Transurethral Resection of the Prostate, Serum Glycine Levels, and Ocular Evoked Potentials

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Complications of transurethral resection of the prostate (TURP syndrome) when glycine is used as the irrigating fluid include cardiovascular and central nervous system abnormalities that occasionally include transient blindness. Serum sodium, glycine, potassium, chloride, ammonia, osmolality, carbonate, and blood urea nitrogen of 17 patients having TURP and 10 having cystoscopic examination were measured. Electroretinograms and visually evoked potentials (VEPs) were recorded in the preanesthetic preparatory area and in the recovery room immediately after surgery. Four patients reported visual aberrations coincident with increases in serum levels of glycine from a mean before surgery of 137.7 \pm 45.1 to 7,812.2 \pm 2,486.6 μ M/l, mean \pm SD, after TURP. These patients also showed a reduction of serum sodium from 138 \pm 4.5 to 122 ± 8.6 mEq/l that correlated significantly with serum levels of glycine (rho = -0.81). There were no statistically significant changes of serum ammonia and osmolality. Electroretinograms consistently demonstrated complete loss of oscillatory potentials. Thirty hertz flicker-following was also abolished. VEPs were more variably affected with prolongation of component "P100" latency found in both groups and probably resulting from sedative effects of diazepam. Patients experiencing the TURP syndrome showed abolishment of 30 Hz flicker-following in their VEPs. The elevated serum levels of glycine may contribute directly to visual aberrations resulting from glycine's role as an inhibitory transmitter in the retina. (Key words: Blood: hyperammonemia; hyperglycinemia; hyponatremia. Monitoring: electroretinogram; visual evoked potentials. Surgery, urologic: transurethral resection of the prostate.)

THE "TURP (transurethral resection of the prostate) syndrome" classically consists of central nervous system (CNS) and cardiovascular aberrations. 1-7 These include hemodynamic instability and occasionally cardiovascular collapse, 1-3 excessive sedation, 4,5 coma, 6 or visual disturbances, sometimes described as "blindness." Case reports documenting visual aberrations have attributed water intoxication, hyponatremia, hyperammonemia, and hyperglycinemia as probable causes. We recently demonstrated that glycine blood levels similar to those that can be achieved clinically in humans can cause changes in the visual evoked potential (VEP) of dogs. 9 In the pres-

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ent study we measured the serum biochemical profile of patients having TURP and correlated changes in concentrations of sodium, glycine, and ammonia with abnormalities of vision by changes in the VEP and electroretinogram (ERG). We hypothesized that high serum levels of glycine account for visual aberrations in the TURP syndrome.

Methods

The protocol was approved by the investigational committee for human study at the Veteran's Administration Hospital in Salt Lake City. Informed consent was obtained from 27 patients, 17 scheduled for TURP and 10 for cystoscopic examination and biopsy of bladder or prostate (controls). Although patients experiencing only a biopsy are not true controls particularly considering the surgical procedure, they are controls for separating possible effects of sedation produced by fentanyl and diazepam. The patients ranged in age from 55 to 78 years and were ASA physical status 1 to 3. Six of the 10 having biopsies received premedication of 5-10 mg diazepam po. The other four received 2.5-5 mg diazepam iv during surgery. Ten of the 17 patients having TURP received 5-10 mg diazepam po approximately 1 h before surgery. The remaining seven patients, including the four patients having TURP who were to experience visual aberrations, received no premedication. Upon arrival at the operating suite, a 16or 18-G intravenous catheter was inserted in all patients. Additional monitors included manual blood pressure cuff, ECG, and precordial stethoscope. Spinal anesthetic was administered via the L2-3 or L3-4 interspace. Depending on the anticipated duration of the procedure or the height of the patient, either tetracaine 10-14 mg in D₁₀ W, lidocaine 50-75 mg, or procaine 75-100 mg was given intrathecally. Intravenous fluid administration consisted of 500-800 ml of Plasma-Lyte®. One patient, with a sodium level of 111 mEq/l, received 2 units packed RBCs. Ephedrine 5-15 mg IV was given as needed to maintain the systolic blood pressure above 100 mmHg. Intraoperative sedation for all patients consisted of intravenous fentanyl 50-100 μg and/or diazepam 2-10 mg. No inhalational anesthetics were given.

