Temporary elimination of orthostatic hypotension by norepinephrine infusion

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Received: 8 March 2012 / Accepted: 16 August 2012
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Abstract A cardinal manifestation of chronic autonomic failure is neurogenic orthostatic hypotension (OH), which often is associated with supine hypertension, posing a therapeutic dilemma. We report here success in a first step toward development of a “prosthetic baroreceptor system” to maintain blood pressure during orthostasis without worsening supine hypertension. In all of four patients with neurogenic OH, titrated i.v. NE infusion kept directly recorded intra-arterial pressure at or above baseline during progressive head-up tilt. We conclude that titrated i.v. NE infusion temporarily eliminates OH.

Keywords Norepinephrine · Orthostatic hypotension · Sympathetic nervous system · Baroreflex

Abbreviations

NE Norepinephrine
OH Orthostatic hypotension

Introduction

Orthostatic hypotension (OH) is a cardinal manifestation of chronic autonomic failure. OH is considered to be neurogenic when associated with physiological or neurochemical evidence of deficient baroreflex-mediated release of the neurotransmitter norepinephrine from sympathetic nerves.

Patients with neurogenic OH often have supine hypertension, the magnitude of which is correlated with that of OH and is severe in about half of patients with OH. The co-occurrence of supine hypertension with OH poses an obvious clinical therapeutic dilemma, because treatments for OH, such as fludrocortisone to retain salt and water or midodrine to constrict blood vessels, increase the likelihood of supine hypertension.

The OH attending chronic autonomic failure is associated with attenuated orthostatic increments in plasma norepinephrine levels. In contrast, pressor responses to infused norepinephrine are augmented, due to baroreflex failure and, in some patients, denervation supersensitivity. These considerations lead straightforwardly to the prediction that administration of exogenous norepinephrine should attenuate or prevent OH.

More than a quarter century ago, Polinsky et al. [9] reported successful testing of a “sympathetic neural prosthesis” that coupled intra-arterial blood pressure recording with a computer-controlled infusion pump for varying the rate of i.v. norepinephrine administration. The computer-controlled approach proved inadequate. Since then, case studies have noted sometimes spectacular improvement in orthostatic tolerance in patients receiving norepinephrine by vein or subcutaneously [4–8], without continuous pressure monitoring or titration of the norepinephrine infusion rate. Whether manually titrated i.v. norepinephrine infusion can temporarily eliminate neurogenic OH has not

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been formally tested. This was the main purpose of the present study, which we viewed as a first step toward development of a “prosthetic baroreceptor system” to maintain blood pressure during orthostasis without worsening supine hypertension.

We studied patients with pure autonomic failure or Parkinson’s disease with orthostatic hypotension, since in such patients baroreflex failure and denervation supersensitivity were expected to render i.v. norepinephrine particularly efficacious in raising the blood pressure. For continuous, assured measurement of blood pressure we used an intra-arterial catheter. Hemodynamic responses at progressively increasing angles of head-up tilt were related to arterial plasma concentrations of norepinephrine and of its main neuronal metabolite, dihydroxyphenylglycol.

Methods

Subjects

The subjects were four patients with neurogenic OH associated with pure autonomic failure ($N = 3$) or Parkinson’s disease with OH ($N = 1$). The patients gave written informed consent before participating in the study, which was approved by the Institutional Review Board of the NINDS. OH was defined by a persistent, consistent fall in systolic pressure of at least 20 mmHg or diastolic pressure of at least 10 mmHg between supine rest and 3 min of upright posture. All the patients also had abnormal beat-to-beat blood pressure responses to the Valsalva maneuver and attenuated orthostatic increments in plasma norepinephrine levels, indicating baroreflex-sympathoneural failure.

Experimental design

This was a placebo-controlled study that consisted of two experimental days per participant. Neither the patients nor the investigators were blinded.

