Effect of Posture on Blood and Intraocular Pressures in Multiple System Atrophy, Pure Autonomic Failure, and Baroreflex Failure

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Background—Intraocular pressure (IOP) may be partially under systemic vascular control. This study examined whether a correlation exists between blood and intraocular pressures in patients with autonomic dysfunction.

Methods and Results—Eleven patients with 3 types of confirmed autonomic dysfunction (multiple system atrophy, pure autonomic failure, and baroreflex failure) were compared with age- and gender-matched controls and had IOP, systolic blood pressure, diastolic blood pressure, heart rates, and calculated mean arterial pressures (MAP) and mean ocular perfusion pressures (MOPP) measured in the supine, sitting, and standing positions. Data were analyzed with a general linear model repeated-measures ANOVA. All pressures for patients showed a dramatic decline ($P<0.001$) from supine to standing (MAP $-31\pm14$ mm Hg; IOP $-6\pm3$ mm Hg; MOPP $-25\pm14$ mm Hg) compared with controls (MAP $+4\pm7$ mm Hg; IOP $-1\pm2$ mm Hg; MOPP $+6\pm7$ mm Hg). There was no significant change in heart rate from supine to sitting for patients compared with controls ($P=0.648$). Within both the multiple system atrophy ($n=5$) and pure autonomic failure ($n=4$) groups, all initial pressures were similar to control pressures in the supine position, whereas patients with baroreflex failure ($n=2$) had higher mean pressures than respective controls in the supine position.

Conclusions—In autonomic dysfunction, a large decrease in MAP correlated with a large decrease in IOP. These data suggest that the autonomic nervous system, perhaps through an influence on systemic blood pressure, has a significant role in IOP regulation. (Circulation. 2003;108:2349-2354.)

Key Words: nervous system, autonomic ■ blood pressure ■ pressure, intraocular ■ posture

Patients with autonomic dysfunction and orthostatic hypotension frequently may experience dizziness, tunnel vision, and syncope with standing, which may reflect decreased perfusion to the brain and eye. The autonomic nervous system contributes to blood flow control to vital organs through autoregulation.1 Autoregulation involves local myogenic, metabolic, and circulating humoral agents to maintain relatively constant blood flow to tissues despite perfusion pressure fluctuations.1,2 By definition, autoregulation occurs through changes in vascular resistance, caused by either direct or indirect factors. A corollary is that if autoregulation is defective, then there is greater risk of optic nerve ischemia.

Vascular insufficiency may affect optic nerve blood flow.2 Using fluorescein angiography, Hayreh3 demonstrated a watershed zone of the short posterior ciliary end arterioles that supply the anterior optic nerve. This area may be vulnerable to ischemia when ocular perfusion pressure decreases. Mean ocular perfusion pressure (MOPP) is defined as mean arterial pressure (MAP) minus intraocular pressure (IOP). Therefore, a decrease in MAP or an increase in IOP can decrease ocular perfusion. The exact mechanism of IOP regulation is unknown but may be partially under systemic vascular control.2 If autoregulatory mechanisms are intact, then blood flow remains stable despite a substantial drop in ocular perfusion. However, the system can be overwhelmed with extreme changes, such as in experimentally induced marked IOP elevation4 or presumably in acute angle closure glaucoma.

Joos et al5 found a strong positive linear correlation ($R=0.87$) between MAP and IOP in a patient with baroreflex failure with intact but unbuffered efferent sympathetic and parasympathetic nerves. This unexpected finding suggested the autonomic nervous system may directly or indirectly influence IOP through blood pressure levels. Dumskyj et al6 also found a positive correlation between MAP and IOP in patients on a tilt table with chronic primary autonomic dysfunction. It was not discussed, however, whether these patients discontinued medications before measurements.

