EVALUATION OF INTRAOCULAR PRESSURE IN PATIENTS WITH METABOLIC ACIDOSIS AND COMPARING IT WITH AGE MATCHED CONTROLS USING PERKINS HAND HELD TONOMETER

Dissertation submitted to

The Tamil Nadu Dr. M.G.R Medical University, Chennai

In fulfilment of the requirements for the award of the degree of

Master of Surgery in Opthalmology

Dissertation submitted by

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THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY, CHENNAI, TAMILNADU

APRIL 2020

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To
Dr Sathiya K
Postgraduate
Department of Ophthalmology
Guide: Dr D Sundar
PSG IMS & R
Coimbatore

Ref: Project No. **17/377**

Date: December 26, 2017

Dear Dr Sathiya,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 06.12.2017 to conduct the research study entitled *"Evaluation of intraocular pressure in patients with metabolic acidosis and comparing it with age matched controls using Perkins hand held tonometer"* during the IHEC meeting held on 15.12.2017.

The following documents were reviewed and approved:

1. Project submission form
2. Study protocol (Version 1 dated 06.12.2017)
3. Informed consent forms (Version 1 dated 06.12.2017)
4. Data collection tool (Version 1 dated 06.12.2017)
5. Current CVs of Principal investigator, Co-investigator
6. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 15.12.2017 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr R Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
2	Dr D Vijaya (Member – Secretary, IHEC)	M Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes
3	Dr S Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr Sudha Ramalingam	MD	Epidemiologist, Ethicist Alt. member-Secretary	Female	Yes	Yes
5	Dr G Subhashini	MD	Epidemiologist	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date

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of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

03/9/2018

Dr D Vijaya
Member - Secretary
Institutional Human Ethics Committee

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PLAGIARISM CERTIFICATE II

This is to certify that this dissertation work titled **"Evaluation of Intraocular pressure in patients with metabolic acidosis and comparing it with age matched controls using Perkins hand held tonometer"** of the candidate DR.K.SATHIYA with **Reg. No. 100333** for the award of **MASTER OF SURGERY** in the branch of **OPHTHALMOLOGY**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains pages from Introduction to Conclusion and the result shows **2 percentage** of plagiarism in the dissertation

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Dr.K.Sathiya

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INTRODUCTION

This study was carried out to determine the variations that occur in the intraocular pressure (IOP) of eye, with Metabolic acidosis (MA), a disorder of acid-base balance, frequently encountered in emergency and critical care units.

Metabolic acidosis is the commonest acid-base imbalance that is characterized typically by a reduction in bicarbonate ($HCO_3(-)$), along with compensatory reduction in the Pco_2 (arterial partial pressure of carbondioxide) and a markedly low or subnormal ph. It occurs due to increased acid formation/diminished acid excretion or due to loss of bicarbonate from the body, especially when it exceeds the body's adaptive mechanism to handle this(1).

The commonly encountered causes for the metabolic acidosis in the ICU (intensive care unit) setup are categorized below:-

- **Increased acid production:-**

Lactic acidosis

Ketoacidosis

Ingestions

Drug infusions

- Diminished acid excretion:-

Chronic kidney disease(CKD)

- Loss of bicarbonate:-

Diarrhoea

Ureterostomy (2)

Maintenance of acid base homeostasis and regulation of ph are crucial for normal functioning of body as well as for cellular metabolism. The physiological range of arterial ph is between 7.36 – 7.44. The ph need to be maintained constantly within the physiological limits since many enzyme processes and cellular metabolisms of body are ph dependent(3).

Even a mild variation from the normal ph range can induce deleterious effects such as reduced oxygen delivery to the tissues, electrolyte imbalance and cardiac arrhythmias (alteration in cardiac muscle contractility). A reduction in ph leads to acidosis and an increase in ph causes alkalosis. Therefore the acid and base are to be maintained in a

balanced state. This is achieved by the following three major defensive mechanisms within the body.

The first and the most immediate mechanism of defense are the buffer systems (intracellular and extracellular) in response to a change in ph. This is done by the HCO_3- buffer system predominantly, next is the phosphate and protein buffer systems.