On a day of baseline testing, each patient underwent head-up tilting (20°, 40°, and 60° from horizontal) while blood pressure was monitored non-invasively continuously. Tilt angles were increased until the patient had orthostatic symptoms, systolic pressure decreased to less than 90 mmHg, or there was more than an 80 mmHg decrease in systolic pressure.

On the experimental testing day, patients received norepinephrine and placebo, with the sequence of treatments varied (2 norepinephrine first, 2 placebo first). Placebo consisted of normal saline infused i.v. to keep the vein open. When placebo was given, angles of tilt were increased with the same stopping rules as for the baseline

day. Norepinephrine was infused at doses titrated to keep directly recorded systolic blood pressure at or above the baseline value during exposure to higher tilt angles. The initial infusion rate was 3.5 ng/kg/min and in general was increased to 7, 14, and up to 35 ng/kg/min as tilting progressed.

The main dependent measure was the extent to which norepinephrine infusion maintained systolic blood pressure, by comparison with the changes in pressure at the same tilt angles during saline administration or on the baseline testing day. Secondary dependent measures were plasma levels of norepinephrine and dihydroxyphenylglycol. At each tilt angle during norepinephrine infusion we asked the patients what if anything they felt that was different.

Hemodynamic monitoring

Intra-arterial blood pressure was monitored continuously via a plastic catheter that had been inserted percutaneously into a brachial or radial artery after local anesthesia of the overlying skin. The catheter was flushed periodically with dilute heparin solution. Blood pressure was also monitored noninvasively using a finger cuff device (Nexfin, BMEYE, Amsterdam, The Netherlands). Beat-to-beat heart rate was measured by the electrocardiographic interbeat interval (PowerLab, ADInstruments, Colorado Springs, CO). Cardiac stroke volume was calculated using a software application with the Nexfin device.

Neurochemistry

Plasma levels of catechols were assayed in our laboratory by batch alumina extraction followed by liquid chromatography with electrochemical detection, as described previously [2].

Data analysis and statistics

Values for hemodynamics and arterial plasma catechols across tilt angles were analyzed by repeated measures analyses of variance, with Fisher’s PLSD post hoc test (Kaleidagraph 4.0, Synergy Software, Reading, PA). To compare two values (e.g., baseline vs. maximum attained tilt angle), one-tailed t-tests were used, since there was a directional hypothesis. A p value of less than 0.05 defined statistical significance.

Results

As expected, both on the baseline day and during saline administration on the experimental testing day, blood pressure fell during head-up tilting, in a manner related to

Fig. 1 Mean ($\pm$ SEM) blood pressure and arterial plasma norepinephrine (NE) as a function of tilt angle in patients with neurogenic OH. (*Left*) systolic blood pressure; (*right*) arterial plasma norepinephrine. Numbers are numbers of patients. White circles show data

for i.v. infusion of saline (Placebo); gray circles data on the baseline day; and black circles data during NE infusion. Note tilt angle-related falls in systolic pressure on the baseline day and during placebo administration and elimination of OH by titrated NE infusion

the tilt angle (Fig. 1; Table 1). On the baseline day, only three of the four patients were able to tolerate 60° of tilting, and during saline administration on the testing day only two of the patients were able to tolerate 60° of tilting.

On the baseline day, between 0° and the maximum tolerated tilt angle, systolic blood pressure decreased by $28 \pm 6 \%$ ($p = 0.008$), mean arterial pressure $21 \pm 6 \%$ ($p = 0.02$), and stroke volume $29 \pm 7 \%$ ($p = 0.01$), while total peripheral resistance did not change. During saline administration on the experimental testing day, between 0° and the maximum tolerated tilt angle systolic blood pressure decreased by $28 \pm 5 \%$ ($p = 0.004$), mean

arterial pressure $22 \pm 7 \%$ ($p = 0.02$), and stroke volume $25 \pm 1 \%$ ($p < 0.001$), while total peripheral resistance did not change. Thus, the hemodynamic data were quite similar on the baseline day and during saline administration on the experimental testing day.

