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### **Research Article**

In this study, we evaluated if increased sympathetic stimulation is an essential requirement for the development of neurally mediated syncope (NMS) by manipulating overall sympathetic outflow in subjects susceptible to tilt-induced syncope. Eight previously characterized patients with recurrent NMS (five females and three males; 34±2 yr) were recruited from the Vanderbilt Syncope Unit and eight age-matched controls underwent initial administration of clonidine (CLO) or yohimbine (YHO). This was done, prospectively, to determine doses of these agents that would increase or decrease plasma norepinephrine levels by ≥ 30%. On a different day, in all subjects we determined intraarterial blood pressure, EKG and muscle sympathetic nerve activity (MSNA) both supine and during upright tilt. After this, subjects randomly received either CLO or YHO, and 3 h later another tilt was performed. After 1 wk, a similar procedure with the other drug was performed. During the two basal tilts, all the control subjects completed the study, whereas all the NMS patients developed syncope. Reduction in sympathetic tone by CLO resulted in a decreased tolerance to tilt in three out of eight controls and in all the NMS patients. In contrast, YHO not only increased basal plasma NorEpi levels and MSNA, but also prevented syncope in seven out of eight patients. In a selected population of patients, increased sympathetic activity is not a prerequisite [...]

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# Yohimbine in Neurally Mediated Syncope

## Pathophysiological Implications

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### Abstract

In this study, we evaluated if increased sympathetic stimulation is an essential requirement for the development of neurally mediated syncope (NMS) by manipulating overall sympathetic outflow in subjects susceptible to tilt-induced syncope.

Eight previously characterized patients with recurrent NMS (five females and three males;  $34 \pm 2$  yr) were recruited from the Vanderbilt Syncope Unit and eight age-matched controls underwent initial administration of clonidine (CLO) or yohimbine (YHO). This was done, prospectively, to determine doses of these agents that would increase or decrease plasma norepinephrine levels by  $\geq 30\%$ . On a different day, in all subjects we determined intraarterial blood pressure, EKG and muscle sympathetic nerve activity (MSNA) both supine and during upright tilt. After this, subjects randomly received either CLO or YHO, and 3 h later another tilt was performed. After 1 wk, a similar procedure with the other drug was performed.

During the two basal tilts, all the control subjects completed the study, whereas all the NMS patients developed syncope. Reduction in sympathetic tone by CLO resulted in a decreased tolerance to tilt in three out of eight controls and in all the NMS patients. In contrast, YHO not only increased basal plasma NorEpi levels and MSNA, but also prevented syncope in seven out of eight patients.

In a selected population of patients, increased sympathetic activity is not a prerequisite for the development of syncope. Yohimbine-induced enhancement of sympathetic tone in patients with NMS improves orthostatic tolerance and raises the possibility that this drug may be a useful agent in the treatment of NMS. (*J. Clin. Invest.* 1998; 102: 1824–1830.) Key words: neurocardiogenic syncope • vasovagal • microneurography • tilt • sympathetic function

### Introduction

Neurally mediated (vasovagal, vasodepressor, or neurocardiogenic) syncope is one of the most frequent causes of transient

loss of consciousness not caused by trauma or seizures (1, 2). Clinically, neurally mediated syncope (NMS)<sup>1</sup> most often results from a combination of vasodepressor and cardioinhibitory responses (3–5). In other instances, however, NMS patients may exhibit a predominately cardioinhibitory component (extended period of bradycardia or asystole) or a pure vasodepressor response (5). One of the proposed mechanisms for the development of NMS involves exaggerated sympathetic cardiac stimulation in combination with relative ventricular hypovolemia (6, 7). Presumably, this results in activation of myocardial ventricular afferents that, in turn, triggers a reflex characterized by sudden sympathetic withdrawal and parasympathetic activation (8). This proposed mechanism, which has been termed the “ventricular theory,” seems to provide a rational basis for the therapeutic use of  $\beta$ -adrenergic receptor blockers (7), and the combination of isoproterenol and tilt in the diagnostic workup of neurally mediated syncope (9, 10).

Several experimental observations, however, do not support a predominant role for ventricular receptors in subjects with neurally mediated syncope. Experiments in animals have demonstrated that despite bilateral vagotomy or total cardiac denervation, sympathetic nerve activity falls (in a manner reminiscent of neurally mediated syncope) during hypotensive hemorrhage (11). In humans, neurally mediated hypotension and bradycardia with preceding sympathetic withdrawal have been similarly observed in patients with intact and with denervated ventricles (i.e., heart transplant patients) (12, 13). Furthermore, others, using echocardiographic measurements of left atrial and ventricular chamber size and determinations of stroke volume, found no evidence of excessive cardiac emptying before the onset of syncope in susceptible patients (14). More recently, a different group (15) has assessed left ventricular wall stress and segmental wall thickening preceding syncope, and found no evidence compatible with activation of left ventricular mechanoreceptors.

