

---

# The Possible Role of Prostaglandins in Regulation of the Intra-ocular Pressure and the Value of Electro-retinography in Long Term Pressure Control

---

Ali. A. Elzarga,\* and Gergess S. Youssef\*

---

## Introduction:

The Glaucoma is one of the commonest health problems in the area of the middle-east, it constitutes the 2<sup>nd</sup> cause of blindness in the region.<sup>1</sup> The open angle type (OAG) is due to increase rate of aqueous secretion that exceeds its drainage with a high privilege rate in Africa,<sup>2</sup> while the closed type (CAG) is due to blockade in the drainage system of the aqueous, mostly. It happens due to an inflammatory change in the irido-corneal angle.<sup>3</sup> Glaucoma induces a lot of complications that if untreated end in total loss of vision. The classic lines of treatment especially for the open type rely mainly on one strategy; to decrease the rate of aqueous formation; e.g. by the use of  $\beta$  blockers as timolol.<sup>4</sup>

The formation of aqueous humour is a mixed mechanism that comprises both active secretion and passive filtration.<sup>5</sup> As any secreting cell, it would be expected that the ciliary body would follow the same orders of regulation as any gland. The 1<sup>st</sup> of which is the local factors as prostaglandins which are said to stimulate many glandular functions all over the body.<sup>6</sup> If this is to be applied for the aqueous, then it would be expected for the prostaglandin-analogues to decrease the rate of its formation.

Moreover it was found that the electrical activity of the retina either the electroretinogram or the retinal evoked potential; is a very sensitive test to any fluctuations of the IOP, so that many authors have already declared it as a very sensitive parameter for assessment of the healthiness of the neural tissue of the eye with the IOP changes.<sup>7</sup>

The present study was designated to access the possible role of prostaglandins in regulation of the aqueous humour formation and the value of studying the electrical activity of the retina as a

detector of the state of the retina with IOP fluctuations if checked by prostaglandin-analogues.

## Patients and methods:-

The study was carried out on 30 OAG patients who were regular visitors of the ophthalmology outpatient clinic at Ibn-Sina university hospital in Sirte, Libya. The groups (10 subjects in each) of the study were designated as follows:-

1. Control group.
2. The OAG untreated group of patients.
3. The OAG conventionally treated group, who received the classic treatment of OAG in the form of Acetazolamide (Diamox 250 mg tablets, Sanofi Aventis, France), one tab. t.d.s<sup>8</sup> and 0.5 % Timolol eye drops (Tunolol eye drops, Unimed, Tunisia), 2 drops t.d.s. for 4 weeks.<sup>9</sup>
4. The OAG prostaglandin-analogue treated group which received Latanoprost 0.005% eye drops (Xalatan, 0.005% eye drops, Uretim yeri, Pfizer, Belgium) 2 drops t.d.s for 4 weeks.<sup>10</sup>

Weekly, the IOP was measured by the pneumotonometry technique for all the 4 groups members and at the end of 4 weeks, patients were subjected to the following tests:-

- 1- Measurement of the IOP by the use of pneumotonometry.
- 2- ERG examination.<sup>7</sup>
- 3- Examination of the Visual Evoked Potentials.<sup>7</sup>

## Results:

The present work showed that the IOP was significantly higher in the untreated OAG group all through the 4 weeks of the study ( $23.2 \pm 3.3$ ,  $25.4 \pm 2.9$ ,  $26.2 \pm 3.8$  &  $27.1 \pm 3.1$  respectively) when it was compared to the weekly corresponding values of the control group ( $16.3 \pm 2.1$ ,  $15.3 \pm 2.3$ ,  $17.3 \pm 1.9$  &  $15.2 \pm 2.6$  respectively).

---

\*) Departments of Ophthalmology and Medical Physiology, Sirte and Menoufeya Universities, Libya & Egypt.

Timolol has succeeded to significantly reduce the IOP ( $22.1 \pm 3.4$ ,  $21.1 \pm 2.6$ ,  $23.2 \pm 2.9$  &  $21.4 \pm 3.1$  respectively) when it was compared to the weekly corresponding values of the untreated group but it failed to restore it to the corresponding control values.

The use of the prostaglandin analogue significantly reduced the IOP ( $23.4 \pm 2.1$ ,  $22.5 \pm 2.1$ ,  $19.3 \pm 2.1$  &  $16.6 \pm 2.1$  respectively) all through the study period, when it was compared to untreated group and succeeded to restore it to the control figure by the end of the study, (tab.1).