In the present study, we analyzed 3 well-characterized subgroups of patients with autonomic dysfunction after a medication washout period. These patients were compared with age-, race-, and gender-matched control subjects to assess whether the systemic hemodynamic variables systolic
blood pressure (SBP), diastolic blood pressure (DBP), MAP, and heart rate correlate with IOP after physiological postural changes. If a correlation exists, this may suggest autonomic impairment influences IOP regulation and may be a factor in the lack of ocular perfusion maintenance in these patients. A corollary, not tested here, would be that normal autonomic nervous system function is integral in the maintenance of IOP.

Methods

Subjects
The Autonomic Dysfunction Center at Vanderbilt University Medical Center is a tertiary referral center for orthostatic hypotension. In a review of 100 consecutive autonomic suspect patients referred there in 1994, 15 had multiple system atrophy (MSA), 9 had pure autonomic failure (PAF), and 2 had baroreflex failure (BF). We examined 11 patients with known autonomic dysfunctions (5 MSA, 4 PAF, and 2 BF) and compared them with age-, race-, and gender-matched controls without known systemic or ocular disease. The Vanderbilt Institutional Review Board and the Vanderbilt General Clinical Research Center (GCRC) Review Board approved this study. Complete informed and written consent was obtained from all subjects. The study adhered to the tenets of the Declaration of Helsinki.

Definitions of Specific Autonomic Disorders
MSA (Shy-Drager syndrome) results from neuronal loss and gliosis within the autonomic centers of the brain. 7,8 Males aged more than 50 years old are affected twice as often as females. Signs and symptoms include supine hypertension, impotence, bladder dysfunction, incontinence, headache, neck pain, dimmed vision, sleep apnea, dysarthria, dysphagia, imbalance, and rigidity. Cerebral levels of norepinephrine and dopamine are reduced. There is rapid neurological deterioration, with death of apnea or aspiration an average of 8.5 years after symptom onset.

PAF (Bradbury-Eggleston syndrome) is a degeneration of the peripheral sympathetic nervous system that affects postganglionic parasympathetic and sympathetic neurons. 7,9 Middle-aged men are usually affected. This disorder has a slow, insidious onset, with less disabling symptoms than other dysautonomias. Before PAF can be diagnosed, MSA must be excluded. Signs and symptoms include dizziness, neck or occipital pain, syncope in the morning or after exercise, decreased sweating, urinary incontinence, and impotence. There are no extrapyramidal or cerebellar abnormalities. Recumbent plasma norepinephrine levels are very low, with little increase on standing.

BF occurs with a lesion along the baroreflex arc. The tract originates from the carotid sinus and great vessels of the thorax and neck, passing via the glossopharyngeal and vagal nerves, respectively, to the nucleus tractus solitarii in the brain stem. Patients have volatile and labile changes in blood pressure and heart rate. 5,7,10,11 If a hypertensive crisis occurs, BF can mimic pheochromocytoma. Orthostatic hypotension is usually not a presenting symptom but may occur several years later, especially after treatment of hypertension with clonidine or phenoxybenzamine. Both patients in the present study had prior neck trauma from motor vehicle accidents. One patient complained of sharp eye pain with large blood pressure fluctuations.

Protocol
Recruited patients were hospitalized at the GCRC before testing. Medications were discontinued for 5 half-lives, and a 150-mEq Na⁺, 70-mEq K⁺, low-monoamine diet was provided. Patients and controls underwent mid-morning or early afternoon complete ophthal-mological examination that included medical history, visual acuity, confrontation visual fields, motility, pupil assessment, slit-lamp biomicroscopy, and Goldmann applanation tonometry in the sitting position. Systemic and intraocular pressures for patients and controls were measured in the supine position (after 10 minutes in a quiet room), sitting position (after 5 minutes), and standing position (after 1, 3, and 5 minutes). Blood pressures and heart rates were taken by manual and automated (Dinamap model 8100, Critikon, Inc) sphyg-monomanometry. Eyes were anesthetized with 0.5% proparacaine, and IOP was measured bilaterally with a calibrated Tonopen XL (Mentor O & O, Inc). The Tonopen XL is a portable tonometer that permits accurate measurements in varied positions. 12 Two averaged readings were taken per eye in each position. Patients then underwent infrared pupillometry. Suspected Horner syndrome was confirmed pharmacologically with 10% cocaine and, on a subsequent day, 1.0% hydroxyamphetamine. Pilocarpine (0.1%) confirmed suspected Holmes-Adie tonic pupil. Patients were dilated with 1% tropicamide for optic nerve and retinal examination.

