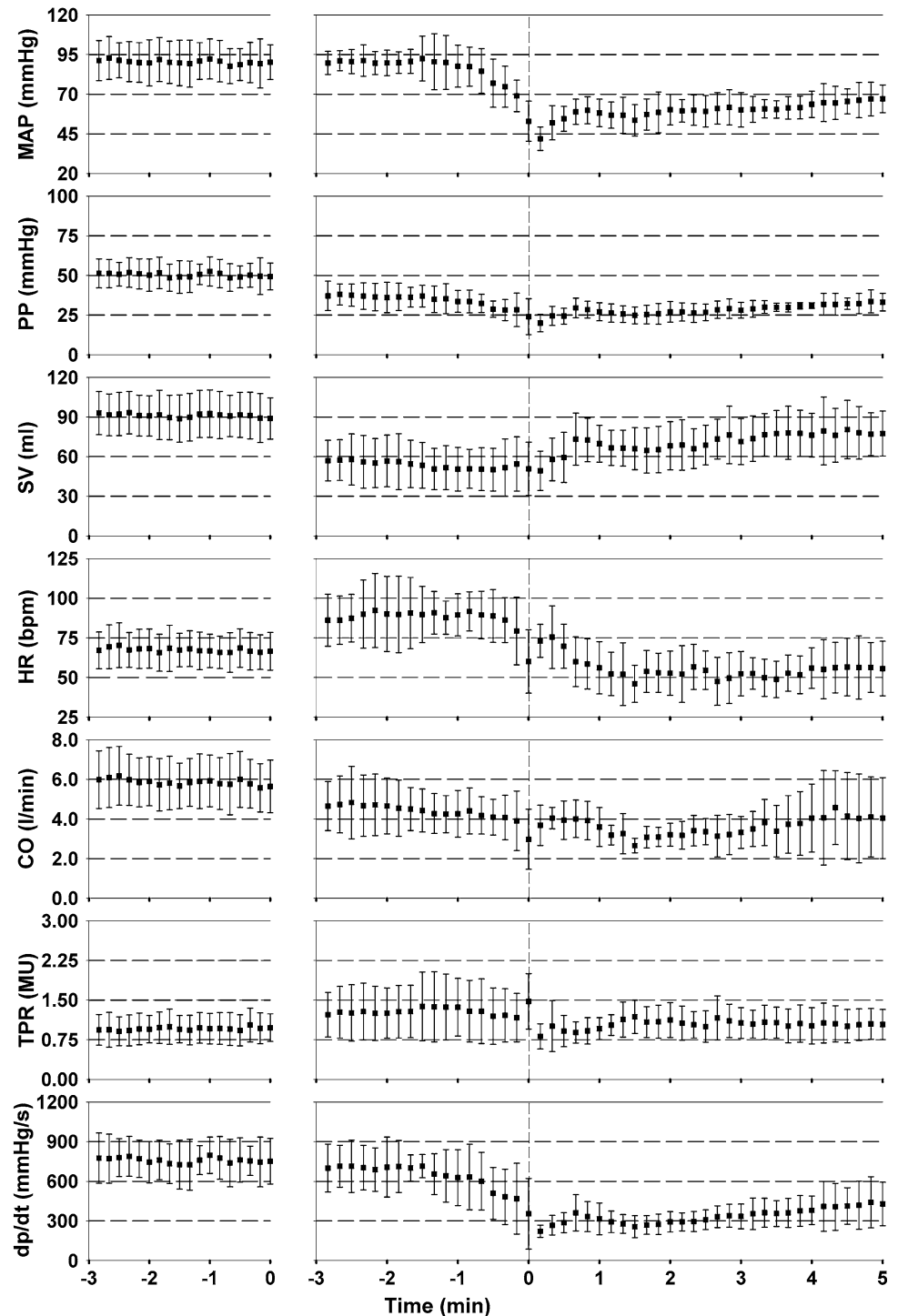
Following tilt-back BP began to increase, but remained very low (Fig. 1). Prominent distension of the neck veins was observed in several patients. Some patients complained of