**Table (1): Shows the weekly IOP changes in the 4<sup>th</sup> group.**

| Timing of measurement                  | The control group | The untreated glaucoma group         | The Timolol treated group                               | The prostaglandin treated group                                                |
|----------------------------------------|-------------------|--------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------|
| By the end of the 1 <sup>st</sup> week | $16.3 \pm 2.1$    | $23.2 \pm 3.3$<br>P <sub>1</sub> S   | $22.1 \pm 3.4$<br>P <sub>1</sub> S<br>P <sub>2</sub> NS | $23.4 \pm 2.1$<br>P <sub>1</sub> VHS<br>P <sub>2</sub> NS<br>P <sub>3</sub> NS |
| By the end of the 2 <sup>nd</sup> week | $15.3 \pm 2.3$    | $25.4 \pm 2.9$<br>P <sub>1</sub> VHS | $21.1 \pm 2.6$<br>P <sub>1</sub> S<br>P <sub>2</sub> NS | $22.5 \pm 2.1$<br>P <sub>1</sub> HS<br>P <sub>2</sub> NS<br>P <sub>3</sub> NS  |
| By the end of the 3 <sup>rd</sup> week | $17.3 \pm 1.9$    | $26.2 \pm 3.8$<br>P <sub>1</sub> HS  | $23.2 \pm 2.9$<br>P <sub>1</sub> S<br>P <sub>2</sub> NS | $19.3 \pm 2.1$<br>P <sub>1</sub> NS<br>P <sub>2</sub> S<br>P <sub>3</sub> NS   |
| By the end of the 4 <sup>th</sup> week | $15.2 \pm 2.6$    | $27.1 \pm 3.1$<br>P <sub>1</sub> VHS | $21.4 \pm 3.1$<br>P <sub>1</sub> S<br>P <sub>2</sub> S  | $16.6 \pm 2.1$<br>P <sub>1</sub> NS<br>P <sub>2</sub> VHS<br>P <sub>3</sub> NS |

P<sub>1</sub> is obtained on comparing the test group to the control one.

P<sub>2</sub> is obtained on comparing the test group to the untreated OAG group.

P<sub>3</sub> is obtained on comparing the test group to the Timolol treated group.

NS means insignificant, S; significant, HS; highly significant and VHS means very highly significant change.

Considering the ERG changes in the untreated glaucomatous group, they showed significant reduction of the amplitude ( $4.1 \pm 1.2$ ,  $5.2 \pm 3.6$  &  $3.1 \pm 0.9 \mu\text{v}$ ) and the duration ( $6.2 \pm 2.1$ ,  $3.6 \pm 1.1$  &  $3.6 \pm 1.1 \text{ msec.}$ ) of the different wave components (A, B & C waves respectively) when they were compared to the corresponding control figures of the amplitude ( $20.3 \pm 1.8$ ,  $45.5 \pm 3.8$  &  $6.2 \pm 1.3$ ) and the duration ( $9.4 \pm 2.3$ ,  $21.4 \pm 3.6$  &  $9.4 \pm 2.1 \text{ msec.}$ ) of the same waves.

Timolol has significantly increased the corresponding amplitude ( $14.3 \pm 3.4$ ,  $37.1 \pm 4.3$  &

$10.2 \pm 2.1$ ) and the duration ( $10.3 \pm 2.6$ ,  $19.3 \pm 3.1$ ,  $6.3 \pm 2.1$ ) values of the different wave components but it failed to restore them to the corresponding control values.

Latanoprost has significantly succeeded to induce amazing bouts of the amplitude ( $22.1 \pm 3.4$ ,  $78.6 \pm 5.3$ ,  $10.4 \pm 2.6$ ), which were significantly comparable or even higher than the corresponding control value. As regard the duration, it significantly succeeded to restore it to the control figures ( $9.4 \pm 3.2$ ,  $19.2 \pm 4.6$  &  $10.3 \pm 2.1$ ) (tab.2, 3 & fig. 1a-d).

**Table (2): The amplitude ( $\mu\text{v}$ ) of the different component waves of the ERG in the 4 groups.**

| The wave | The control group | The untreated glaucoma group        | The Timolol treated group                                                 | The prostaglandin treated group                                                  |
|----------|-------------------|-------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| A wave   | 20.3 $\pm$ 1.8    | 4.1 $\pm$ 1.2<br>P <sub>1</sub> VHS | 14.3 $\pm$ 3.4<br>P <sub>1</sub> S<br>10.4 $\pm$ 2.6<br>P <sub>2</sub> VH | 22.1 $\pm$ 3.4<br>P <sub>1</sub> NS<br>P <sub>2</sub> VHS<br>P <sub>3</sub> S    |
| B wave   | 45.5 $\pm$ 3.8    | 5.2 $\pm$ 3.6<br>P <sub>1</sub> VHS | 37.1 $\pm$ 4.3<br>P <sub>1</sub> S<br>P <sub>2</sub> VHS                  | 78.6 $\pm$ 5.3<br>P <sub>1</sub> VHS<br>P <sub>2</sub> VHS<br>P <sub>3</sub> VHS |
| C wave   | 6.2 $\pm$ 1.3     | 3.1 $\pm$ 0.9<br>P <sub>1</sub> HS  | 10.2 $\pm$ 2.1<br>P <sub>1</sub> S<br>P <sub>2</sub> VHS                  | 10.4 $\pm$ 2.6<br>P <sub>1</sub> S<br>P <sub>2</sub> HS<br>P <sub>3</sub> NS     |

P<sub>1</sub> is obtained on comparing the test group to the control one.

P<sub>2</sub> is obtained on comparing the test group to the untreated OAG group.

P<sub>3</sub> is obtained on comparing the test group to the Timolol treated group.

NS means insignificant, S; significant, HS; highly significant and VHS means very highly significant change.