Statistics
A Student’s t test was used to compare the ages of the patients versus the controls and to compare sitting IOP as measured by the Goldmann application tonometer and the Tonopen XL. A probability value <0.05 was considered statistically significant. A general linear model repeated-measures ANOVA with the Bonferroni correction for multiple comparisons was used to compare postural changes of each pressure variable in patients relative to their matched controls. Patients (all autonomic dysfunctions; n=11) were compared with their matched controls as an entire group and within each subgroup (MSA, PAF, and BF). Nonparametric analysis was performed when normality was not present. Analyses were performed with the statistical package SPSS (version 11.5, SPSS, Inc). Statistical analysis was not performed on the BF subgroup, which had only 2 subjects.

Results
Mean age of the patients was 60.5±11.4 years (range 42 to 74 years) compared with 60.8±10.9 years (range 44 to 77 years) for controls (P=0.717). All subjects were white and were matched as to gender (6 males, 5 females). Patients were diagnosed with their respective autonomic dysfunctions at age 61.2±8.2 (MSA), 61.5±14.5 (PAF), and 49.5±2.1 (BF) years. Retrospectively, onset of symptoms was thought to have occurred 3±1.9 (MSA), 9.5±13.8 (PAF), and 2±0 (BF) years before diagnosis.

No subject had evidence of optic nerve or retinal disease. Many patients showed pupil abnormalities on infrared pupillometry. Three patients with MSA had bilateral Horner syndrome confirmed by absence of pupillary dilation with topical cocaine testing. These were first- or second-order neuron (ie, central) Horner syndromes as indicated by positive dilation responses to topical hydroxyamphetamine. Hydroxyamphetamine releases endogenous norepinephrine. If present, endogenous norepinephrine elicits the pharmacological effect of pupillary dilation. This response confirms that the noradrenergic neurons innervating the pupil are intact and the pupillary lesion must be in more centrally located neurons, consistent with the central neurological defect in MSA. Three of the 4 patients with PAF had pupillary sphincter atrophy consistent with peripheral autonomic loss in PAF. Both patients with BF had Holmes-Adie tonic pupils, with reduced deep tendon reflexes, consistent with afferent dysfunction in BF. 13

Most patients demonstrated orthostatic symptoms, with lightheadedness, dimmed vision, and unsteadiness that limited their ability to stand. Forty-six percent of all patients stood 3 minutes and only 23 percent remained upright for 5 minutes without symptoms. It was therefore not possible to
There was no significant difference in pressures (n sitting IOP obtained by Goldmann applanation tonometry. standing longer than 1 minute).

compare changes between patients and control subjects for standing longer than 1 minute.

Sitting IOP taken by the Tonopen XL was compared with sitting IOP obtained by Goldmann applanation tonometry. There was no significant difference in pressures (n=36 eyes, 13±4 mm Hg for both devices, P=0.841), thus verifying the accuracy of the Tonopen XL.

Changes between supine and sitting positions for all pressures and heart rate in all groups were compared by nonparametric analyses. When total patients and control subjects were compared, SBP (difference 17.2±19.5 mm Hg, P=0.016) and IOP (difference 4.1±2.1 mm Hg, P=0.003) decreased significantly from supine to sitting positions in patients, whereas DBP (difference 5.5±3.8 mm Hg, P=0.005) increased significantly in controls.

