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Catecholamine response during haemodynamically stable upright posture in individuals with and without tilt-table induced vasovagal syncope

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Aim Changes in circulating catecholamine concentrations during vasovagal faints have been the subject of considerable study. However, whether catecholamines are part of the triggering mechanism, or principally reflect attempted compensation for an evolving circulatory crisis is unknown. To address this issue, we determined whether the circulating catecholamine response to upright posture differs among patients with and without inducible vasovagal faints at a time when there is no detectable haemodynamic compromise.

Methods and Results Blood samples for measurement of adrenaline and noradrenaline (Norepi) concentrations were obtained in the baseline state, and at both 2–3 min and 4–6 min of upright posture in 22 patients undergoing head-up tilt-table testing for evaluation of syncope of unknown cause. In 11 individuals tilt-testing induced syncope at >5 min head-up posture (Group 1). In 11 other individuals tilt testing did not result in syncope (Group 2). Supine arterial catecholamine levels were comparable in the two groups. However, adrenaline concentratrions during upright posture tended to be greater at 2–3 min and were significantly greater at 4–6 min in Group 1 than in Group 2 ($P<0{\cdot}01$). These differences occurred in the absence of significant intergroup differences in mean arterial pressure or cardiac cycle lengths. Norepi concentrations also increased in both groups, but without significant differences.

Conclusion Circulating adrenaline concentrations in posturally induced vasovagal faints rise more rapidly in vasovagal fainters than in comparably posturally stressed non-fainters, and were significantly greater in fainters prior to either detectable haemodynamic compromise or diminution of circulating Norepi levels. These findings suggest that a premonitory rise in adrenaline concentrations occurs in vasovagal fainters unassociated with an evolving circulatory crisis.
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Key Words: Vasovagal syncope, tilt-table testing, catecholamines.

Introduction

Increased concentrations of circulating catecholamine (particularly adrenaline, Epi) have been well documented in conjunction with both spontaneous and posturally induced vasovagal faints[1–9]. However, it is uncertain whether this neuro-endocrine response is a unique marker of susceptibility to an evolving vasovagal faint as implied by Jardine *et al.*[9], or primarily reflects an appropriate physiological attempt to compensate for an evolving circulatory crisis[1–4]. The objective of this study was to further investigate whether the catecholamine response to immediate upright posture (before there is evidence of haemodynamic compromise) differs in individuals who ultimately exhibit a posturally induced vasovagal faint during head-up tilt table testing, compared with those who did not.

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Methods

Patient population

Thirty-five patients (19 males and 16 females: 16 to 73 years of age) were initially included in this study. Each

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of these individuals had a history of recurrent syncope (the cause of which remained uncertain despite careful review of the medical history, physical examination, and electrocardiographic recordings), absence of clinically significant structural heart disease (left ventricular ejection fraction estimated to be >45%), and absence of use of drugs known to predispose to orthostatic-hypotension. In all cases any cardioactive medications were withdrawn at least five half lives prior to study. Additionally, in order to obtain blood samples during a relatively stable haemodynamic state, it was necessary to exclude patients in whom head-up tilt testing induced syncope at <5 min after assumption of upright posture. All patients provided written informed consent for these studies.

Upright tilt-table testing protocol

Informed consent was obtained from all patients prior to study. Head-up tilt-table testing was deemed indicated in an attempt to clarify the basis of syncope in each case[10–12]. In all studies, arterial pressure was monitored continuously utilizing a 5 French intra-arterial catheter positioned within the femoral artery. Arterial pressure was calibrated to right atrial level throughout the study. A minimum 20 min equilibration period with the patient resting in the supine position was allowed after placement of lines and prior to commencement of baseline recordings. To minimize potential effects of volume depletion associated with the fasting state, each individual received 500 to 750 ml of normal saline during the equilibration period (i.e., approximately 75 ml per fasting hour prior to study). Further, the withdrawal site from the arterial line was positioned in a manner designed to minimize patient perception of blood withdrawal during the procedure.

Head-up tilt testing comprised 70° upright posture without pharmacological intervention. Head-up posture was maintained until development of either syncope or intolerable pre-syncopal symptoms, or completion of a maximum 45 min tilt duration. Following achievement of a clinical endpoint, or completion of the head-up tilt test duration, the patient was promptly returned to the supine position.

Catecholamine sampling and measurements

Arterial blood samples (approximately 5 cc each) were withdrawn from the arterial line (actual sampling site being approximately at the level of the mid abdominal aorta) for measurement of Epi and noradrenaline (Norepi) plasma concentrations by high-pressure liquid chromotography (HPLC) technique. In all individuals, initial samples were obtained after the patient had been resting undisturbed in the supine position for at least 20 min during the equilibration period, and subsequently at approximately 2–3 min and 4–6 min after commencement of head-up tilt. Since blood sampling required slow withdrawal and subsequent fluid re-infusion to minimize haemodynamic impact of blood withdrawal, the exact timing of samples varied and is consequently reported as being within the time ranges noted. In all cases, care was taken to re-infuse excess blood and to replace fluid by an equivalent volume of normal saline.