**Table (3): The duration (msec.) of the different component waves of the ERG in the 4<sup>th</sup> group.**

| The wave | The control group | The untreated glaucoma group        | The Timolol treated group                                 | The prostaglandin treated group                                                |
|----------|-------------------|-------------------------------------|-----------------------------------------------------------|--------------------------------------------------------------------------------|
| A wave   | 9.4 $\pm$ 2.3     | 6.2 $\pm$ 2.1<br>P <sub>1</sub> NS  | 10.3 $\pm$ 2.6<br>P <sub>1</sub> NS<br>P <sub>2</sub> NS  | 9.4 $\pm$ 3.2<br>P <sub>1</sub> NS<br>P <sub>2</sub> NS<br>P <sub>3</sub> NS   |
| B wave   | 21.4 $\pm$ 3.6    | 3.6 $\pm$ 1.1<br>P <sub>1</sub> VHS | 19.3 $\pm$ 3.1<br>P <sub>1</sub> NS<br>P <sub>2</sub> VHS | 19.2 $\pm$ 4.6<br>P <sub>1</sub> NS<br>P <sub>2</sub> VHS<br>P <sub>3</sub> NS |
| C wave   | 9.4 $\pm$ 2.1     | 3.6 $\pm$ 1.1<br>P <sub>1</sub> VHS | 6.3 $\pm$ 2.1<br>P <sub>1</sub> NS<br>P <sub>2</sub> NS   | 10.3 $\pm$ 2.1<br>P <sub>1</sub> NS<br>P <sub>2</sub> VHS<br>P <sub>3</sub> S  |

P<sub>1</sub> is obtained on comparing the test group to the control one.

P<sub>2</sub> is obtained on comparing the test group to the untreated OAG group.

P<sub>3</sub> is obtained on comparing the test group to the Timolol treated group.

NS means insignificant, S; significant, HS; highly significant and VHS means very highly significant change.

Considering the visual evoked potentials (VEP), they were significantly extinguished in the untreated glaucomatous and the timolol treated groups as regards their amplitude (5.3 $\pm$ 2.1 & 2.5 $\pm$ 1.4 $\mu\text{v}$  respectively) and duration (12.5 $\pm$ 2.8 & 15.6 $\pm$ 3.7 m.sec

respectively). The use of the prostaglandin analogue, Latanoprost significantly restored both parameters (7.3 $\pm$ 1.4  $\mu\text{v}$  & 25 $\pm$ 3.1msec) to the corresponding control value (6.5 $\pm$ 1.9  $\mu\text{v}$  & 27.5 $\pm$ 3.7 msec) (tab.4& fig.2a-d).

**Table (4): The VEP changes; the amplitude ( $\mu\text{V}$ ) and the duration (msec) in the studied 4 groups**

| The wave      | The control group | The untreated glaucoma group         | The Timolol treated group                              | The prostaglandin treated group                                              |
|---------------|-------------------|--------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------|
| The amplitude | $6.5 \pm 1.9$     | $5.3 \pm 2.1$<br>P <sub>1</sub> NS   | $2.5 \pm 1.4$<br>P <sub>1</sub> S<br>P <sub>2</sub> NS | $7.3 \pm 1.4$<br>P <sub>1</sub> NS<br>P <sub>2</sub> NS<br>P <sub>3</sub> HS |
| The duration  | $27.5 \pm 3.7$    | $12.5 \pm 2.8$<br>P <sub>1</sub> VHS | $15.6 \pm 3.7$<br>P <sub>1</sub> VHS<br>P <sub>2</sub> | $25 \pm 3.1$<br>P <sub>1</sub> NS<br>P <sub>2</sub> VHS<br>P <sub>3</sub> HS |

P<sub>1</sub> is obtained on comparing the test group to the control one.

P<sub>2</sub> is obtained on comparing the test group to the untreated OAG group.

P<sub>3</sub> is obtained on comparing the test group to the Timolol treated group.

NS means insignificant, S; significant, HS; highly significant and VHS means very highly significant change.

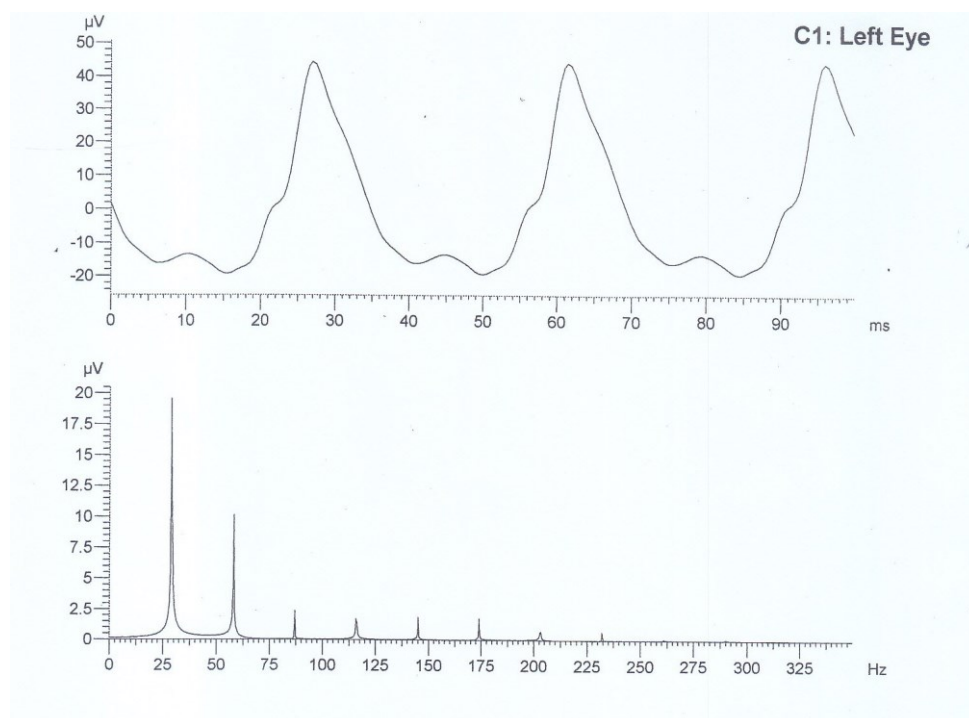
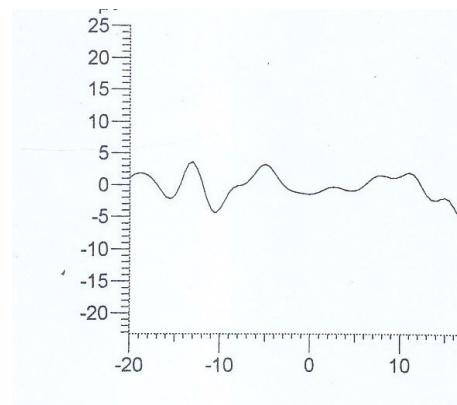