The other postulate of the ventricular theory (the presence of excessive sympathetic activation), has been recently challenged by experimental evidence obtained by our group (16) and by others (17, 18). In patients with recurrent neurally mediated syncope, we found no evidence of increased sympathetic activation in any of the stages of head-up tilt preceding fainting. These patients had a clearly attenuated sympathetic response to orthostatic stress characterized by a significantly blunted increase in muscle sympathetic nerve activity (MSNA) at low levels of tilt followed by progressive inhibition until complete disappearance before syncope (16, 17). Furthermore, they had abnormal baroreflex (16) function, which seemed to underlie their failure to increase sympathetic tone in response

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1. Abbreviations used in this paper: BP, blood pressure; CVP, central venous pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity; NMS, neurally mediated syncope.

to changes in gravitational stress. Our observations, however, did not rule out the possibility that a selective increase in cardiac sympathetic tone was present in this population or that the small increment in MSNA and neurohumoral norepinephrine might be enough to activate hypersensitive ventricular receptors in these patients.

The overall purpose of the present study was to investigate whether selective manipulation of sympathetic tone in patients with neurally mediated syncope can modulate the hemodynamic responses to tilt. We hypothesized that if patients with neurally mediated syncope have ventricular receptors that are sensitive to noradrenergic stimulation, an increment in sympathetic tone should aggravate and accelerate the development of syncope whereas restraint of sympathetic activity should ameliorate this syndrome. Alternatively, if the main defect resides in reduced sympathetic response, then an increment in overall sympathetic tone should enhance orthostatic tolerance and prevent the development of this type of syncope.

## Methods

**Study groups.** Patients were recruited from the Syncope Unit at the Vanderbilt Autonomic Dysfunction Center (Nashville, TN). Of 26 previously characterized patients (16) suffering from recurrent neurally mediated syncope, 11 agreed to participate in this research protocol and 8 completed it. In these patients, tilt-table testing consistently evoked syncope due to hypotension and bradycardia in the absence of any other contributory medical finding. Eight normotensive age and sex-matched controls ( $34 \pm 2$  yr) were also selected from a pool of 26 subjects who had previously participated in a related protocol (16). These subjects had normal tilt table testing on repeated occasions. All the controls and patients were familiar with all the procedures including the placement of an intraarterial line and microneurography.

**Experimental protocol.** The experimental protocol was approved by the Vanderbilt University Institutional Review Board and all subjects gave written consent before any procedure was initiated. The subjects abstained from caffeine-containing products and smoking for at least 7 d. In the patients, any medication was stopped for at least five drug half-lives before the study.

The first phase of the protocol was designed to determine the effect of a test dose of clonidine or yohimbine on plasma norepinephrine levels in each subject. These drugs were selected for their ability to decrease or increase overall sympathetic tone. For this purpose, subjects were instrumented on two different days with an intravenous antecubital line (for blood sampling) and with a Dynamap system (for noninvasive determination of arterial blood pressure and heart rate). After the subjects rested supine for at least 30 min, a blood sample was obtained for plasma catecholamines and supine, and 5-min standing basal blood pressure and heart rate were obtained. Immediately after, the subjects received a test dose of either clonidine (0.15 mg) or yohimbine (8.1 mg), and the effects on blood pres-

sure and heart rate were determined every 15 min with hourly evaluations of plasma catecholamines for 3 h. At the end of this period, supine and standing blood pressure and heart rate were again obtained. 1 wk after this, the procedure was repeated except that the other drug (either clonidine or yohimbine) was given. The changes produced by these agents on plasma norepinephrine were evaluated, and an approximate dose that would increase or decrease norepinephrine levels by at least 30% was estimated in each subject.

For the second part of the study, all subjects were admitted to the Vanderbilt Clinical Research Center and fasted overnight. Blood pressure (BP) was recorded from an intraarterial line placed in the radial artery, central venous pressure (CVP) was obtained using a high-fidelity 3-French Millar Mikro-Tip™ transducer (Millar Instruments Inc., Houston, TX) placed through the median or basilic vein at the level of the antecubital fossa, and heart rate (HR) was obtained from lead II of the surface electrocardiogram. An intravenous line was positioned in an antecubital vein for blood sampling. MSNA was recorded from the right peroneal nerve using the microneurography technique described elsewhere (19, 20). Basal recordings were made 30 min after instrumentation, including a blood sample for catecholamine determination. Subsequently, the subjects underwent an upright tilt at 15° intervals every three minutes until reaching 75°. The controls were maintained in this position until 30 min of tilt were completed whereas the patients were placed supine when presyncope or syncope developed. Samples for plasma catecholamines were obtained at the end of each tilt interval and twice at the maximal tilt angle or, in the corresponding subjects, immediately after syncope or presyncope.

Subjects were allowed to rest quietly for at least 45 min after the initial tilt. Then a predetermined dose of clonidine or yohimbine was administered. Subjects remained supine for the next 3 h, and the tilt was then repeated. One week after this study day, subjects returned to the Clinical Research Center and the same experimental protocol as described before was performed, except that the subjects received the alternative drug (either clonidine or yohimbine).

**Analyses.** For the evaluation of the hemodynamic responses during tilt, we analyzed the entire last minute of each tilt angle and four different 1-min periods during the 75° position. Measurements of MSNA were made from the tracings of the microneurogram using a digitizer tablet and computer software. Results were evaluated as number of bursts per minute or as total MSNA (arbitrary units) calculated as bursts per minute times the mean burst amplitude. Results are presented as percentage changes in MSNA (bursts per minute) from baseline values. Concentrations of plasma NorEpi and epinephrine (Epi) were obtained using an HPLC method as reported previously (21).