Definitions

A positive response to upright tilt table testing was defined as development of syncope or intolerable pre-syncopal symptoms in conjunction with demonstrable hypotension (i.e., mean arterial pressure reduction >25 mm Hg).

Data analysis

In each individual, cardiac cycle length and arterial blood pressure were recorded continuously throughout the study. Reported data comprise an average of three cycle lengths and blood pressure values most closely corresponding to the relevant catecholamine measurements. Unless otherwise indicated, findings are expressed as mean ± SD.

The statistical significance of cardiac cycle length, blood pressure and catecholamine concentrations was evaluated by Student's t-test, and by analysis of variance (ANOVA) as appropriate. A P value of <0·05 was considered statistically significant.

Results

Baseline findings

Among the 35 syncope patients included in this study, 5 were excluded due to having had positive studies at <5 min. Fourteen patients had a positive response to head-up tilt-table testing at 5 min, and 16 remained asymptomatic. Among the 14 tilt-positive patients, a complete complement of blood samples was not obtained in 3 individuals. Thus, the tilt-table positive syncope patients (Group 1) comprised 11 individuals (5 males and 6 females, ages 19 to 73 years) (Table 1). The time from onset of tilt to syncope ranged from 6 to 27 min. Among the 16 tilt-negative patients, a complete complement of blood samples was obtained in 11 individuals (8 males and 3 females, age range 16 to 66 years). Apart from the preponderance of males in Group 2, other demographic factors such as age, baseline arterial blood pressure, and baseline cardiac cycle length, did not differ significantly among the two groups (Table 1). Similarly, baseline supine arterial Epi (Group 1, 61 ± 32 pg/ml vs Group 2, 73 ± 49 pg/ml) and Norepi

Table 1 Baseline data

Patient no.	Age	Sex	Time to syncope (min)	CL (ms)	EPI (pg/ml)	NEPI (pg/ml)	MBP (mm Hg)
Group 1							
1	36	F	6	740	42	178	83
2	55	M	7	920	39	418	110
3	27	M	5	880	42	200	97
4	31	F	7	840	84	442	89
5	24	F	5	600	98	320	85
6	35	M	17	1224	81	128	81
7	19	M	8	1034	58	218	110
8	63	F	25	741	129	330	112
9	46	M	7	967	33	186	80
10	73	F	27	638	44	242	127
11	65	F	25	769	26	167	79
AVG	43		13	850	61	257	96
SD	18		9	182	32	105	16
Group 2							
1	36	M	N/a	880	65	177	100
2	16	M	N/a	710	32	176	94
3	66	M	N/a	860	52	245	113
4	49	M	N/a	900	51	132	90
5	61	M	N/a	1034	28	240	90
6	52	M	N/a	1000	20	137	90
7	47	M	N/a	880	73	287	100
8	28	M	N/a	1020	132	226	100
9	48	F	N/a	1000	132	89	90
10	31	F	N/a	900	166	220	90
11	60	F	N/a	645	51	281	102
AVG	45			894	73	201	96
SD	16			125	49	64	7

N/a=not applicable, CL=cycle length, MBP=mean arterial pressure.

(Group 1, 257 ± 105 pg/ml vs Group 2, 201 ± 64 pg/ml) levels were comparable (P=NS for both parameters).

Initial response to upright tilt

At the initial head-up measurement period (2–3 min), mean arterial pressure was not significantly different from supine values in either group, whereas cardiac cycle length shortened comparably in both Group 1 and Group 2 patients from supine values (Fig. 1, panel A and B). Similarly, both arterial Epi and Norepi concentrations did not differ between the two groups (Epi: Group 1, 127 ± 118 pg/ml vs Group 2, 124 ± 100 pg/ml; Norepi: Group 1, 356 ± 85 pg/ml vs Group 2, 359 ± 141 pg/ml) (Fig. 1, panel C and D).

Responses at 4–6 min of head-up tilt

Mean arterial pressure at 4–6 min did not differ significantly from the 2–3 min time period in either patient group (Fig. 1, panel A). Further, mean arterial pressure did not differ significantly between the two groups at the 4–6 min sampling point. Similarly, cardiac cycle length changes did not differ between the two groups at the 4–6 min time point, and had not changed substantially from 2–3 min values (Fig. 1, panel B). On the other hand, there was a greater increment in circulating arterial Epi concentrations from both baseline values and 2–3 min upright values in Group 1 patients compared with Group 2 (365 ± 259 pg/ml and 141 ± 101 pg/ml, respectively) (P<0·05) (Fig. 1, panel C). Norepi also increased from baseline in both groups, but the increment did not differ significantly in the two groups (412 ± 139 pg/ml and 404 ± 162 pg/ml) (Fig. 1, panel D).