Figure (1-a) Shows the ERG in the control group.

Figure (1-b) Shows the ERG in the untreated glaucomatous group.



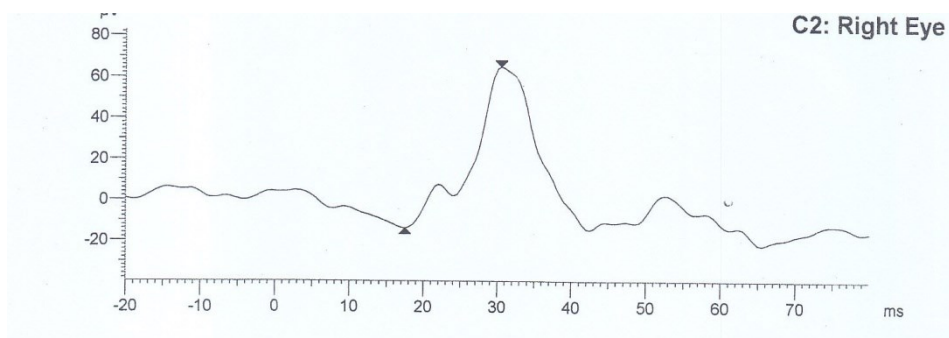


Figure (1-c) Shows the ERG in the Timolol-treated group.

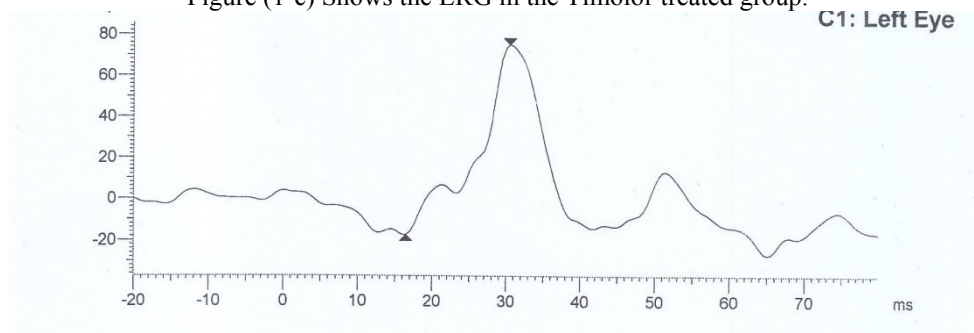


Figure (1-d) Shows the ERG in the Latanoprost-treated group.

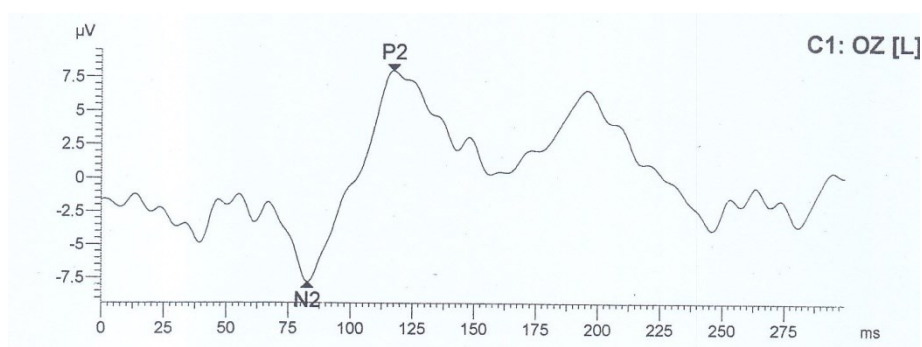


Figure (2-a) Shows the VEP in the control group.