For every case the duration of the prostatic resection, the estimated size of the gland, and the number of liters of irrigation fluid (1.5% glycine or sterile water) used were recorded. Blood loss was estimated visually by the surgeon

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TABLE 1. Serum Chemical Profile before and after TURP (mean ± SD)

	Na (mEq/l)	K (mEq/l)	CI (mEq/I)	HCO _s (mEq/l)	BUN (mEq/l)	NH ₃ (μΜ/l)	GLYC (μM/l)	OSM (mOsm/l)
Control (n = 10)	139.9 ± 3.6	4.2 ± 0.5	107.5 ± 5.0	25.2 ± 4.3	19.8 ± 6.7	35.8 ± 17.2		283.3 ± 9.4
	138.1 ± 4.4	4.3 ± 0.5	107.4 ± 7.0	23.8 ± 5.0	19.0 ± 10.5	43.0 ± 20.0		283.2 ± 6.2
Asymptomatic (n = 13)	138.5 ± 4.2	4.2 ± 0.4	108.0 ± 4.7	25.0 ± 4.4	20.0 ± 7.2	37.2 ± 16.2	138.2 ± 52.1	283.1 ± 7.5
	130.0 ± 4.2	4.0 ± 0.5	105.0 ± 6.0	23.9 ± 4.9	18.0 ± 9.4	65.0* ± 27.6	1,855.4† ± 1,346.0	270.0 ± 12.7
Symptomatic (n = 4)	138.2 ± 4.5	4.3 ±0.6	109.3 ± 6.6	25.5 ±4.5	24.0 ± 4.1	40.7 ± 20.7	137.7 ± 45.1	284.6 ± 10.7
	122.2* ± 8.6	3.7 ± 0.5	105.7 ± 8.0	23.1 ± 4.2	19.2 ± 6.5	202.7 ± 246.7	7,812.2† ± 2,486.6	278.2 ± 12.5

^{*} P < 0.05 compared with other groups in the same vertical column.

 $\dagger P < 0.001$ compared with other groups in the same vertical column.

in each case. Abnormalities of mental status, vision, or cardiovascular status were also charted.

Serum levels of sodium, potassium, and blood urea nitrogen and osmolality and ammonia levels were obtained before and after operation in all patients. These same laboratory studies, plus serum glycine levels, were determined in the patients having TURP.

Visually evoked potentials and ERGs were performed before operation in the preanesthetic preparatory area and in the recovery room within 10 min after the surgery had been completed.

Visually evoked potentials were recorded with the use of the midoccipital electrode location (OZ) referred to the earlobe. The contralational earlobe served as the ground location. A lamp of a Grass® photostimulator was positioned 30 cm from the nasion of the patient, and flashes of maximum brightness using the highest setting, PS = 16, were presented through closed eyelids. The 200ms time period after each flash was analyzed. Seventyfive to 100 flashes were presented at a rate of 1/s and flicker at 30/s. Electrode resistance was less than 5,000 ohms. The evoked potentials were averaged on a Nicolet CA-2000® with frequency response bandpass of 1-100 Hz and sensitivity of $\pm 25 \mu V$. The averaged evoked potentials were repeated three times for reliability and stored on floppy disk. The evoked potentials were plotted and principal components were measured with cursors on the oscilloscope display.

Electroretinograms were recorded with the use of a monopolar Burian-Lawwill® speculum contact lens electrode with the ipsilateral earlobe as reference. A drop of methyl cellulose (Goniosol®) and a drop of sterile physiologic saline were placed on the contact lens. The pupil of one eye was dilated and the other left undilated so that pupillary reactions could be observed. The ocular fundus in the dilated eye was examined. Single flashes were pre-

sented with the lamp of a Grass® photostimulator positioned 30 cm from the patient's eye. Retinal responses to 30-Hz flicker were also recorded. A minimum of four artifact-free ERGs to the above conditions were stored on a floppy disk. Frequency response bandpass filters of 1–250 Hz were used. The analysis time was 100 ms, and sensitivity was $\pm 500~\mu V$. The implicit times (peak latency) and amplitudes of the a- and b-waves were measured with cursors. Peak-to-peak amplitudes of the 30-Hz flicker-following were measured.

Analyses of variance for repeated measurements and paired and unpaired t tests were used to analyze the hemodynamic and biochemical data, and latencies and amplitudes of components of the ERGs and VEPs. Coefficients of correlation (rho) were computed comparing serum levels of glycine, sodium, and ammonia; length of surgery; liters of glycine irrigating solution; and comparisons between these measures. Pearson product moment correlation (r) could not be used because these data did not satisfy the requirement of linearity. Statistical significance is considered at P < 0.05. All data are presented as mean \pm SD.