Table 1 Hemodynamic changes during baseline, early HUT, presyncope and recovery in 7 patients with PPFH

	Baseline (3 min)	Early HUT (60–180 s)	Presyncope (last 60 s)	Recovery: (60–120 s) PPFH	Recovery: (240–300 s) PPFH
SYS (mmHg)	121 \pm 18	119 \pm 11	94 \pm 17*	75 \pm 14*	88 \pm 13*
MAP (mmHg)	90 \pm 13	93 \pm 8	74 \pm 13*	57 \pm 10*	66 \pm 10*
DIAS (mmHg)	71 \pm 9	78 \pm 7	65 \pm 11	49 \pm 9*	55 \pm 7*
HR (beats/min)	67 \pm 12	77 \pm 11	83 \pm 17*	52 \pm 14*	56 \pm 18
SV (ml)	91 \pm 17	62 \pm 18*	51 \pm 18*	66 \pm 16*	78 \pm 20*
CO (L/min)	5.9 \pm 1.3	4.5 \pm 1.0*	3.8 \pm 1.0*	3.1 \pm 0.6*	4.2 \pm 2.1*
TPR (MU)	0.96 \pm 0.29	1.30 \pm 0.44	1.27 \pm 0.54	1.11 \pm 0.3	1.04 \pm 0.32
dP/dt (mmHg/s)	759 \pm 160	767 \pm 110	508 \pm 235*	277 \pm 77*	420 \pm 174*

* $p <$ 0.05 versus control (Holm–Sidak method)

Fig. 1 Hemodynamics during baseline and prolonged faint hypotension. The three time periods indicate: **a** the last 3 min in the supine position before HUT (baseline), **b** the last 3 min before tilt-back to the horizontal position, **c** the 5 min following tilt-back to the horizontal position (recovery). During the first minute of recovery, there were no data points for 20–30 s in two patients with prolonged asystole and we were unable to record for the first 10 s in another patient, because of a technical problem. For these reasons we present the values from the second minute of recovery. The data include the periods with head-down tilt performed in four patients (see text)



fatigue, nausea and light-headedness for some minutes, and were observed to be pale and sweaty. During the first minute of recovery, there were no data points for 20–30 s in the two patients with prolonged asystole and we were unable to record for the first 10 s in another patient, because of a technical problem. For these reasons, we present the values from the second minute of recovery for all patients. These values were very similar to what we measured during the

first minute in the four patients with good recordings. The data in Fig. 1 include the periods with head-down tilt performed in 4 patients (see below).

SYS in the second minute of recovery was decreased compared to baseline: 75 ± 14 versus 121 ± 18 mmHg ($p < 0.05$). Systolic pressure at this time was more than 20 mmHg lower than baseline in all seven patients (range 29–77 mmHg). HR was also lower compared to baseline:

52 ± 14 versus 67 ± 12 beats/min ($p < 0.05$). In five patients, the HR was below 50 beats/min (range 38–49 beats/min) There was a fall in CO of 47 % (range 31–61): 5.9 ± 1.3 versus 3.1 ± 0.6 L/min. TPR was not different from baseline: 0.96 ± 0.29 versus 1.11 ± 0.3 MU ($p = 0.229$), dP/dt decreased by 64% (range 48–76 %): 277 ± 77 mmHg/s versus 759 ± 160 ($p < 0.05$).

During the fifth minute after tilt-back BP ($p < 0.05$) remained below baseline.

Effects of 30° head-down tilt

Thirty degree head-down tilt was performed in four patients (Fig. 2). The 30° head down tilt started at minute 1, 2 (two patients) or 4 of the 5-min period of PPFH. The maneuver was performed for 2 min. The head-down tilt maneuver resulted in an increase in CO from 3.5 to 4.6 L/min at the end of the maneuver (35% increase), but pronounced hypotension persisted (SYS increase from 73 to 89 mmHg). No improvement in symptoms occurred.