As a group, autonomic dysfunction patients had significant declines in all pressures (SBP, DBP, MAP, IOP, and MOPP) from supine to standing positions (all P<0.001) compared with controls by univariate ANOVA. In addition, comparisons of paired differences relative to matched controls by nonparametric analysis from supine to standing positions were also large and significantly negative in patients (all P<0.001). Control subjects had the expected significant increase in DBP from supine to standing (5.9±6.2 mm Hg, P=0.010), but all other pressure parameters did not change significantly (Table).

Patients within the MSA subgroup had similar MAP, IOP, and MOPP in the supine position as controls. As they assumed an upright posture, patients had a statistically significant decline in all pressure components relative to matched controls (Figure 1). With nonparametric analysis of paired differences between the supine and standing positions, there was an obvious negative difference in patients’ pressures, whereas pressure differences in controls were centered around zero (Figure 4). Systemic pressures were not found to have a statistically significant decline in PAF patients, but the pressures showed a similar trend as those in MSA patients.

The relative trend for decline in all pressures for patients with BF between supine and standing was similar to patients with MSA and PAF, although the sample size was too small for statistical analysis (Figures 3 and 4). Patients with BF had higher MAP, IOP, and MOPP than their respective controls in the supine position. On standing, however, BF patients’ pressures decreased to levels closer to controls in the standing position (Figure 3).

There was no significant difference in heart rate with change in position in patients with autonomic dysfunction compared with controls (P=0.648). Both patients (4.2±8.3 bpm) and controls (6.2±8.2 bpm) had an increase in heart rate <10 bpm from supine to standing position.

Discussion

The results from this study indicate an association of systemic blood pressure with IOP in patients with autonomic dysfunction. There was a decline of IOP, MAP, and MOPP below normal values with a positional change from supine to standing in patients with peripheral or central autonomic
dysfunction. The values in patients with MSA or PAF were closest to corresponding control values in the supine position. The values in patients with BF were closest to corresponding control values in the standing position. There was an increase in IOP, MAP, and MOPP values from standing to supine in patients with BF. In these patients, the efferent sympathetic pathway was intact but unbuffered. These results suggested that the autonomic system has a significant role in stabilizing IOP and may act indirectly through blood pressure maintenance.

The changes in the normal healthy subjects were small. There were no statistically significant changes in MAP, IOP, or MOPP. There was a significant yet small increase in DBP with standing in the present study. Several large population studies of normal subjects found a positive correlation between SBP and IOP, although measured in only 1 position.\(^\text{14-16}\) A summary of positional studies suggested an averaged IOP increase of 0.5 to 4 mm Hg when sitting and subsequent supine positions were compared in healthy subjects.\(^\text{15}\) The positional IOP changes of control subjects in the present study were within this range.

The change in SBP and IOP with posture is exaggerated in patients with systemic hypertension, diabetes mellitus, glaucoma, or central retinal vein occlusions.\(^\text{17-19}\) Friberg and Weimert\(^\text{20}\) found that IOP dramatically increased to levels >30 mm Hg and retinal arterioles markedly constricted with a head-down vertical position. An autoregulatory mechanism causing increased vascular resistance was believed to maintain constant ocular flow. Changes in IOP with a head-down position were believed to be due to either increased episcleral venous pressure, increased aqueous production with increased ciliary body blood flow, choroidal vascular engorgement, or a baroreceptor-type reflex phenomenon.\(^\text{17,20}\)