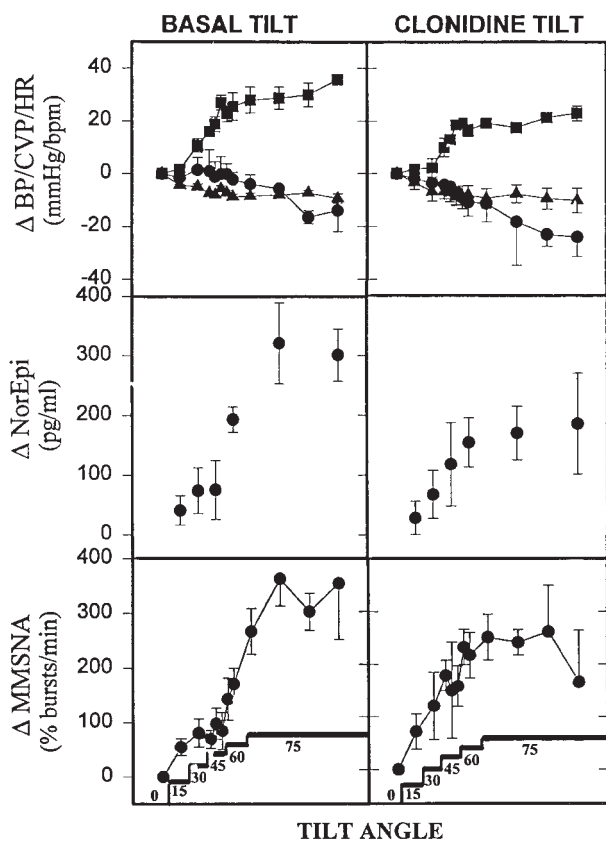
Neurally mediated syncope was defined as a transient loss of consciousness that was not compatible with other altered states of consciousness in the patient's history. Presyncope was defined as a prodromal period characterized by signs and symptoms of imminent syncope. These included severe lightheadedness preceded by nausea or yawning, severe weakness, transient graying or "tunnel" vision, and/or hearing loss. A positive response to tilt was defined as the development of syncope or presyncope due to hypotension, bradycardia, or both.

All data are expressed as mean  $\pm$  SEM. Comparisons were ana-

Table I. Clinical Characteristics of the Study Subjects

	Age Yr	Sex ♂/♀	Weight Kg	SBP mmHG	DBP mmHG	HR Beats/min	MSNA Brst/min	NorEpi pg/ml	Epi pg/ml	n
CON	34 $\pm$ 2.25	3/5	78.88 $\pm$ 4.38	145 $\pm$ 7.35	73 $\pm$ 3.12	60 $\pm$ 3.64	15 $\pm$ 2.52	234 $\pm$ 33	20 $\pm$ 7	8
SYN	34 $\pm$ 2.14	3/5	75.63 $\pm$ 4.26	125 $\pm$ 7.20*	66 $\pm$ 1.96	74 $\pm$ 5.36	18 $\pm$ 2.13	228 $\pm$ 28	16 $\pm$ 5	8

CON: control group; SYN: group with recurrent syncope. \*Significantly different from CON ( $P < 0.05$ ).



**Figure 1.** Hemodynamic and microneurographic responses to tilt before and after clonidine treatment in the control group. The diagram at the top left presents the changes in systolic blood pressure (filled circles), central venous pressure (filled triangles), and heart rate (filled squares), during different levels of tilt before clonidine treatment. The diagram in the left middle and left bottom presents the changes in plasma norepinephrine (in pg/ml) and sympathetic nerve traffic (MSNA) recorded as percentage change over baseline in bursts/min. For hemodynamics and MSNA diagrams there is one value for 0, 15, and 30°, two for 45°, three for 60°, and four for 75°. For plasma norepinephrine there is one value for 15°, one for 30°, one for 45°, one for 60°, and two for 75°. The diagrams to the right present the

lyzed by Student's *t* test for paired or unpaired observations or by ANOVA followed by Dunnett's test for significant differences, as appropriate. A *P* value of < 0.05 was considered significant.

## Results

**Clinical characteristics.** From the 11 patients, 3 did not complete the entire protocol. One patient withdrew after the clonidine phase, due to aggravation of his syncope, and did not want to continue to the yohimbine phase; in the other two, complete or adequate recordings of muscle sympathetic nerve activity were not obtained (i.e., nerve activity was lost or not obtained during the tilts). We decided not to include the partial data obtained from these two patients for the final analysis. There was a total of eight patients with recurrent neurally mediated syncope, who successfully completed the protocol (five females and three males;  $34 \pm 2$  yr). The duration of symptoms ranged from 2 to 10 yr, with a mean frequency of  $4.6 \pm 1.1$  episodes per month. Age, weight, diastolic BP, HR, and basal NorEpi and Epi values were not significantly different from controls. Intraarterial systolic BP was higher in control subjects when compared to patients with recurrent syncope (Table I).