Discussion

The immediate symptoms of a vasovagal faint are usually brief, but during a severe episode, persistent hypotension, with malaise and weakness may last for hours [10, 35, 49]. The hemodynamics underlying PPFH have not been studied. Our hypothesis that vasodilatation is the hemodynamic mechanism underlying PPFH is not supported by our results. TPR during PPFH was not decreased, but very similar to the supine control value prior to tilt-up (Fig. 1). The hemodynamic mechanism responsible was found to be major fall in CO (47%). This was mediated by persistent bradycardia and decreased SV. Pronounced distension of the neck veins was observed during PPFH. Furthermore, cardiac output was only marginally improved by head-down tilting (Figs. 2 and 3) (an intervention that increases central blood volume and cardiac filling) [20]. This would suggest that the main mechanism for delayed recovery of cardiac output was more likely to be transiently impaired LV contractility than decreased cardiac filling. This is supported by the marked decrease in dP/dt (Fig. 1; Table 1) we observed. Studies dealing with cardiac contractility in patients during an ongoing vasovagal syncope show conflicting results, both the increased and decreased contractility have been reported (for review see [15]). Post-faint data on LV contractility have, to the best of our knowledge, not been reported.

Vasovagal fainting and the arterial baroreflex

The arterial baroreflex is the main feedback mechanism whereby short-term fluctuations in systemic blood pressure

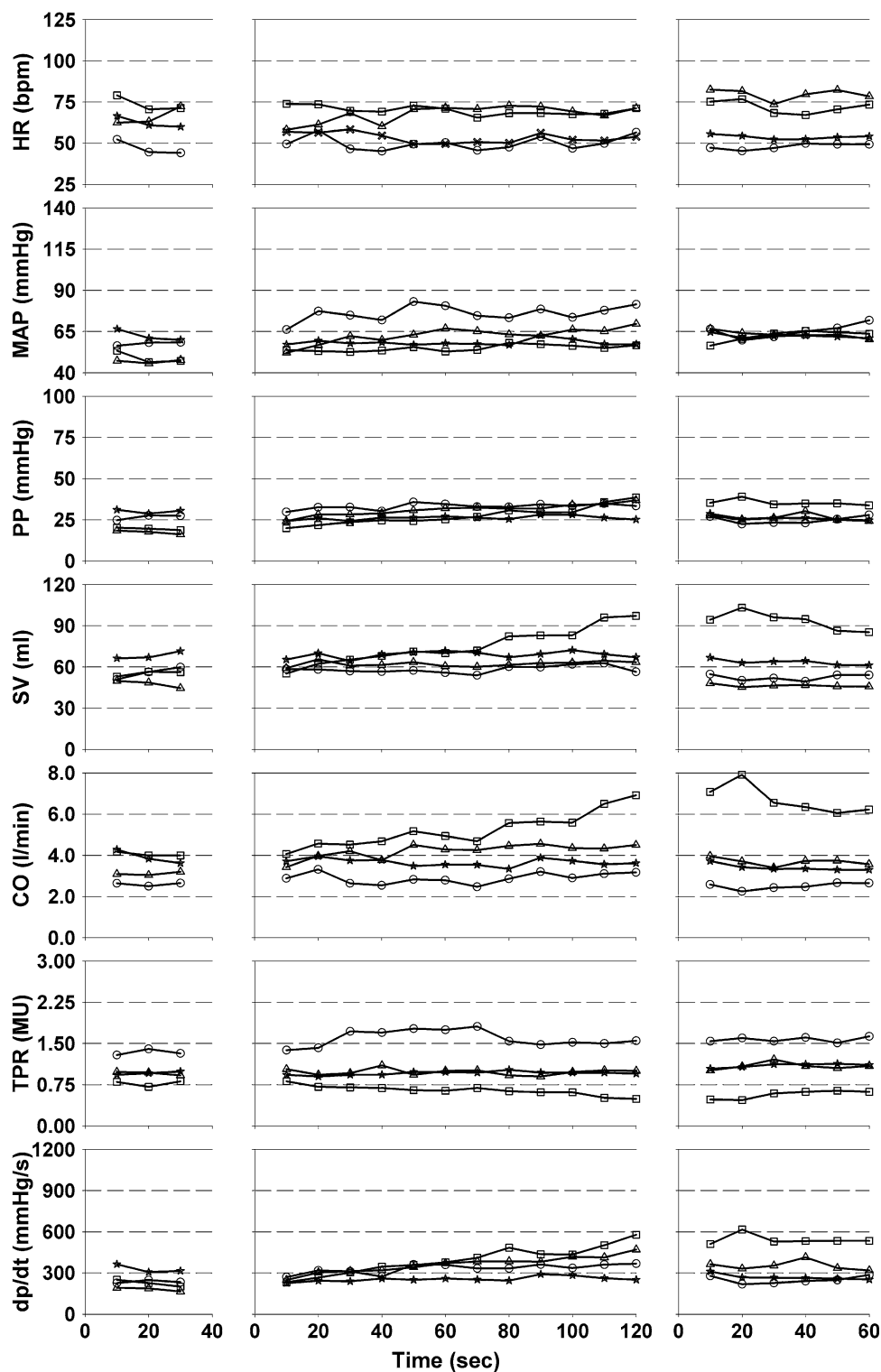
will be buffered by changes in heart rate, cardiac contractility and systemic vascular resistance [25, 36, 47]. During vasovagal presyncope, a depressor reflex overrides the normal baroreflex control of arterial blood pressure. The origin of the afferent signal initiating this depressor reflex is unknown. Activation of receptors in the ventricles of the heart has been postulated, but this afferent pathway is debated. Activation of receptors from other parts of the central circulation or a mechanism causing the switch within the brain has been suggested. Pathways involving opioid and serotonin transmission and or a central effect of vasopressin potentiating arterial baroreflexes have been implicated [19, 33].