The second line of defense mechanism for ph regulation of extracellular fluid (ECF) is by control of carbonic acid (H_2CO_3) concentration in the ECF. This is achieved by either hyperventilation / hypoventilation (i.e,.increased /decreased rate of breathing), which exhales out or retains carbon dioxide (and thus H_2CO_3) in blood plasma.

The third line of defense is by the renal system which can either add or remove bicarbonate ions from the extracellular fluid. When the renal adaptive mechanisms fails to handle the acid load, it leads to disorders in acid base balance since the kidneys play an important role in handling the acid load (4)(6)(7).

For a better understanding of metabolic acidosis, the bicarbonate buffer system is discussed briefly as follows.

The bicarbonate buffer system is the most important of all, which is described by the following two equations.

The Henderson-hasselbach equation (equation-1), shows the relationship between the ph, $HCO_3(-)$ and Pco_2.Equation-2 represents the formation of carbonic acid (H_2CO_3), mediated by the enzyme carbonic anhydrase(c.a.) and its dissociation to form bicarbonate and hydrogen ions (H(+))

Equation-1:-

$$Ph = 6.1 + \frac{\log HCO_3(-)}{0.03 \times Pco_2}$$

$HCO_3(-)$ in milliequalents/litre; Pco_2 in millimeters of mercury

Equation-2:-

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H(+) + HCO_3(-)$$

This system is critically important buffer system due to its capacity to buffer acid or alkali load quantitatively as well as for regulation of

bicarbonate and partial pressure of the carbon dioxide mainly by renal system (kidneys) and respiratory system (lungs).

The latter aspect of regulation being the most powerful of this system. Even though the lungs and kidneys can undergo changes to compensate for disorders of each other, CO_2 and $HCO_3(-)$ levels should be in optimal range for the homeostasis(5,6)

In general the disorders due to CO_2 are termed to as respiratory disorders, and disorders due to $HCO_3(-)$ are termed to as metabolic disorders.

The arterial CO_2 level is predominantly regulated by alveolar ventilation after being produced in the peripheral tissues. Upon its addition to the aqueous solution, the carbondioxide which is a gaseous acid yields carbonic acid, which then produces $H(+)$ and $HCO_3(-)$ (Equation-2 will then be driven to the right).

Plasma $HCO_3(-)$ regulation is predominantly carried out by the kidneys. Dietary acids and metabolic acids form the main source of plasma $HCO_3(-)$. As depicted in Equation 1 , increase in $HCO_3(-)$ or a decrease in

P_{CO2} will raise the ph and decrease in $HCO_3(-)$ or an increase in P_{CO2} will lower the ph respectively.

For acid-base regulation, the physiological addition of an acid and loss of alkali has to be equivalent; for instance, as in Equation 2, the loss of $HCO_3(-)$ will pull the equation towards right, producing more H(+). e.g- Loss of $HCO_3(-)$ that happens in proximal renal tubular acidosis and diarrhea .

Similarly, the addition of alkali and the loss of acid are also essentially equivalent. Hence, the excretion of acid by the kidneys is equivalent to the production of a base or $HCO_3(-)$ (3)(7)

In metabolic acidosis, there is derangement of this acid base homeostasis, either due to an increased production of acids or a loss of bicarbonate as described earlier. The normal range for bicarbonate is estimated to be 22 – 29mEq/L (24). Levels < 22meq/L or > 30meq/L results in derangement of the acid base balance thereby leading to significant complications (1-2).

Metabolic acidosis is classified into high anion gap and normal anion gap acidosis by means of serum anion gap.

USE OF ANION GAP IN DIAGNOSIS OF METABOLIC ACIDOSIS

The serum anion gap (AG) is the difference between unmeasured anions and unmeasured cations which is calculated by a formula as below:-

$$AG = (Na(+) + K(+)) - (Cl- + HCO_3(-)) \text{ (normal=14-16 mmol/l)}$$

Since the change in serum potassium concentration is meagre, potassium is neglected from the calculation. Therefore,

$$AG = Na(+) - (Cl(-) + HCO_3(-)) \text{ (normal= 10-12 mmol/l)}$$

here, Na(+) = sodium,

Cl(-) = chloride and

K(+) = potassium ions

The major unmeasured anions in serum are albumin, phosphate, sulfate, and other organic anions. The major unmeasured cations include calcium, magnesium, and other minor cations.