**Basal hemodynamic and microneurographic responses to tilt.** All the control subjects completed the 30-min-period of both pre-drug tilt table tests. The hemodynamic responses to tilt were characterized by a minimal decrease in systolic BP, no significant change in diastolic BP, and a progressive increase in HR (Fig. 1). Muscle sympathetic nerve activity increased by a maximum of 363%, whereas there was a more than threefold increase in plasma NorEpi and an increase of  $50 \pm 2$  pg/ml on epinephrine levels. The increments in sympathetic tone roughly correlated with the angle and duration of tilt (Fig. 1 and Table II). There were no significant or consistent differ-

changes in hemodynamics, plasma norepinephrine, and MSNA after clonidine treatment. The vertical lines represent SEM. The staircase-like lines and numbers in the diagrams at the bottom represent the tilt angle.

**Table II. Epinephrine Values in Controls and in Syncope Patients before and after Treatment with Clonidine or Yohimbine**

Tilt	Controls								Syncope patients							
	Pre-CLO	<i>n</i>	Post-CLO	<i>n</i>	Pre-YOH	<i>n</i>	Post-YOH	<i>n</i>	Pre-CLO	<i>n</i>	Post-CLO	<i>n</i>	Pre-YOH	<i>n</i>	Post-YOH	<i>n</i>
0°	26±10	8	21±6	8	20±7	8	30±13	8	16±5	8	10±5	8	19±11	8	39±8 <sup>β</sup>	8
15°	6±4	8	-1±4	8	3±3	8	13±4	8	0±2	8	-3±5	8	8±11	8	18±9*	8
30°	12±4	8	7±5	8	8±5	8	19±13*	8	24±17*	8	81±24**	8	31±21*	8	25±15*	8
45°	22±4*	8	26±26*	8	24±9*	8	49±16**	8	583±58 <sup>a</sup>	7	714±41 <sup>a</sup>	6	437±67 <sup>a</sup>	7	45±18**	8
60°	24±4*	8	46±20*	8	38±8*	8	60±17**	8	597±51 <sup>a</sup>	6	873±122 <sup>a</sup>	5	623±84 <sup>a</sup>	6	65±13**	8
75°	50±2**	8	46±17*	5	47±6**	8	78±14**	8	709±182 <sup>a</sup>	4	N.A.	4	870±199 <sup>a</sup>	4	82±25**	8
SYN	N.A.		69±23**	3	N.A.		N.A.		871±151 <sup>a</sup>	8	966±158 <sup>a</sup>	8	569±237 <sup>a</sup>	8	267	1

All 0° numbers correspond to plasma epinephrine values in pg/ml. The numbers between 15° and SYN rows represent the change in plasma epinephrine from baseline; Pre-Clo: tilt values before clonidine treatment; Post-Clo: tilt values after clonidine treatment; Pre-Yoh: tilt values before yohimbine treatment; Post-Yoh: tilt values after yohimbine; *n* = number of subjects for each tilt angle; SYN = value immediately before or during syncope; N.A. = not applicable; \*significantly different from corresponding baseline (*P* < 0.05); \*\*significantly different from corresponding baseline value (*P* < 0.01); <sup>a</sup> indicates significant difference from corresponding baseline (*P* < 0.001); <sup>β</sup> indicates significant difference from baseline value of untreated tilt (*P* < 0.05).

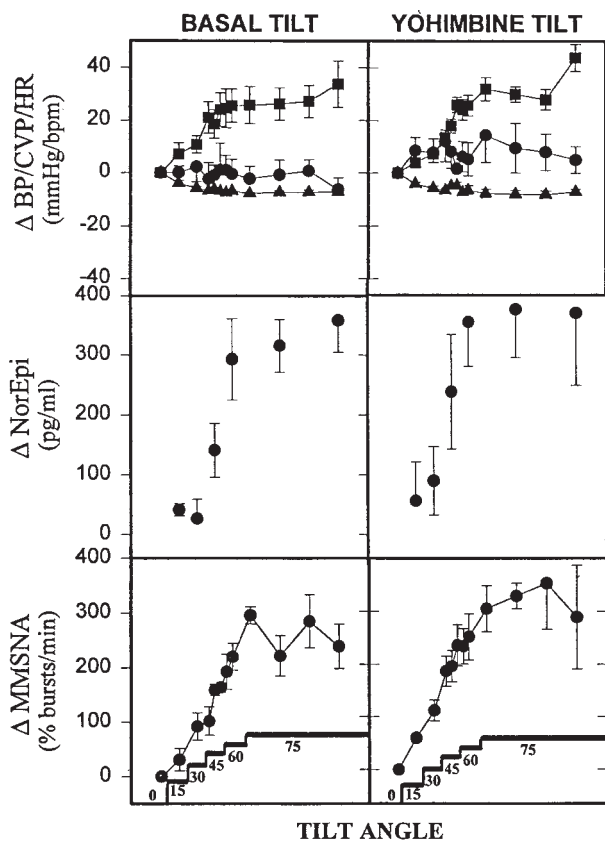


Figure 2. Hemodynamic and microneurographic responses to tilt before and after yohimbine treatment in the control group. Similar arrangement and symbols as in Fig. 1.

ences between the two basal tilts in control subjects (Figs. 1 and 2).