Results

The "control" group of patients having biopsies showed no significant change in preoperative and postoperative serum chemistries (table 1) or retinal electrophysiologic condition. Comparison of preoperative and postoperative amplitudes and implicit times (peak latency) of a- and b-waves of the ERG yielded no significant changes (all P > 0.05). All of these patients were hemodynamically stable and had no alteration of mental status. All had received diazepam and half had received fentanyl at some time. Most procedures were of fairly brief duration, lasting an average of 25 min, for which lidocaine 50–75 mg was

TABLE 2. Coefficients of Correlation after TURP

Comparison	rho	Significance level
Surgery length versus serum glycine Surgery length versus serum sodium	+0.625 -0.27	P < 0.05 NS
Amount of glycine irrigant versus surgery length Amount of glycine irrigant versus	+0.815	P < 0.001
serum glycine Amount of glycine irrigant versus	+0.88	P < 0.001
serum sodium	-0.30	NS
Serum glycine versus serum sodium	-0.81	P < 0.001
Serum glycine versus serum ammonia	+0.31	NS
Serum sodium versus serum ammonia	-0.37	NS

NS = nonsignificant.

used intrathecally. No blood transfusions were required, and the range of amount of irrigation was 1-8 l of sterile water. Their VEPs were not significantly altered in am-

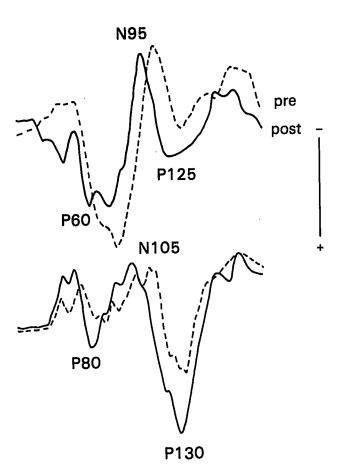


FIG. 1. Flash visually evoked potentials recorded before transurethral resection of the prostate (pre) and immediately after the procedure (post) from two patients with uneventful resections with no significant changes in serum glycine or sodium levels. Vertical calibration bar = 10 μV . Polarity (P or N) and peak latency are indicated for some components.

plitude by these medications, however, the positive component appearing around 100 ms was prolonged in latency. Before operation mean latency was 105.7 ms (SD 21), which was prolonged to 112.3 ms (SD 24) after surgery, t = 3.03 (P < 0.02). There was no loss of oscillatory potentials on the ascending limb of the b-wave of the ERG or diminution of 30 Hz flicker-following recorded from the retina or occipital cortex.

The average length of the TURP procedures was 1 h 20 min, which was skewed by the fact that one of the procedures (patient D) took 3 h 30 min. The shortest TURP procedure was 35 min. Coefficients of correlation computed by comparing length of procedure versus serum glycine and sodium levels, amount of glycine used during each procedure versus length of surgery, and serum levels of glycine and sodium, serum levels of glycine versus serum sodium, serum sodium versus serum ammonia, and serum glycine versus serum ammonia are summarized in table 2.

The patients having the TURP procedure can be divided into two subgroups based on symptoms. Thirteen of the 17 patients were little affected by the surgical procedure (asymptomatic group, table 1). These patients had uneventful operative courses, stable hemodynamics, some increase in serum glycine but no loss of vision, nausea, or hypotension. Representative VEPs from two of these 13 are shown in figure 1. The VEPs of the patients having the TURP procedure varied, but, as a group, similar to the 10 patients having biopsy, demonstrated prolonged "P100" latency after surgery. The latency increased from 93 ms (SD 9) to 103 (SD 13.9) after surgery, t = 3.48 (P < 0.01). The b-wave of the ERG of the TURP group was prolonged from 29.8 (SD 4) to 31.2 (SD 3.6), t = 2.21 (P < 0.05). Their serum glycine levels ranged from 55 to $208 \,\mu\text{M}/\text{l}$ before operation and increased to 537 to 2,462 µM/l after operation, whereas ammonia levels increased from a preoperative mean of 37.2 to 65.0 μ M/l after operation (table 1). In these patients, tetracaine 10-14 mg in 10% dextrose in water was used for spinal anesthesia. Blood loss was visually estimated by the surgeons at 300-900 ml. Patients received between 500-800 ml of Plasma-Lyte[®]. The prostatic size ranged from 40 to 120 g. The amount of glycine used for irrigation varied from 12 to 66 l with an average of 31 l.