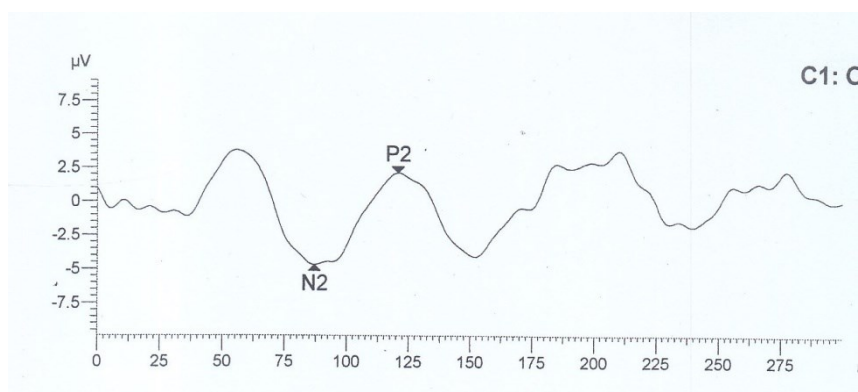


Figure (2-b) Shows the VEP in the untreated glaucomatous group.

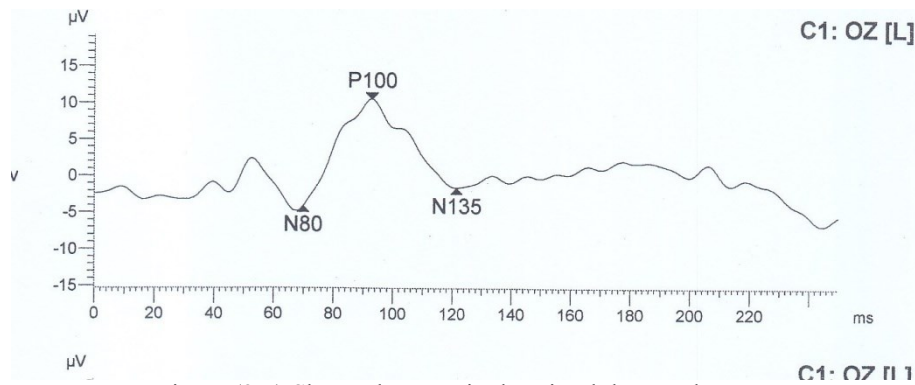


Figure (2-c) Shows the VEP in the Timolol-treated group.

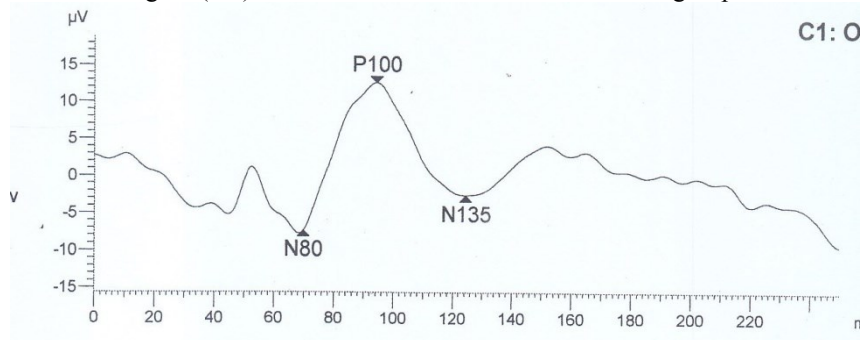


Figure (2-d) Shows the VEP in the Latanoprost-treated group

#### Discussion:

In the present study patients with OAG showed significant elevation of the IOP with significantly extinguished electrical activity of the retina. There was significant reduction of both the amplitude, duration of both the electroretinogram (ERG) and the visual evoked potential records (VEP). There was also prolongation of the absolute latency of both records. This is in agreement with the findings of Ventura et al.<sup>11</sup>, Bode et al.<sup>12</sup> and Todorova et al.<sup>13</sup> The significantly extinguished electrical activity could be due to mechanical compression upon the neural tissues of the eye with subsequent reduction of their excitability, a common physiological phenomenon in the neural tissues in general. Ischemia due to mechanical compression upon the retina was declared by many authors to induce significant thinning out especially in the retinal nerve fibre layer (RNFLT) with subsequent suppression of the electrical activity of the retina.<sup>14</sup>

The blockade of the beta adrenergic receptors by Timolol together with the help of the famous diuretic acetazolamide has significantly reduced the elevated IOP, enhanced one aspect of the retinal electrical activity; the amplitude of the A and B waves of the ERG and both of

the amplitude and the duration of the VEP but not to the control values. However, it succeeded to restore the duration of the ERG waves and the amplitude of its C component to the corresponding control figures. Reduction of the rate of aqueous secretion with the use of timolol is attributed to a vasoconstrictor effect upon the ciliary's blood vessels which are dilated on stimulation of their plain muscle beta-2 adrenergic receptors (15-Metheetraitut 2012). The partial improvement of the electrical activity could be attributed to partial recovery of the neural elements of the eye from the pressure induced-ischemia where Ventura et al.<sup>16</sup> 2012 have declared that lowering of the IOP hindered the progressive degenerative changes of some retinal layers especially the ganglion cell layer (RGCL). Some authors declared that it is Timolol that can partially recover the extinguished REG pattern that was induced by a high level of IOP.<sup>17</sup> Moreover, some other authors have praised timolol for a retinal protective effect against retinal ischemic degeneration.<sup>18-19</sup> The restoration of the amplitude of the C wave and the duration of the different wave components of the ERG back to the normal control figure is an interesting finding that clarifies how valuable is the use of the beta adrenergic blockade in

the management of the rise of the IOP. The restoration of just the C wave amplitude could be explained in the light of being a late slow wave of depolarization of the pigment cell layer of the retina which came 3<sup>rd</sup> in the trace and not as early as the A or the B wave where the beta blockade with its mild beneficial action could come into effect. This is strongly supported by the result that it exerted the same action upon the duration of the different wave components of the ERG. It could be said that the timolol-induced pressure relief might restore the duration of action of the healthy non-ischemic ion channels in the retinal cells back to the normal level that is why it restored the wave duration to normal but it could do nothing to the already damaged channels and that is why it couldn't do the same for the amplitude of Acetazolamide i.e. Diamox therapy which has a great role in the reduction of the IOP through its potent diuretic activity.