The hemodynamic and neurohumoral responses during basal tilts were significantly different in patients with recurrent syncope when compared to controls. Even at low levels of tilt, patients with recurrent syncope developed a significant reduction in blood pressure (Figs. 3 and 4), which progressively worsened and resulted in syncope between 45 and 75°. The decrease in BP during tilt in these patients was associated with blunted tachycardia, minimal increments in MSNA, reduced increments in plasma NorEpi, and exaggerated increases in EPI shortly before syncope. The type of NMS in all the patients was characterized by severe hypotension and relative bradycardia (mixed type). In these subjects, the abnormally low increment in MSNA was followed by a progressive decrease followed by total neural silence immediately preceding syncope. Tracings from a representative patient illustrating the changes in blood pressure, heart rate, and the progressive decrease in MSNA followed by neural silence syncope and recovery are shown in Fig. 5. Similar differences were observed when the levels of plasma NorEpi in controls, and patients were compared. Although supine basal levels were alike, the angle increase in plasma NorEpi in patients was significantly less than the one observed in controls (Figs. 1–4). On the other hand, in the syncope group, plasma Epi levels were significantly higher than in controls (Table II).

**Hemodynamic and sympathetic responses to tilt after clonidine treatment.** Administration of clonidine (0.23±0.02 mg) to

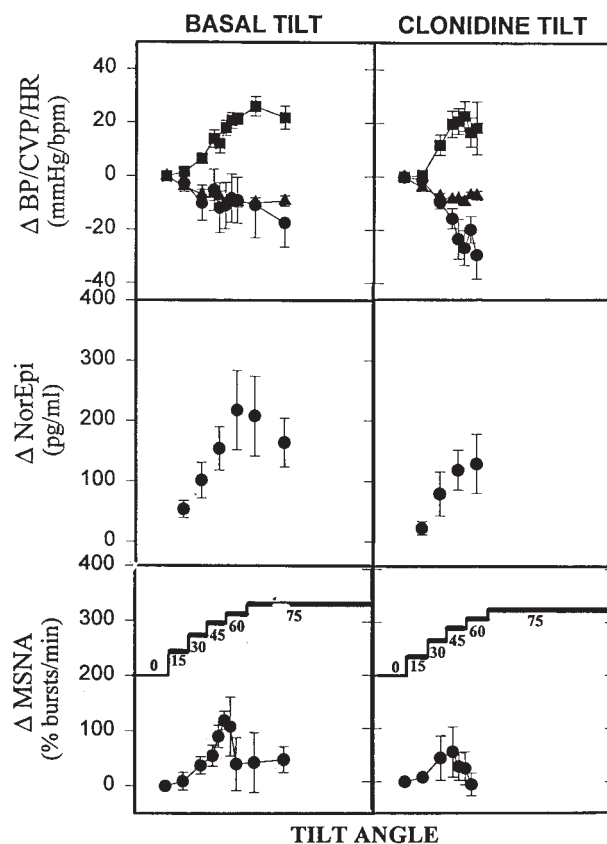


Figure 3. Hemodynamic and microneurographic responses to tilt before and after clonidine treatment in patients with recurrent neurally mediated syncope. Similar arrangement and symbols as in Figs. 1 and 2.

control subjects decreased supine NorEpi from 235±33 pg/ml to 150±45 pg/ml ( $P < 0.05$ ), MSNA by  $-41 \pm 18\%$  bursts/min ( $P < 0.02$ ), and diastolic BP from 73±3 mmHg to 60±5 mmHg ( $P < 0.02$ ). Systolic BP, HR, and Epi levels, were not significantly affected (from 145±7 mmHg to 140±6 mmHg, from 60±4 bpm to 55±8 bpm, from 26±10 to 21±6 pg/ml, for systolic BP, HR, and Epi levels, respectively). The hemodynamic responses at lower levels of tilt were not significantly different from the basal tilts in these control subjects. However, there was a blunted maximal increase in MSNA and plasma norepinephrine (Fig. 1). The reduction in sympathetic tone during tilt resulted in a progressive decrease in arterial blood pressure and presyncope or syncope in three of the eight control subjects. Interestingly, at the time of syncope, plasma Epi levels were only moderately elevated and significantly less than for NMS patients (Table II).

In patients, clonidine treatment (0.12±0.02 mg) decreased supine NorEpi from 228±28 pg/ml to 162±23 pg/ml ( $P < 0.05$ ), MSNA by 35±19% bursts/min ( $P < 0.02$ ), systolic BP from 125±7 mmHg to 116±4 mmHg ( $P < 0.05$ ), diastolic BP from 66±2 mmHg to 53±6 mmHg ( $P < 0.01$ ), and HR from 74±5 bpm to 61±8 bpm ( $P < 0.02$ ). Plasma Epi was not significantly affected (Table II). The hemodynamic and sympathetic responses to tilt after clonidine treatment in the syncope patients were characterized by further worsening of hypotension, a virtually absent increment in MSNA, severe attenuation of the increase in plasma NorEpi, similar changes in Epi levels, and acceleration in the development of syncope in all the patients (Fig. 3).