Responses at completion of head-up tilt

At the completion of the tilt test (i.e., termination due to symptoms in Group 1, completion of 45 min in Group 2) mean arterial pressure was lower and cardiac cycle length was longer in Group 1 (P<0·05) than in Group 2 (Fig. 1, panel A and B). Further, in Group 1 the arterial Epi concentration was significantly greater in Group 1 compared with Group 2 (933 ± 517 pg/ml and 190 ± 176 pg/ml, respectively) (P<0·01). Conversely, the Norepi tended to be less in Group 1 patients but the difference was not statistically significant (521 ± 255 pg/ml vs 547 ± 175 pg/ml in Group 2).

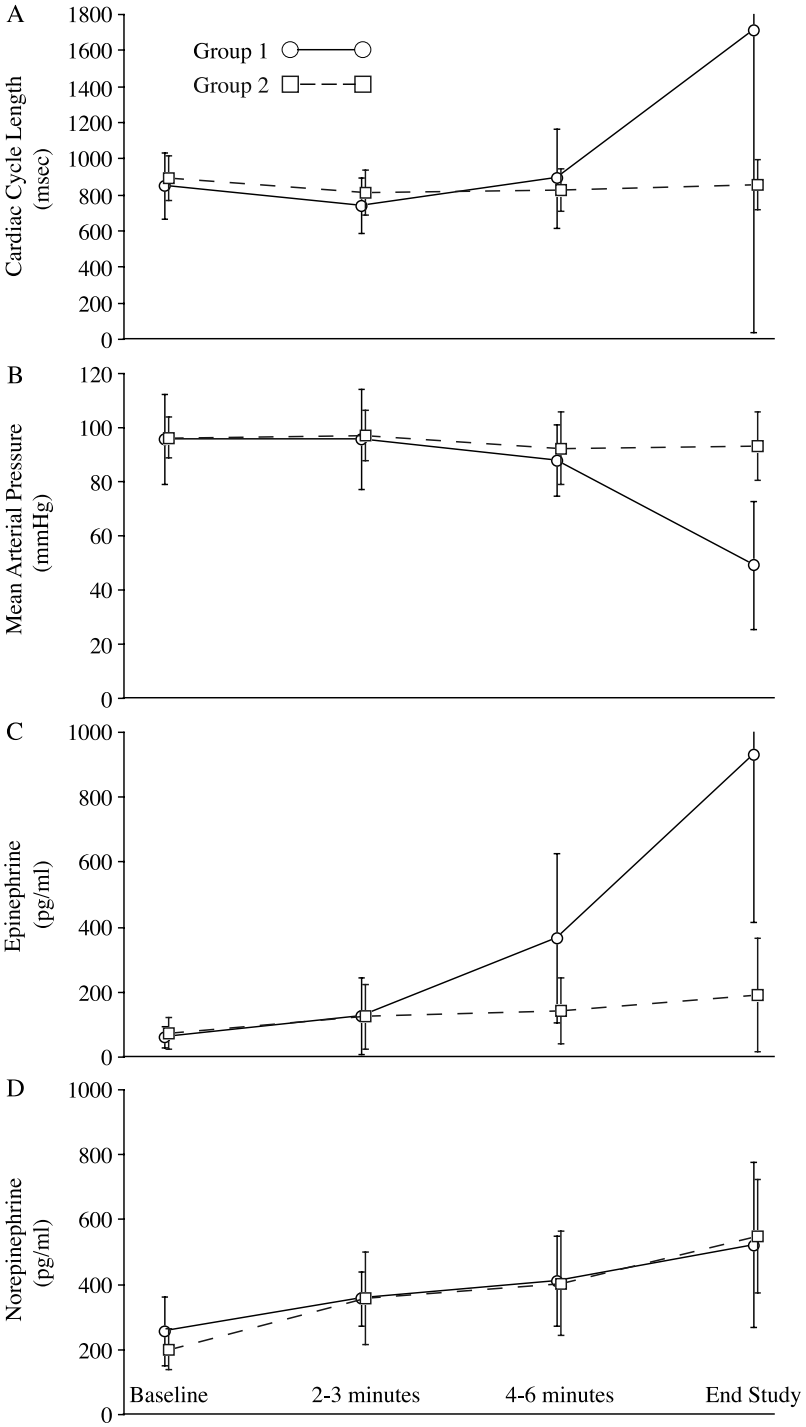


Figure 1 **Graphs depicting changes in cardiac cycle length (Panel A) and mean arterial blood pressure (Panel B), arterial Epi (Panel C), and arterial Norepi (Panel D) at baseline and at 2–3 min, 4–6 min and at syncope or completion of the tilt table test. Findings in Group 1 patients are indicated by solid lines, and findings in Group 2 patients are shown in hatched lines. In both groups, cardiac cycle length and blood pressure were well maintained both at the 2–3 min point and at the 4–6 min point. Norepi concentrations tended to increase comparably in both Group 1 and Group 2 patients throughout the study. On the other hand, increased circulating Epi concentrations were evident in Group 1 patients as early as the 4–6 min time period even though neither cardiac cycle length nor blood pressure differ from those observed in Group 2 patients.**