In complete contrast, during norepinephrine infusion on the experimental testing day, systolic and mean arterial pressure did not change during tilt. Although stroke volume decreased by $21 \pm 3 \%$ ($p = 0.003$), total peripheral resistance increased by $17 \pm 4 \%$ ($p = 0.009$). In all patients, titrated norepinephrine infusion maintained the systolic blood pressure at or above the baseline value.

Table 1 Hemodynamic and neurochemical mean ($\pm$ SEM) values as a function of angle of head-up tilt on the baseline day, during saline administration on the experimental testing day, and during i.v. norepinephrine infusion

COND.	ANGLE	BPs (mmHg)	BPd (mmHg)	MAP (mmHg)	HR (bpm)	SV (mL)	CO (L/min)	TPR (units)	NE (nmol/L)	DHPG (nmol/L)
Baseline (N = 3)	0	156 $\pm$ 15	83 $\pm$ 7	107 $\pm$ 10	62 $\pm$ 4	76 $\pm$ 15	4.6 $\pm$ 0.6	22.4 $\pm$ 1.6	0.78 $\pm$ 0.29	3.42 $\pm$ 0.26
	20	148 $\pm$ 11	85 $\pm$ 6	106 $\pm$ 8	57 $\pm$ 2	70 $\pm$ 15	3.9 $\pm$ 0.7*	26.9 $\pm$ 3.1	0.89 $\pm$ 0.34	3.44 $\pm$ 0.22
	40	131 $\pm$ 48	79 $\pm$ 4	96 $\pm$ 45	55 $\pm$ 3	62 $\pm$ 13	3.4 $\pm$ 0.5**	27.7 $\pm$ 3.5	1.04 $\pm$ 0.40*	3.82 $\pm$ 0.46
	60	112 $\pm$ 3**	73 $\pm$ 3	86 $\pm$ 3*	65 $\pm$ 3	52 $\pm$ 5*	3.4 $\pm$ 0.4*	24.5 $\pm$ 2.8	1.30 $\pm$ 0.48*	4.39 $\pm$ 0.56*
Saline (N = 2)	0	158 $\pm$ 16	83 $\pm$ 2	108 $\pm$ 7	55 $\pm$ 8	66 $\pm$ 20	3.8 $\pm$ 1.6	34 $\pm$ 16	0.82 $\pm$ 0.33	4.01 $\pm$ 0.32
	20	149 $\pm$ 9*	84 $\pm$ 3	106 $\pm$ 5	56 $\pm$ 3	62 $\pm$ 20	3.5 $\pm$ 1.3	33 $\pm$ 14	0.65 $\pm$ 0.22	3.97 $\pm$ 0.28
	40	128 $\pm$ 4*	81 $\pm$ 4	97 $\pm$ 4*	58 $\pm$ 3*	56 $\pm$ 18**	3.3 $\pm$ 1.2*	32 $\pm$ 13	0.97 $\pm$ 0.39	4.18 $\pm$ 0.30
	60	120 $\pm$ 3	80 $\pm$ 4	93 $\pm$ 3	63 $\pm$ 4	50 $\pm$ 14	3.2 $\pm$ 1.1	30 $\pm$ 9	2.32 $\pm$ 0.02	5.00 $\pm$ 0.33
NE (N = 4)	0	179 $\pm$ 14	95 $\pm$ 6	123 $\pm$ 9	58 $\pm$ 5	83 $\pm$ 13	4.9 $\pm$ 1.0	27 $\pm$ 6	0.73 $\pm$ 0.22	4.07 $\pm$ 0.40
	20	173 $\pm$ 10	95 $\pm$ 4	121 $\pm$ 6	60 $\pm$ 4	82 $\pm$ 13	5.1 $\pm$ 1.0	26 $\pm$ 7	1.99 $\pm$ 0.67	4.05 $\pm$ 0.34
	40	167 $\pm$ 11	92 $\pm$ 5	116 $\pm$ 7	59 $\pm$ 4	76 $\pm$ 11	4.6 $\pm$ 0.9	28 $\pm$ 7	3.73 $\pm$ 0.94**	4.12 $\pm$ 0.45
	60	175 $\pm$ 15	98 $\pm$ 7	124 $\pm$ 9	63 $\pm$ 2	67 $\pm$ 12	4.2 $\pm$ 0.8	31 $\pm$ 6	7.83 $\pm$ 1.40*	4.47 $\pm$ 0.52*