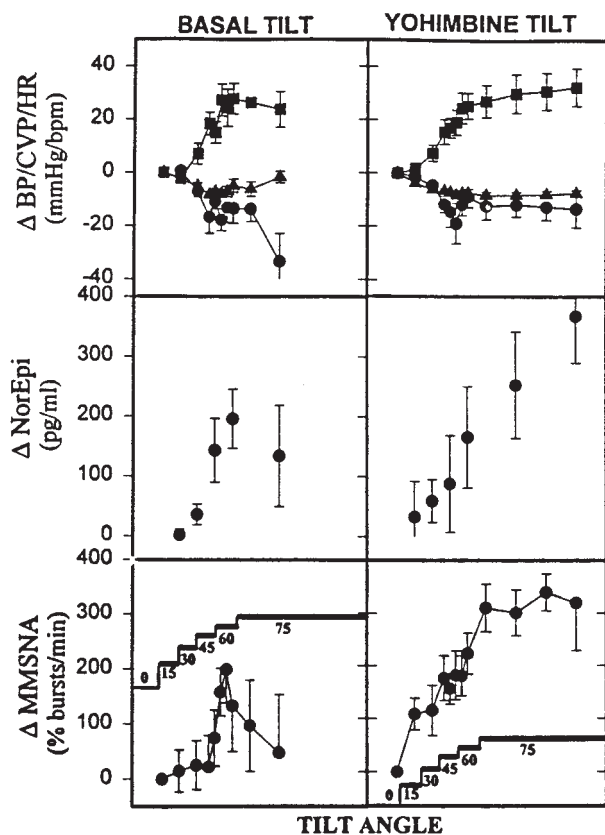


Figure 4. Hemodynamic and microneurographic responses to tilt before and after yohimbine treatment in patients with recurrent neurally mediated syncope. Similar arrangement and symbols as in Figs. 1 and 2.

*Hemodynamic and sympathetic responses to tilt after yohimbine treatment.* Administration of yohimbine ( $14 \pm 0.9$  mg) to control subjects increased supine NorEpi from  $265 \pm 23$  pg/ml to  $347 \pm 28$  pg/ml ( $P < 0.05$ ), MSNA by  $138 \pm 22\%$  bursts/

min ( $P < 0.01$ ), systolic BP from  $141 \pm 8$  mmHg to  $155 \pm 5$  mmHg ( $P < 0.05$ ), and diastolic BP from  $68 \pm 5$  mmHg to  $76 \pm 7$  mmHg ( $P < 0.05$ ). HR and Epi levels were not significantly affected by yohimbine (from  $68 \pm 6$  bpm to  $73 \pm 5$  bpm and from  $20 \pm 7$  to  $30 \pm 13$  pg/ml, respectively) in this group of subjects. The hemodynamic responses to tilt (Fig. 2) were characterized by more pronounced fluctuations in blood pressure with corresponding inverse changes in HR. The increments evoked by tilt in MSNA and plasma norepinephrine concentrations appeared to be more pronounced after yohimbine treatment. All the subjects in this group completed the tilt study without the development of orthostatic hypotension, excessive tachycardia, bradycardia, or syncope. However, two of the subjects reported chest palpitations, whereas five subjects reported anxiety or felt tremulous.

In patients, yohimbine treatment ( $9.1 \pm 0.71$  mg) increased supine NorEpi from  $207 \pm 32$  pg/ml to  $288 \pm 35$  pg/ml ( $P < 0.05$ ), Epi from  $19 \pm 11$  pg/ml to  $39 \pm 8$  pg/ml, MSNA by  $44 \pm 25\%$  bursts/min ( $P < 0.01$ ), systolic BP from  $117 \pm 9$  mmHg to  $130 \pm 9$  mmHg ( $P < 0.02$ ), diastolic BP from  $62 \pm 5$  mmHg to  $73 \pm 4$  mmHg ( $P < 0.01$ ), and HR from  $74 \pm 8$  bpm to  $85 \pm 12$  bpm ( $P < 0.02$ ). There was a significant improvement in the hemodynamic and sympathetic responses to tilt after yohimbine treatment in these patients (Fig. 4). First, blood pressure was better sustained and decreased less than in the baseline or clonidine tilts. Second, MSNA not only increased during supine posture or low levels of tilt but also the maximal increase in MSNA was significant higher than in the basal or clonidine tilts. Overall, the correction in the hemodynamic and sympathetic responses resulted in a clear improvement in orthostatic tolerance, with seven of the eight patients completing the targeted 30 min of tilt. In the patient in whom the tilt was terminated earlier, a reduction in MSNA and hypotension were observed at 25 min of tilt. Although this time exceeded by almost 15 min his previous maximal duration of tilt tolerance, he reported symptoms compatible with presyncope, and the study was terminated.