Four of 17 TURP patients (symptomatic group, table 1), however, did have symptoms of nausea and vomiting, visual disturbances ranging from altered vision to altered light perception only, hypotension, and dropout of ERG oscillatory potentials associated with serum glycine levels exceeding 4,000 μ M/l measured in the recovery room. These four patients had glycine levels ranging from 4,919 to 9,790 μ M/l. The following is a summary of the data on these four patients:

Patient A had a 60-min resection, received 25 l of 1.5% glycine solution, and was nauseated with "blurry" vision after operation. He

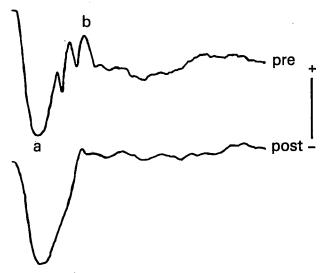


FIG. 2. Flash electroretinogram recorded before transurethral resection of the prostate (pre) and immediately after the procedure (post) from patient A, whose postoperative serum glycine level was 4,919 μ M/l, ammonia 223 μ M/l, and sodium 132 mEq/l. Analysis time, 100 ms. Vertical calibration bar, 100 μ V.

received no premedication and was given 2 mg diazepam and 50 µg fentanyl iv during the procedure. His ERG showed no amplitude changes after operation but did demonstrate complete loss of the oscillatory potentials normally seen on the ascending limb of the b-wave that were present in all preoperative tracings (fig. 2). His flash VEP did not change in form nor slow in latency, but the amplitude was attenuated 40%. The 30-Hz VEP responses were not recorded from patient A. Before surgery his serum glycine level was 132 µm/l, ammonia 24 µm/l, and sodium 142 mEq/l. His recovery room serum glycine level was 4,919 µm/l, ammonia 223 µm/l, and sodium lowered only to 132 mEq/l.

Patient B had a longer resection, lasting 1 h 45 min, requiring 52 l of 1.5% glycine solution. He received neither premedication nor iv diazepam or fentanyl. In the recovery room he complained of blurred vision and nausea. His visual acuity was reduced to perception of hand motion for more than 1 h. The ERG demonstrated complete dropout of oscillatory potentials. The amplitude of his 30-Hz flicker-following was reduced from 73 to 15 μ V after operation. The "P100" component of his averaged VEP was prolonged in time and changed in form (fig. 3). His 30-Hz VEP was nearly obliterated after operation but returned in 1 h (fig. 4). Before surgery his serum glycine level was 89 μ M/l, ammonia 41 μ M/l, and sodium 132 mEq/l. Recovery room serum glycine level was 9,984 μ M/l. Hyponatremia also developed, and he had a postoperative serum sodium level of 123 mEq/l and ammonia 36 μ M/l. He received 50 ml 5% saline and furosemide 80 mg in the recovery room.

Patient C received 30 l of glycine during a 1-h, 10-min resection. He received no premedication nor iv sedation. After operation, he was nauseated for about 45 min and he complained that his vision was "a little blurry." He was initially able to count fingers at a distance of 1 m and he believed his vision improved after 3 h. Before surgery his glycine level was 86 μ M/l, ammonia 17 μ M/l, and sodium 145 mEq/l. Postoperative serum sodium level was 123 mEq/l and glycine 6,556 μ M/l. Ammonia level, however, was only 56 μ M/l. His ERG demonstrated attenuation 30-Hz flicker-following. However, his VEPs were not significantly affected.

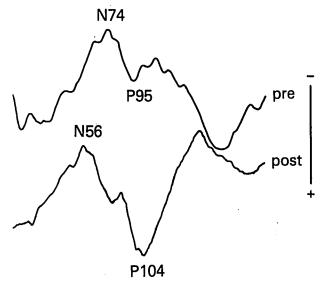


FIG. 3. Flash visually evoked potential recorded from midoccipital scalp before transurethral resection of the prostate (pre) and immediately after the procedure (post) from patient B, whose postoperative serum glycine level was 9,984 μ M/l, ammonia 36 μ M/l, and sodium 123 mEq/l. Analysis time, 200 ms. Vertical calibration bar = 10 μ V. Polarity (P or N) and peak leatency are indicated for some components.