During PPFH, the arterial baroreflex is unloaded and the persistent inappropriately low HR and BP are consistent with a sustained central suppression of excitatory mechanisms [25]. Pronounced bradycardia in combination with complaints of abdominal discomfort and nausea is consistent with increased vagal outflow from the nucleus ambiguus (main vagal output to the heart) and the dorsal nucleus (vagal output to the stomach). Pancreatic polypeptide is believed to be primarily under vagal control [37] and is elevated immediately after tilt-induced syncope [23]. Similarly, there is an increase in high frequency heart rate variability, another surrogate for vagal cardiac nerve activity, after syncope. No direct recordings of vagal nerve activity are possible in this situation. We hypothesize that the decreased cardiac contractility we observed in our patients with PPFH is due to a combination of increased vagal [4, 27, 32] and decreased sympathetic neural outflow to the heart [12]. The origin of the persistent strong vagal stimulation within the central autonomic network during PPFH remains to be established [6].

Comparison with earlier findings

In his first observation on fainting in 1919, Lewis reported on fainting attacks in seven young soldiers invalidated by a condition termed the effort syndrome. In five out of seven of these soldiers the fainting attack was elicited by blood taking and pronounced PPFH was present in 4 out of 7. A prompt (within 30 s) recovery of the circulation after atropine administration was observed in a 21-year-old soldier with PPFH. The fall in heart rate and the clinical manifestations of the faint in these 7 soldiers were reported to go hand in hand [5]. Lewis attributed the fainting attacks to the “reduction of the force of heart beat”. In a critical re-evaluation of his work in 1932, Lewis changed this view. In his famous lecture entitled “Vasovagal syncope and the carotid sinus mechanism”, he states that appreciable weakening of the force of ventricular contractions has not been demonstrated in mammals by vagal stimulation and that atropine, while raising the pulse rate beyond normal

Fig. 2 Effects of a 30° head-down tilt on cardiac output and blood pressure in four patients with PPFH. The three time periods indicate **a** a 30-s period prior to head down tilting, **b** a 2-min period of head down tilting, **c** a 60-s period after return to the horizontal position. Ten second averages are given



levels, left the blood pressure below normal level. Lewis concludes here that “undoubtedly the main cause of the fall in blood pressure in the attacks, and the enfeeblement or loss of pulse, is independent of the vagus and lies in the blood vessels” [28]. It is important to note that Lewis’

views on the decisive role of vasodilatation were based on *clinical impressions*, not actual measurements.