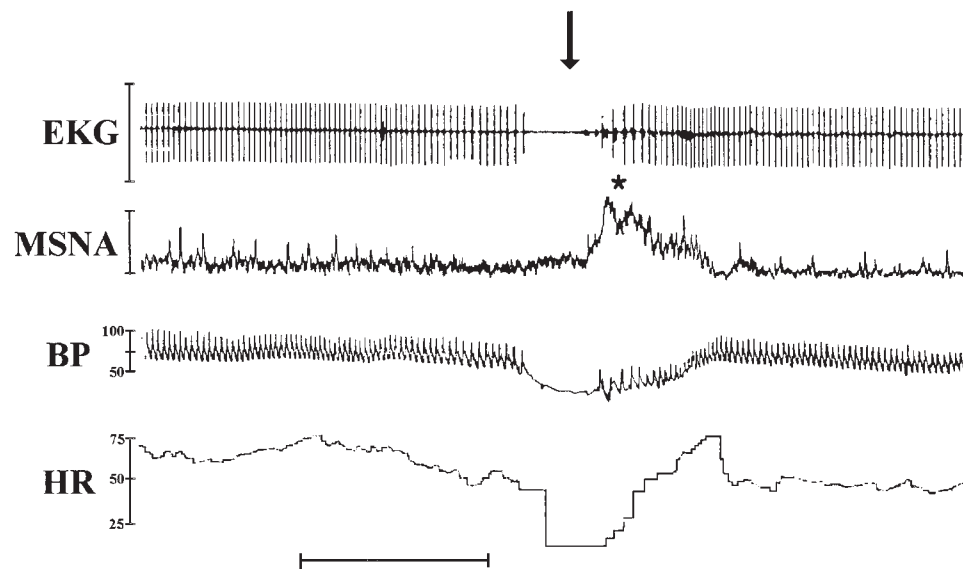


Figure 5. Hemodynamic and microneurographic tracings of a patient suffering neurally mediated syncope during tilt. The patient was a 36-year-old male who developed syncope during the second minute of a  $45^\circ$  upright tilt. He had been previously instrumented with surface leads for continuous monitoring of the electrocardiogram (EKG, top tracing) and heart rate (HR, bottom tracing), with a left radial intraarterial line for beat to beat recording of arterial blood pressure (BP, third tracing), and with a microneurography electrode for recording of muscle sympathetic nerve activity (MSNA, second tracing). Note that the patient was developing progressive hypotension and reduction in MSNA, progressing to total MSNA disappearance before the onset of asyn-

cope and abrupt hypotension. The increase in microneurography baseline (\*) during syncope corresponds to the period in which the patient was experiencing seizure-like activity. In spite of this, note that after the patient was placed supine, typical burst of MSNA (similar to his baseline activity) reappeared indicating that the electrode continued recording from muscle sympathetic fibers. The arrow indicates the time that the patient was returned to the supine position whereas the horizontal line represents 30 s.

## Discussion

It has been unclear how changes in overall sympathetic tone affect the development of neurally mediated syncope. This investigation tested the hypothesis that increased sympathetic stimulation is essential for the development of neurally mediated syncope in susceptible subjects (a crucial postulate of the ventricular theory). We used clonidine and yohimbine to investigate this hypothesis because of their ability to decrease or increase, respectively, overall sympathetic tone. Subjects were pretreated with these agents and challenged by an orthostatic stimulus (upright tilt) known to be well tolerated in one study group (controls) or consistently result in syncope in the other (patients). If the ventricular theory were correct, the reduction in sympathetic tone caused by clonidine would be expected to increase orthostatic tolerance and/or prevent syncope, whereas the increase in noradrenergic outflow caused by yohimbine would be expected to aggravate or accelerate the development of neurally mediated syncope. Alternatively, if neurally mediated syncope results from a reduction in sympathetic tone, yohimbine should ameliorate or correct the development of syncope, whereas clonidine should aggravate it further. Our present results indicate that this latter possibility is the case.

In this study, we show that a decrement in sympathetic outflow resulted in hemodynamic deterioration evoking syncope or presyncope in both, patients and volunteers. Orthostatic hypotension after administration of clonidine to normotensive and hypertensive subjects is a well known side effect. Therefore, clonidine facilitation of tilt-induced orthostatic intolerance in controls was not a totally unexpected finding. More relevant for the objectives of this study is the fact that the previous administration of clonidine aggravated orthostatic intolerance and accelerated the development of syncope in all patients. This is probably the result of impairment by clonidine of an already abnormal reflex sympathetic response in NMS patients, as we have previously documented (16). It might be argued that the reduction by clonidine of not only cardiac, but also neurovascular sympathetic tone, facilitates syncope by an unrelated mechanism. This possibility, however, is unlikely as the characteristics of syncope after clonidine treatment were very similar to those experienced under basal conditions (except for a faster onset and development) and by the results obtained with yohimbine (see below).

It may also be argued that these patients did not suffer from classical NMS, as early on during the tilt significant hypotension was recorded. This seems to be in disagreement with previous reports in which no significant changes in arterial blood pressure were noted except for few seconds before syncope (3, 22). Part of this discrepancy may be related to the method used to determine arterial blood pressure. For instance, in this and in a previous study (16), we determined intraarterial blood pressure with the values representing the average of individual pressures during an entire minute. In the other studies, blood pressure was obtained by cuff sphygmomanometry (3) or by finger photoplethysmography (22) (Finapres). Cuff determination of blood pressure, although generally reliable, provides only one reading at the time and is unlikely to detect small and/or rapid fluctuations in pressure. Photoplethysmography has been shown to record significantly higher blood pressure readings when compared to intraarterial determinations (23) and, as shown for similar devices (24), is not able to detect accurately discrete blood pressure changes during tilt (25). Furthermore, significant differences in blood

pressure determination that increase over time have been observed with photoplethysmography when compared to intraarterial recordings during tilt (25) or during prolonged anesthesia (26). Overall, we consider that our data with intraarterial recordings clearly demonstrate that patients with NMS exhibit a significant decrease in blood pressure, which develops much more early than previously recognized.