The use of the prostaglandin-analogue latanoprost induced significant reduction of the IOP down to the control figure together with a significant amazing improvement of all the test parameters of the ERG and the VEP which were significantly brought back to the control value and may be even higher as in case of the amplitude of the B wave of the ERG. The effect of the prostaglandin agonist upon the rate of aqueous secretion came in agreement with the findings of many authors who praised the use of prostaglandins as an effective tool for the control of the IOP especially in case of OAG.<sup>20</sup> They attributed their beneficial effect of lowering the IOP mainly through widening of the uveoscleral drainage veinular vessels possibly as a part of their vasodilator action. Thus they can increase the rate of the aqueous drainage at the limbus of the eye.<sup>21</sup> Prostaglandins are said to be potent vasodilators for many blood vascular beds all over the body including their venous sides.<sup>22</sup> Prostaglandins induce vasodilatation through many possible mechanisms, the 1<sup>st</sup> of which may be through activation of the Ca<sup>+</sup> dependant K<sup>+</sup> channels resulting in hyperpolarization of the vascular smooth muscle cells.<sup>23</sup> One other possible mechanism may be an ATP- mediated as it is known to be one of the potent endothelium-dependant vasodilators. Prostaglandins are said to augment its vasodilator effects.<sup>24</sup>

In general, prostaglandins control the glandular secretion from variable sites all over the body,

starting from the salivary glands,<sup>25</sup> and passing through the gastric secretion<sup>26</sup> to end on the endometrium.<sup>27</sup> It would not be un-logic to expect them to control the secretion of the ciliary processes. They may affect them through many cellular mechanisms possibly by controlling the Na<sup>+</sup>-k<sup>+</sup> pump or changing the cell wall permeability to Ca<sup>+</sup> ion; the key player for any secretion to be released (25) or through a control mechanism over the cell protein receptors.<sup>25-28</sup> Exactly in the same manner where in some places there are vasoconstrictors and plain muscle stimulants and in other places there are vasodilators and plain muscle relaxants,<sup>29-30</sup> it could be said that they stimulate glandular secretion at some places as in the stomach and to inhibit it in others as in the ciliary body.<sup>31</sup>

The beneficial effect of prostaglandins upon the electrical activity of the retina could be also attributed to partial recovery of the neural element of the eye from high IOP induced-ischemic changes. Prostaglandins could also improve the electrical activity through other non- pressure relief mechanisms. It may be the interference with the membrane permeability for ions as they are known as one of the commonest humoral factors that alter the cell membrane permeability toward various ions including Na. Na ion is the key player for the development of the photoreceptor potential and neural excitability of the brain cells. This could explain the more significant recovery of the ERG and VEP with the prostaglandin-analogue Latanoprost much more than those recorded with the timolol treated group and this is came in agreement with those of Phan et al.<sup>32</sup> and Lejeune et al.<sup>33</sup>

Prostaglandins also exert their physiological functions through what is called the 2<sup>nd</sup> messengers which are cellular cyclic compounds as cAMP and cGMP. They are said to control many neural cellular functional aspects especially the cell wall permeability, the development of the neural action potentials and the excitability changes.<sup>34</sup> The prostaglandin-induced effect upon the electrical activity of the retina may come through the intervention of either the synthesis and or breakdown of such cyclic compounds.<sup>35</sup> Moreover prostaglandins are said to modulate the functions of many neural elements through stimulation or sometimes inhibition of many cellular neural proteins or even receptors as neurokinin; a mechanism that can be added to

the non pressure-relief mechanisms through which the prostaglandins have distinguished the retinal electrical activity.<sup>36</sup>

The Latanoprost-induced restoration of the electrical activity of the retina and the VEP back to their normal values is really a promising sign of hope for those suffering from the neuroretinal malignant degenerative consequences of glaucoma. Of course, it appears that it is of utmost significance for those with an idiopathic rise of the IOP where the iridocorneal angle is still open and functioning well draining the aqueous but the pressure is running high and continuously threatening the neural integrity of the retina especially on the long term. Nevertheless the success of the prostaglandin Latanoprost in achieving one goal that was not reached by the double agent therapy i.e. timolol and acetazolamide is one extra-advantage for the latanoprost.