BPs systolic blood pressure, BPd diastolic blood pressure, MAP mean arterial pressure, HR heart rate, SV cardiac stroke volume, CO cardiac output, TPR total peripheral resistance, NE norepinephrine, DHPG dihydroxyphenylglycol

* Different from 0°, $p < 0.05$; ** different from 0°, $p < 0.01$

On the baseline day, between 0° and the maximum tolerated tilt angle, arm venous plasma norepinephrine increased by $46 \pm 18 \%$ ($p = 0.04$) and dihydroxyphenylglycol tended to increase by $17 \pm 8 \%$ ($p = 0.06$). During saline administration on the norepinephrine infusion day, between 0° and the maximum tolerated tilt angle arterial plasma norepinephrine increased by $46 \pm 21 \%$ ($p = 0.06$) and dihydroxyphenylglycol by $7 \pm 2 \%$ ($p = 0.02$). During norepinephrine infusion, arterial plasma norepinephrine increased by $1262 \pm 362 \%$ ($p = 0.02$) and dihydroxyphenylglycol by $9 \pm 2 \%$ ($p = 0.008$).

There were no adverse events or symptoms related to i.v. norepinephrine infusion.

Discussion

The results of this study demonstrate that titrated i.v. infusion of norepinephrine temporarily eliminates OH. All four patients had tilt angle-related OH both on the baseline day and during saline administration on the experimental testing day, and in all four blood pressure was maintained at or above the baseline level at the maximum tilt angle in the study, 60°, without adverse events or symptoms.

Orthostatic hypotension was associated with substantial decreases in cardiac stroke volume without a change in total peripheral resistance, consistent with decreased venous return to the heart and deficient reflexive sympathetically mediated vasoconstriction. During norepinephrine infusion, cardiac stroke volume decreased during tilting, but total peripheral resistance increased, reflecting vasoconstriction evoked by circulating norepinephrine.

At a tilt angle of 60°, mean arterial pressure was decreased by about 20 mmHg on the baseline day and during saline administration on the experimental testing day, whereas norepinephrine infusion maintained the mean arterial pressure at or above the baseline value. The corresponding arterial plasma norepinephrine concentration was about 7 nmol/L above baseline. In healthy volunteers, norepinephrine infusion to increase mean arterial pressure by 20 mmHg is associated with an increment in the arterial plasma norepinephrine concentration of about 28 nmol/L above baseline [1]. Thus, the patients in the present study required only about one-fourth the arterial plasma norepinephrine concentration that healthy volunteers have been found to require to produce a 20-mm increment in blood pressure. Adrenoceptor supersensitivity and baroreflex failure [3, 10] can explain the much lower plasma norepinephrine concentration required to evoke the same pressor response.

During norepinephrine infusion, the mean increment in arterial plasma levels of dihydroxyphenylglycol was smaller than expected for the increment in plasma

norepinephrine [1]. A straightforward explanation for this phenomenon is that the increment in plasma dihydroxyphenylglycol depends importantly on neuronal uptake of circulating norepinephrine, and the patients had evidence for cardiac and extra-cardiac sympathetic noradrenergic denervation.

The stage is now set for the second phase of development of a prosthetic baroreceptor system for OH, which is norepinephrine infusion via a centralized i.v. coupled with non-invasive continuous blood pressure monitoring in ambulatory inpatients.

Acknowledgments The research reported here was supported by the Division of Intramural Research of the National Institute of Neurological Disorders and Stroke.

Conflict of interest The authors have no conflicts of interest to disclose.

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