Yohimbine, the principal alkaloid in extracts from the bark of the *Pausinystalia yohimbe*, has been used as a pharmacological probe for the  $\alpha_2$ -adrenergic receptor. In man, yohimbine enhances blood pressure and heart rate responses to a variety of stimuli that reflexly increase sympathetic outflow (27). In our study, the increases in basal or reflex sympathetic outflow did not evoke neurally mediated syncope in subjects not susceptible to tilt-induced syncope. This does not necessarily contradict the ventricular theory, as it could be argued that in these subjects ventricular hypovolemia was not present. However, in NMS patients, yohimbine would have been expected to aggravate the development of tilt-induced syncope. This was clearly not the case. Pretreatment of patients with yohimbine increased the sympathetic reflex response to tilt, precluded the development of hypotension, and prevented syncope in seven of the eight subjects. These effects are particularly impressive considering that previous tilts in these patients had consistently resulted in syncope well in advance of the targeted tilt time. In these previous studies, syncope developed even after treatment with multiple agents including  $\beta$ -adrenergic receptor blockers, fluid load, atropine, ergotamine, disopyramide, and sertraline.

As judged by the yohimbine dose needed to increase plasma norepinephrine by  $\geq 30\%$ , subjects with NMS appeared to be more sensitive than controls. Lower yohimbine doses in patients increased MSNA and plasma norepinephrine approximately by the same levels and elevated blood pressure and heart rate more than in controls. This may indicate an increased sensitivity to the effects of yohimbine (i.e.,  $\alpha_2$ -adrenergic receptor blockade) and to the hemodynamic actions of norepinephrine (vascular adrenoceptor sensitivity). None of these results, however, supports the notion of increased ventricular receptor sensitivity in NMS patients.

The ability to obtain recordings of muscle sympathetic nerve activity has greatly increased our understanding of the adaptive changes in sympathetic function during orthostatic stress. Wallin and Sundolf were the first to describe sympathetic withdrawal preceding syncope in an otherwise healthy volunteer undergoing microneurography (28). Subsequently, others have reported isolated cases in which microneurography was recorded during the development of syncope evoked by infusion of nitroprusside (12, 29). In these reports (with a total of three subjects [12, 28, 29]), a significant increase in sympathetic traffic seems to be present before the development of neural silence. Although these are case reports and were not intended to evaluate whether a pronounced increase precedes the development of syncope, they seem to be at variance with our present observations. It is important to emphasize, however, that we studied patients with spontaneous NMS, who in addition, developed syncope when tilted. The other reports (12, 28, 29) studied subjects who were healthy or under evaluation for unrelated reasons. As we have previously demonstrated (16), the mechanisms leading to NMS in patients differ significantly from that experienced by healthy subjects undergoing experimental or medical procedures. In view of these differences, we believe that it is inadequate to extrapolate findings obtained in



otherwise healthy volunteers to patients suffering recurrent NMS. Additional support for this idea comes from reports by other groups in which they also failed to demonstrate exaggerated increases in MSNA in patients with NMS (17, 18, 22).

Consistent and sometimes pronounced elevations on plasma epinephrine have been reported by several authors in subjects experiencing neurally mediated syncope (16, 30–32). Some of them have suggested that Epi may play a role in the pathogenesis of this syndrome. In this study, Epi did not differ between controls and patients while supine. During tilt, an important increase in Epi values was observed during the hypotensive phase in patients indicating an adrenomedullary response similar to the one observed under other stressors (20). Interestingly, clonidine and yohimbine treatment affect differently Epi levels in patients. Whereas clonidine administration did not affect significantly baseline Epi and did not prevent its important raise, yohimbine increased the baseline values and apparently halted the pronounced increase in Epi values. However, after yohimbine administration, the subjects were not fainters, and this probably precluded the adrenomedullary response. This possibility is further supported by comparison of the Epi values in patients after yohimbine with those obtained in the control group (see Table II).

Overall, our results indicate that changes in sympathetic tone affect importantly the development of tilt-induced syncope. Contrary to the ventricular theory, we found no evidence compatible with a role of excessive sympathetic stimulation preceding the development of neurally mediated syncope. Our results support the concept that impairment of sympathetic tone with defective reflex activation is a major factor in the development of this type of syncope. In addition, we believe that our results provide the basis for a more rational potential treatment of this syndrome. Although the main site responsible for the development of neurally mediated syncope remains elusive, it is clear that enhancement of noradrenergic tone can significantly ameliorate and improve orthostatic tolerance in many of these patients. We are currently investigating whether agents such as midodrine (producing pressor effects through direct  $\alpha$ -adrenergic vascular stimulation) or yohimbine (increasing overall sympathetic tone) are effective in the long-term clinical treatment of neurally mediated syncope.

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