Discussion

The association of vasovagal syncope with markedly elevated circulating Epi concentrations has been amply documented in previous reports[1–9]. The principal finding in this study is that the excess Epi levels associated with the vasovagal faint are detectable well before significant changes in heart rate or arterial pressure occur. Further, the rise in Epi occurs at a time when Norepi levels are still comparable with those recorded in non-fainters subjected to upright posture. Consequently, our findings tend to support the view previously expressed by Jardine *et al.*[9] that the magnitude of the initial posturally induced Epi response in vasovagal fainters does not appear to be secondary to an evolving circulatory crisis. More likely, the observed catecholamine changes are one among several primary neuro-endocrine factors associated with the vasovagal event.

Adrenaline in neurally mediated syncope

In vasovagal syncope, symptomatic hypotension is usually the consequence of both bradycardia (which may or may not be severe) and peripheral vasodilatation[10–14]. The afferent neural signals triggering the episode may originate directly from the cerebral cortex, or from any of a variety of peripheral 'receptors' which respond to mechanical or chemical stimuli, pain, or possibly even temperature change.

Whether catecholamines have a direct role to play in triggering vasovagal syncopal symptoms is unknown. Nevertheless, the association increased catecholamine levels with vasovagal episodes has been recognized for some time. Chosy and Graham[1] noted that urinary catecholamine levels were substantially higher prior to syncope in fainters than in control subjects, while Vingerhoets[3] observed an increase of more than 60% in plasma catecholamines in 2 patients just prior to vasovagal faints compared to supine control values. Fitzpatrick *et al.*[6] and Sra *et al.*[7] also documented markedly higher Epi levels at the time of syncope in tilt-table test positive patients than in control subjects. However, only Jardine *et al.*[9] provided observations sufficiently early in the evolving faint to support the view that the catecholamine changes precede haemodynamic events. Our findings are consistent with this latter concept.

Circulating catecholamines and heart rate

Sinus tachycardia is a common and anticipated finding after assumption of upright posture. Further, in regard to tilt-table testing it has been suggested that the magnitude of tachycardia at this stage provides an indicator of syncope-susceptible individuals[6,12–14]. Additionally, sinus tachycardia would be expected in the presence of high circulating Epi levels. Nevertheless, in our study, despite elevated Epi levels early during head-up tilt in Group 1 patients, cycle length shortening (heart rate increments) during the early phase of testing did not differ significantly from those observed in Group 2 patients.

Failure of early increments of circulating Epi to be associated with a greater degree of sinus tachycardia in Group 1 patients suggests that a balancing restraint on heart rate response was also present in these individuals. Most probably, the restraining effect results from either a gradual increase in efferent parasympathetic tone as the event evolves, or alternatively failure of parasympathetic 'withdrawal' to occur as is usually expected in association with assumption of upright posture. The latter possibility is supported by observations of Morillo *et al.*[15] which indicate that parasympathetic restraint (as assessed by heart rate variability indices) persists for longer periods after assumption of upright posture in syncope-prone individuals than in control subjects. Conceivably, such a tendency would require higher compensatory levels of sympathetic tone in order to maintain circulatory stability, and may thereby be the basis for the early demand for adrenal adrenergic activity in syncope prone patients. In this regard, the precise balance between adrenal and peripheral catecholamine contributions to circulating catecholamine levels has yet to be reported.

Conclusions

This study confirms the close association between markedly elevated circulating Epi levels and the development of neurally mediated syncope in young and middle-aged patients. Further, since elevated Epi concentrations antedate either measurable heart rate and blood pressure changes or diminished Norepi levels, our findings support the proposition expressed by Jardine *et al.*[9] that Epi release cannot be considered solely a compensatory response to circulatory stress. In fact, this neuroendocrine response may be an independent marker of susceptibility to an imminent faint. Conceivably, Epi may enhance sensitivity of the peripheral receptors thought to participate in the afferent limb of the reflex, and thus the propensity to an initial Epi surge may be one of the factors characterizing individual susceptibility to posturally induced vasovagal faints. The development of surrogate measures of Epi activity may thereby be useful as a means of detecting an imminent faint.

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