It could be concluded that prostaglandins may have a major role in regulating the rate of

aqueous secretion and if they would be applied clinically by the use of the prostaglandin-analogues as Latanoprost, they could be of a much greater value for the control of the high levels of the IOP especially in cases of OAG. Its beneficial effect regarding the electrical activity of the retina; what is called the retino-protecting effect could be an additive advantageous feature for their clinical application. Moreover, it could be said that examining the electrical activity of the neural element of the eye could be taken as a long-term assessment tool for the effects of the high IOP on the retinal neural element. However, these results need further thorough investigation to uncover the exact sites and possible mechanisms through which prostaglandins act, the timing and the frequency of the examination of the ERG & VEP throughout the course of the disease. Prostaglandins and the ERG may be a new hope for those who suffer from glaucomatous-damage of the neural elements of the eye.

#### References:

1. Cook C and Foster P. (2012) Epidemiology of glaucoma: what's new? *Can J Ophthalmol.* 2012 Jun; 47 (3):223-6.
2. Wolfram C and Pfeiffer N (2012). Glaucoma diseases in Rhineland-Palatine 2010. Epidemiology and utilization of healthcare. *Ophthalmologe.* Mar; 109(3):271-6.
3. Cassard SD, Quigley HA, Gower EW, Friedman DS, Ramulu PY and Jampel HD (2012). Regional Variations and Trends in the Prevalence of Diagnosed Glaucoma in the Medicare Population. *Ophthalmology.* Apr 3. [Epub ahead of print]
4. Aptel F, Cucherat M and Denis P (2012). Efficacy and tolerability of prostaglandin-timolol fixed combinations: a meta-analysis of randomized clinical trials. *Eur J Ophthalmol.* Jan-Feb;22 (1):5-18.
5. Yang Y, Li Z, Wang N, Wu L, Zhen Y, Wang T, Ren C, Peng X, Hao J and Xia Y (2012). Intraocular Pressure Fluctuation in Patients with Primary Open-angle Glaucoma Combined With High Myopia. *J Glaucoma.* Jun 4. [Epub ahead of print]
6. Pinard CL, Gauvin D, Moreau M, Martel-Pelletier J, Pelletier JP and Troncy E (2011). Measurements of canine aqueous humor inflammatory mediators and the effect of carprofen following anterior chamber paracentesis. *Vet Ophthalmol.* Sep;14 (5):296-303. doi: 10.1111/j.1463-5224.2011.00876.x
7. Poloschek CM and Bach M (2012). [Electrophysiological examination methods in glaucoma diagnostics]. *Ophthalmologe.* Apr; 109(4):358-63.
8. Hussein A and Madhesia D. (2011) Heterocyclic compounds as carbonic anhydrase inhibitor. *J Enzyme Inhib. Med Chem.* Oct 10. [Epub ahead of print]
9. Goto W, Ota T, Morikawa N, Otori Y, Hara H, Kawazu K, Miyawaki N and Tano Y.(2002). Protective effects of timolol against the neuronal damage induced by glutamate and ischemia in the rat retina. *Brain Res.* Dec 20; 958(1):10-9.
10. Digiuni M, Fogagnolo P and Rossetti L. (2012). A review of the use of latanoprost for glaucoma since its launch. *Expert Opin Pharmacother.* Feb 21. [Epub ahead of print]
11. Ventura LM, Golubev I, Feuer WJ and Porciatti V (2011). Pattern Electroretinogram Progression in Glaucoma Suspects. *J Glaucoma.* Nov 7. [Epub ahead of print]
12. Bode SF, Jehle T and Bach M (2011). Pattern electroretinogram in glaucoma suspects: new findings from a longitudinal