Patient D received 64 l of glycine, 50 μ g fentanyl, and 2.5 mg diazepam iv during a 3-h, 30-min procedure. He reported visual changes during surgery, first complaining of dizziness and then loss of visual

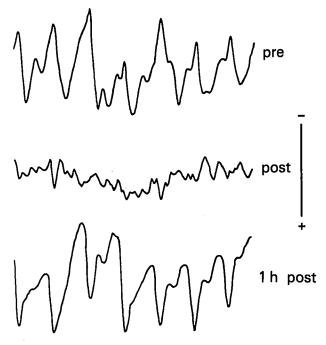


FIG. 4. Flash visually evoked potential after presentation of 30-Hz flicker recorded from midoccipital scalp before transurethral resection of the prostate (pre), immediately after the procedure (post), and 1 h after the procedure (1 h post) from patient B. Analysis time, 200 ms. Vertical calibration bar = $10~\mu V$.

perception. He reported "light perception only" for an hour. Blood loss was estimated at 1,000 ml, and he received 2 units packed red blood cells and 1,200 ml of Plasma-Lyte. He was the only patient requiring transfusion. Before surgery his glycine level was 274 μ M/l, ammonia 51 μ M/l, and sodium 144 mEq/l. Initial postoperative serum sodium level was 111 mEq/l, which was treated with 50 ml 5% saline and furosemide 100 mg over the next 3 hours. Serum ammonia level was 496 μ M/l, whereas glycine concentration was 9,790 μ M/l. His ERG demonstrated reduced b-wave amplitude and complete dropout of the oscillatory potentials. We were unable to record the VEPs on this patient until his vision had recovered, so do we not know the extent of disruption of cortical visual processing in patient D during the time of maximum affect.

In general, those patients with high serum glycine and decreased serum sodium were found to have ERG changes with abolished 30-Hz flicker-following, prolonged ERG b-wave implicit times (latency), and complete loss of the oscillatory potentials appearing on the ascending limb of the b-wave (fig. 2). The VEP was more variably affected (fig. 1). Significant slowing of the component response time was seen along with significant attenuation of the 30-Hz VEP. The most obvious change in the electrophysiologic condition of these four patients was the complete dropout of both oscillatory potentials in the ERG and 30-Hz flicker-following both in the ERG and in the VEP recorded from occipital scalp (figs. 2-4). Pupillary response to light was maintained in patients, and there were no observable changes in the appearance of the ocular fundus. Vision, determined by asking each patient to count fingers at 2 m or less and asking their opinion of their vision, was found to return to normal within 2-12 h.

Discussion

We believe that high serum levels of glycine are mainly responsible for the visual changes described in the TURP syndrome. Glycine is an inhibitory neurotransmitter in the CNS, retina, and spinal cord. High glycine levels are suspected of causing abnormal electroencephalographic activity as well as visual and auditory evoked potentials in patients with congenital nonketotic hyperglycinemia. Glycine has been shown to inhibit ganglion cells in the retina, as well as to suppress the waveforms of both the ERG and VEP in rabbits. In addition, we have demonstrated suppression of VEPs in dogs after infusions of large quantities of glycine.

A possible confounding influence is the administration of fentanyl and diazepam. Five of the 10 patients having biopsy received at least 5 mg diazepam and two received fentanyl during the procedure. Nine of the patients having TURP received fentanyl and six received diazepam during their procedures. Although fentanyl does not usually produce changes in evoked potentials, diazepam increases latency of VEPs and sometimes reduces amplitude. Is In both groups, the "P100" component was significantly prolonged in latency. The most noticeable change in elec-

trophysiologic condition was the loss of oscillatory potentials on the ascending limb of the ERG b-wave (fig. 2) and the 30-Hz flicker-following recorded from the scalp (fig. 4) in those patients experiencing visual aberrations. The implicit time (latency) of the ERG b-wave also slowed significantly only in the patients having TURP.