Two studies have noted correlations between systemic blood pressure and IOP in primary autonomic dysfunction patients,\(^\text{5,6}\) but none have done this for a full range of patients with MSA, PAF, and BF for whom medications have been discontinued. It seemed important to study a variety of dysautonomias without pharmaceutical masking to infer whether the effect being studied was specific to a particular lesion or could be extrapolated. We chose 3 pathophysiologies because of their distinct mechanisms. In MSA, the neurological lesion is impaired central autonomic control, with intact (efferent) peripheral nerves. In PAF, the lesion involves peripheral (efferent) autonomic nerves, without central impairment. In BF, both central and peripheral autonomic nerves are intact, but afferent input is absent. Inclusion
of all 3 disorders permits us to generalize about the relation of blood and intraocular pressures. The present study indicated that IOP in MSA or PAF became lower than IOP in matched controls with standing, whereas IOP in undampened BF became closer to IOP in matched controls with standing. Values in all patients with autonomic dysfunction were higher in the supine than in the standing positions. It is unknown whether ocular autoregulatory mechanisms are dysfunctional in patients with autonomic dysfunction. A dramatic decrease in MOPP and the development of dimming of vision or eye pain in some of our patients on standing could suggest an overwhelmed ocular autoregulatory capacity. Perhaps such large fluctuations may increase risk of optic nerve ischemia and optic neuropathy over time.

Two studies investigated cerebral autoregulation in patients with autonomic dysfunction, specifically PAF and MSA. Both used the radioactive xenon washout technique to measure cerebral blood flow during dynamic tilt. Thomas and Bannister noted that cerebral blood flow was maintained until SBP dropped below 80 mm Hg in patients with MSA. Brooks et al found that despite a linear decline in middle cerebral velocity by transcranial Doppler as MAP declined, cerebral blood flow remained constant at least until an MAP of 85 mm Hg. An adaptive phenomenon of decreased vascular resistance, perhaps at the arteriolar level, was thought to preserve cerebral flow. After 1 minute of standing, the patients with MSA and PAF in the present study averaged an MAP < 80 mm Hg. Loss of cerebral blood flow autoregulation at this level may account for the need of many patients to discontinue standing at this point in the present investigation.

Ocular autoregulation has been examined with manipulated MAP, autonomic, and IOP parameters. Weinstein et al altered the MAP in cats while IOP was measured. The IOP change correlated with 10% of the change in systemic blood pressure. In addition, optic nerve blood flow as measured by quantitative 14C-iodoantipyrine autoradiography remained relatively constant, which suggests autoregulatory compensation, until MAP dropped below 80 mm Hg, when flow markedly decreased. A comprehensive investigation by Reitsamer and Kiel with anesthetized and paralyzed rabbits in a stereotactic head holder to eliminate extraocular movements demonstrated corresponding reductions in all components of IOP, ciliary body blood flow, choroidal blood flow, and ocular venous pressure as MAP was reduced below the baseline of 65 mm Hg. Braslow and Gregory demonstrated that unilateral cervical ganglionectomy prevented normal nocturnal IOP elevation in rabbits but did not affect the baseline IOP. Gallar and Liu examined IOP changes in rabbits with low-frequency electrical stimulation of cervical sympathetic nerves that innervate the eye. Associated with an elevated aqueous concentration of norepinephrine, there was an immediate and sustained elevation of IOP and pupillary mydriasis of the stimulated eye without a corresponding increase in MAP. In regard to manipulated IOP, Grunwald et al suggested that ocular autoregulation could occur at an IOP as low as 6 mm Hg in acutely induced ocular hypotension in healthy subjects.

No sign of optic nerve damage was present in any of the patients in the present study despite the large decrease in MAP and MOPP on standing. Perhaps an adaptive phenomenon exists to preserve ocular autoregulation in these patients. Blood pressure changes, whether due to a central reduction, a peripheral reduction, or an excessive autonomic response, did affect the IOP in these patients. Additional studies in patients with autonomic dysfunctions will be useful to determine the effects of reduced MAP and IOP on ocular hemodynamics, although adaptation of current techniques will be required to capture measurements during the short intervals of standing that patients can tolerate.

Acknowledgments
This study was supported by NIH grants 5PO1-HL56693 and 5MO1-RR00095 and the Olive Lewellyn Glaucoma Research Fund. The authors acknowledge the technical assistance of the GCRC staff.
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*Circulation*. 2003;108:2349-2354; originally published online November 3, 2003; doi: 10.1161/01.CIR.0000097114.11038.26
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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