- study. *Invest Ophthalmol Vis Sci.* Jun 16; 52(7):4300-6.
13. Todorova MG and Palmowski-Wolfe AM (2011). MfERG responses to long-duration white stimuli in glaucoma patients. *Doc Ophthalmol.* Apr; 122(2):87-97.
14. Fortune B, Burgoyne CF, Cull GA, Reynaud J and Wang L.( 2012) Structural and functional abnormalities of retinal ganglion cells measured in vivo at the onset of optic nerve head surface change in experimental glaucoma. *Invest Ophthalmol Vis Sci.* Jun 22; 53(7):3939-50.
15. Methetrairut A, Leumsamran P, Rojananin S and Kitnarong N. (2012).A comparison of 0.1% timolol eye gel and 0.5% timolol eye drop in patients with chronic angle-closure glaucoma. *J Med Assoc Thai.* Apr; 95 Suppl 4:S116-22.
16. Ventura LM, Feuer WJ and Porciatti V. (2012) Progressive loss of retinal ganglion cell function is hindered with IOP-lowering treatment in early glaucoma. *Invest Ophthalmol Vis Sci.* Feb 13; 53(2):659-63.
17. Colotto A, Salgarello T, Giudiceandrea A, De Luca LA, Coppè A, Buzzonetti L and Falsini B (1995). Pattern electroretinogram in treated ocular hypertension: a cross-sectional study after timolol maleate therapy. *Ophthalmic Res.*; 27 (3):168-77.
18. Goto W, Ota T, Morikawa N, Otori Y, Hara H, Kawazu K, Miyawaki N and Tano Y(2002). Protective effects of timolol against the neuronal damage induced by glutamate and ischemia in the rat retina. *Brain Res.* Dec 20; 958(1):10-9.
19. Wood JP, Schmidt KG, Melena J, Chidlow G, Allmeier H and Osborne NN(2003).The beta-adrenoceptor antagonists metipranolol and timolol are retinal neuroprotectants: comparison with betaxolol. *Exp Eye Res.* Apr; 76(4):505-16.
20. Digiuni M, Fogagnolo P and Rossetti L (2012). A review of the use of latanoprost for glaucoma since its launch. *Expert Opin Pharmacother.* Feb 21.[Epub ahead of print]
21. Allaire C, Dietrich A, Allmeier H, Grundmane I, Mazur-Piotrowska G, Neshev P and Kahle G(2012). Latanoprost 0.005% test formulation is as effective as Xalatan® in patients with ocular hypertension and primary open-angle glaucoma. *Eur J Ophthalmol.* Jan-Feb;22(1):19-27
22. Montenegro MF, Ceron CS, Salgado MC, Desta Z, Flockhart DA, Tanus-Santos JE (2011). Tamoxifen and its metabolites cause acute vasorelaxation of aortic rings by inducing vasodilator prostanoid synthesis. *J Cardiovasc Pharmacol.* Dec; 58 (6):647-53.
23. Li Y, Connolly M, Nagaraj C, Tang B, Bálint Z, Popper H, Smolle-Juettner FM,Lindenmann J, Kwapiszewska G, Aaronson PI, Wohlkoenig C, Leithner K, OlschewskiH and Olschewski A.(2012) Peroxisome proliferator-activated receptor- $\beta/\delta$ , the acute signaling factor in prostacyclin-induced pulmonary vasodilation. *Am J Respir Cell Mol Biol.* Mar;46(3):372-9
24. Crecelius AR, Kirby BS, Richards JC, Garcia LJ, Voyles WF, Larson DG, Luckasen GJ and Dinunno FA(2011). Mechanisms of ATP-mediated vasodilation in humans: modest role for nitric oxide and vasodilating prostaglandins. *Am J Physiol Heart Circ Physiol.* Oct;301 (4):H1302-10.
25. Passafaro D, Reina S, Sterin-Borda L and Borda E (2010). Cholinergic autoantibodies from primary Sjögren's syndrome modulate submandibular gland Na<sup>+</sup>/K<sup>+</sup>-ATPase activity via prostaglandin E2 and cyclic AMP. *Eur J Oral Sci.* Apr;118 (2):131-8.
26. Cargile JL, Burrow JA, Kim I, Cohen ND and Merritt AM (2009). Effect of dietary corn oil supplementation on equine gastric fluid acid, sodium, and prostaglandin E2 content before and during pentagastrin infusion. *J Vet Intern Med.* 2004 Jul-Aug;18 (4):545-9.
27. Wacławik A, Jabbour HN, Blitek A and Ziecik AJ(2009). Estradiol-17 $\beta$ , prostaglandin E2 (PGE2), and the PGE2 receptor are involved in PGE2 positive feedback loop in the porcine endometrium. *Endocrinology.* Aug;150(8):3823-32
28. Iyú D, Jüttner M, Glenn JR, White AE, Johnson AJ, Fox SC and Heptinstall S(2011). PGE1 and PGE2 modify platelet function through different prostanoid receptors. *Prostaglandins Other Lipid Mediat.* Feb;94(1-2):9-16
29. De La Cruz JP, Jebrouni N, López-Villodres JA, Muñoz-Marín J, Guerrero A and González-Correa JA (2012). Effects of terutroban, a thromboxane/prostaglandin endoperoxide receptor antagonist, on retinal vascularity in diabetic rats. *Diabetes Metab Res Rev.* Feb;28 (2):132-8.
30. Luria O, Bar J, Barnea O, Golan A and Kovo M (2012). Reactivity of blood vessels in response to prostaglandin E2 in placentas from pregnancies complicated by fetal growth restriction. *Prenat Diagn.* May;32 (5):417-22.

31. Yamato M, Nagahama K, Kotani T, Kato S and Takeuchi K. (2005) Biphasic effect of prostaglandin E2 in a rat model of esophagitis mediated by EP1 receptors: relation to pepsin secretion. *Digestion.*; 72(2-3):109-18.
32. Phan MN, Leddy HA, Votta BJ, Kumar S, Levy DS, Lipshutz DB, Lee SH, Liedtke W and Guilak F(2009). Functional characterization of TRPV4 as an osmotically sensitive ion channel in porcine articular chondrocytes. *Arthritis Rheum.* Oct;60 (10):3028-37.
33. Lejeune M, Moreau F and Chadee K (2011). Prostaglandin E2 produced by *Entamoeba histolytica* signals via EP4 receptor and alters claudin-4 to increase ion permeability of tight junctions. *Am J Pathol.* Aug; 179(2):807-18
34. Sharif NA and Crider JY(2011). Intracellular signaling in human iridial fibroblasts and iridial melanocytes in response to prostaglandins, endothelin, isoproterenol, and other pharmacological agents. *Curr Eye Res.* Apr;36 (4):310-20.
35. Jahn U, Galano JM and Durand T (2008). Beyond prostaglandins--chemistry and biology of cyclic oxygenated metabolites formed by free-radical pathways from polyunsaturated fatty acids. *Angew Chem Int Ed Engl.*; 47(32):5894-955
36. Segond von Banchet G, Scholze A and Schaible HG (2003). Prostaglandin E2 increases the expression of the neurokinin1 receptor in adult sensory neurones in culture: a novel role of prostaglandins. *Br J Pharmacol.* Jun;139(3):672-80.