Another confounding influence is the appearance of hyponatremia in some patients. The patients who had high postoperative glycine levels and aberrations of their electrophysiologic condition were also generally the patients with hyponatremia. Serum glycine and sodium levels correlated significantly (rho = -0.81, P < 0.001, table 2). Whether the observed ERG changes were secondary to the effects of low serum sodium or high glycine levels is not positively discernible. A combination of these factors cannot be ruled out. Those who favor hyponatremia as the cause believe that cerebral edema and change in osmolality from water intoxication disturb the visual pathways. 3,6 Our patients had no decreases in plasma osmolality despite hyponatremia. This is compatible with the report of Desmond, 14 who found that hypoosmolality was only associated with severe hyponatremia and life-threatening cerebral or cardiopulmonary problems. Ammonia has also been suggested as a factor affecting vision. 4,5 Our results show a significant but small increase between preoperative and postoperative serum ammonia levels in the asymptomatic group, however, the symptomatic patients, because of large variations of the data, did not exhibit a significant association between hyperammonemia and the TURP syndrome. Serum ammonia level did not correlate significantly with levels of either serum glycine or sodium (table 2). Only two of the four patients experiencing visual aberrations demonstrated significant changes in their VEPs. Perhaps retinal physiologic condition and cortical physiologic condition are affected by different mechanisms in the TURP syndrome.

After TURP, patients can be separated into two categories: those who absorb minimal to moderate quantities of glycine and have minimal symptoms and those who absorb large quantities of glycine who demonstrate clinically observable side effects. It seems that only tremendously elevated serum levels of glycine (>4,000 μ M/l) produce overt symptoms. Although length of surgery, quantity of glycine used for irrigation, and serum glycine levels may all contribute to potential side effects (table 2), it is not possible to predict from the size or duration of the prostatic resection how much glycine will be systemically absorbed. Absorption of glycine also depends on the number of open venous sinuses and the amount of dense fibrous tissue in the gland.

Our control group of patients, who had cystoscopic examination for bladder or prostatic biopsies, is not a perfect control group for patients having TURP. These control patients were not subjected to the same length of procedure and trauma as the TURP patients and received

sterile water as a bladder irrigant. Their blood chemistries were similar before and after surgery, suggesting minimal influence of their surgery, bladder irrigant, and spinal anesthesia. Results from these patients did confirm that intraoperative administration of diazepam and possibly fentanyl slowed evoked potentials recorded from occipital scalp.

Because serum sodium correlated significantly with levels of glycine, it can be argued that it is not possible to separate effects of elevated glycine and lowered serum sodium levels. Sodium, however, is nearly nonspecific as far as visual physiologic condition is concerned, ¹⁵ whereas glycine has been shown to specifically affect retinal physiologic condition in controlled animal studies in the same manner as recorded from our TURP patients with high serum levels of glycine. ^{16–18} Also, one of the patients with complete dropout of ERG oscillatory potentials (fig. 2) had a postoperative serum sodium level of 132 mEq/l.

Multiple roles have been proposed for glycine in the retina, including that of being a major inhibitory transmitter. 10,18 Korol et al. 16 studied the effects of glycine injected intravitreally on the retina by recording the ERG of the rabbit. They reported the transient loss of oscillatory potentials. Wachtmeister and Dowling¹⁷ reported that glycine selectively depressed oscillatory potentials in the ERG recorded from the retina of the mudpuppy. In 1980 Wachtmeister 18 proposed that oscillatory potentials were generated by an inhibitory feedback system initiated by the amacrine cells. More recently, Wachtmeister¹⁹ speculated that bipolar cells or interplexiform cells may contribute to the generation of oscillatory potentials in the retina. Although the role of specific retinal cells has not been determined, glycine has been shown to be a contributing factor as an inhibitory neurotransmitter. 18

There is a gradation of effects of complications of the TURP syndrome. If serum sodium levels decrease to less than 125 mEq/l, nausea is usually reported. If the sodium ion level decreases to less than 120 mEq/l, cardiac complications are often reported with widening of the QRS complex and T-wave inversion. When glycine absorbed through the prostatic venous sinuses exceeds 4,000 μ M/l in the blood, visual impairment is also reported. The ammonia level increases seem to be more idiosyncratic. In our four patients with significantly elevated levels of glycine, it ranged from remaining normal (36–56 μ M/l) to between 223 and 496 μ M/l. Dramatic elevation of glycine level is often associated with normal levels of ammonia. 5

These data, previous clinical reports, and concordant animal research $^{16-19}$ indicate an association between increased glycine levels and the visual impairment reported by some patients experiencing the TURP syndrome. Among the patients in this study, only the four patients with serum glycine levels of greater than 4,000 μ M/l complained of visual impairment, and only these same

four patients demonstrated loss of oscillatory potentials from their ERGs and attenuation of 30-Hz flicker-following, similar to the effects of glycine on the retina of animals in which sodium levels were not lowered. Reduction of levels of sodium may also play a role, but glycine appears to affect retinal physiologic condition similarly in humans with the TURP syndrome and in animals independent of reduced serum sodium.

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