The first evidence that pronounced vasodilatation occurs during fainting was provided by Barcroft’s studies [2]. In his classical studies performed in seven healthy young

volunteers, fainting was induced by occluding cuffs and allowing a large amount of venous blood (1 L). Cardiac output, measured by the Fick method at the moment of the onset of faint (no hypotension yet), had decreased by about 40% (from about 5 L/min to about 3 L/min) [1, 2], but did not decrease further during the actual faint. Barcroft concluded, therefore, that the fall in pressure must have been due to peripheral vasodilatation. A large increase in forearm blood flow (increase in flow from about 2.5 supine to 5 cc/100 cc limb/min measured by water plethysmography during a faint supported this view [1, 2]. The findings in Barcroft's classical studies seem contradictory to our observations of little change in TPR during PPFH. However, the induction of fainting, the analysis of the hemodynamic events and the subjects involved in Barcroft's studies are quite different from our study. The vasovagal faints induced by Barcroft in young healthy volunteers were severe. Loss of consciousness was prolonged (up to 5 min) and hypotension (systolic blood pressures 40–70 mmHg for >5 min) was profound. Our studies were performed in the older subjects (31–72 years) with a typical clinical history of vasovagal fainting, and *presyncope* was the intended endpoint of tilt-table induced orthostatic stress. Furthermore, Barcroft's analysis relied on infrequent hemodynamic measurements, whereas we had the luxury of continuous hemodynamic recordings. For example, Barcroft's analysis of one faint was based on only three measurements of CO (1 just prior to the onset of syncope and 2 during syncope) over an 8-min period. The Fick CO measurements Barcroft used probably took 30 s to 2 min [9].

Fick CO measurements are based on accurate measurement of oxygen uptake in the lung and saturation of arterial and mixed venous blood. They require a stable respiratory rate, heart rate, oxygen consumption and respiratory exchange ratio to fulfill the assumptions underlying the measurement [14]. Under the very rapid changes in these variables during a vasovagal faint, these steady-state requirements are obviously not met. Only general trends can be interpreted from the Fick cardiac outputs during cardiovascular collapse and during an unsteady state, the data on Fick cardiac output are meaningless [13].

It is also important to note that some of the earlier investigators like Weissler [45] emphasized that the fall in TPR was not compensated for by a rise in cardiac output, as occurs in normal individuals in the presence of widespread vasodilatation. Glick [17] concluded from hemodynamic changes during spontaneous vasovagal reactions at the time of cardiac catheterization that a combination of a fall both in cardiac index and in systemic vascular resistance occurred.

Why cardiac output remained inappropriately low remained unclear to these investigators. A decrease in central blood volume was supposed to play a major role, but cardiac depression could not be excluded [44]. The predominant role of a decrease in CO as the main mechanism underlying hypotension during PPFH in the present study is in excellent agreement with our recent studies on tilt-induced syncope [16, 41, 42].

Limitations of the study

There are several limitations of the present study. First, the numbers are small and it is a retrospective study. Second, ideally, traditional pulse wave analysis methods for estimating CO during orthostasis in individual subjects require calibration against a standard method for each body position. However, the supine group average hemodynamic parameters obtained by Modelflow in the present study are in excellent agreement with values obtained by rebreathing [39], and the indicator dilution technique [31]. Third, the dP/dt calculation from a peripheral vessel has only recently been introduced. Finally, there is a theoretical concern that nitro-glycerine may cross the blood–brain barrier and mediate central sympathoinhibition [29]. However, in practice this does not seem to be important. Several tilt studies comparing haemodynamics in patients with and without GTN have found no evidence of a central effect on heart rate during presyncope [16, 42].

Conclusion

Prolonged post faint hypotension seems to originate from severe cardiac depression. This novel observation obtained in a retrospective study with a small number of subjects should be confirmed in future studies.

Conflict of interest The authors declare that they have no conflict of interest.

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