An increase in anion gap may be due to a reduction in unmeasured cations / increase in unmeasured anions. When unmeasured anions, such as acetoacetate in diabetic ketoacidosis or lactate in lactic acidosis, accumulate in the body, AG increases because the hydrogen ions buffer the bicarbonate

causing a drop in serum bicarbonate, while the retained anions (lactate / acetoacetate) adds to unmeasured anions.

The loss of bicarbonate either from the gastrointestinal tract (e.g., diarrhea) or the kidney (e.g., RTA) will lead to hyperchloremic MA because the bicarbonate loss must be accompanied by the rise of serum chloride to maintain neutrality.

The serum AG is also dependent on the level of serum albumin.

For every fall in serum albumin of 1 g/dL, the AG drops by about 4 mmol/l, e.g- An increase of unmeasured cations with the accumulation of cationic immunoglobulins in patients with plasma cell dyscrasia, which decreases the AG(8,9).

HIGH ANION GAP METABOLIC ACIDOSIS:-

The frequent causes for high AG MA are:-

1. Lactic acidosis
2. ketoacidosis
3. Renal failure
4. Intoxication(10)

1. Lactic acidosis is induced by either lactic acid overproduction in case of tissue hypoxia (e.g. shock) or defective utilization (e.g., liver disease, thiamine deficiency).

E.g- D-Lactic acidosis, which occurs in patients with short-bowel syndrome. The patients presenting features are recurrent episodes of encephalopathy and metabolic acidosis. (11–14).

2. Ketoacidosis occurs when the quantity of free fatty acids to the liver rises or conversion of free fatty acids to ketoacids (acetoacetate, β-hydroxybutyrate) is increased.

E.g- Starvation ketoacidosis- occurs when insulin is absent, as in the fasting state

Diabetic ketoacidosis- most common in insulin dependent diabetes mellitus

Alcoholic ketoacidosis- when glucagons and cortisol action is enhanced(15–17).

3. Renal failure, both acute and chronic, can also cause high AG MA. The pathology is mainly due to a decrease in ammonium excretion as a result of reduced renal mass(18–20).

4. Ingestion of toxins such as ethylene glycol, methanol and salicylate are causes of high AG MA. Few less common causes include pyroglutamic acid (5-oxoproline), propylene glycol and djenkol bean (djenkolism).

Pyroglutamic acidemia in patients after acetaminophen exposure also causes severe high AG MA. Affected patients present with altered sensorium ranging from confusion to coma. High concentrations of pyroglutamic acid are detected in the blood and urine in parallel to increase in the AG.

Propylene glycol, a solvent used in drug formulations, has been reported to cause a high AG MA with an elevated osmolal gap, especially in patients receiving lorazepam in high doses than the recommended dosage range (0.1 mg/kg per hr).

Ingestion of djenkol beans, also cause acute renal failure and consequent high AG MA. It is common in Indonesia and Malaysia. These beans are found to posses high djenkolic acid. The presentation varies from person to person with some developing renal failure while others do not. The mechanism is unclear(2).

HYPERCHLOREMIC (NORMAL ANION GAP) METABOLIC ACIDOSIS

Diarrhea commonly causes loss of large quantities of bicarbonate and leads to MA, especially when the kidney is unable to cope up to the loss by increasing net renal acid excretion. The intestinal mucosa has an apical Cl- / HCO_3- exchanger.

In ureterosigmoidostomy, when urine is diverted to the loop of bowel, the chloride in urine is exchanged for HCO_3(-) , leading to a hyperchloremic MA(21).

The typical findings in proximal and distal renal tubular acidosis is a hypokalemia with hyperchloremic MA. This is due to renal bicarbonate loss as in proximal RTA or impaired net H(+) secretion as in distal RTA. Chronic kidney disease can lead to metabolic acidosis when the glomerular filtration becomes 30 - 59 mL/min (18-20).

Drugs such as ACE inhibitors, spironolactone, amiloride, trimethoprim, pentamidine, nonsteroidanti inflammatory drugs (NSAIDs) and cyclosporine can induce hyperkalemia with ahyperchloremic MA.

The administration of an acid containing Cl- (e.g., NH4 Cl) can result in a hyperchloremic MA. Infusion of arginine or lysine hydrochloride during parenteral nutrition also produces hyperchloremic MA. If isotonic saline is infused rapidly, the serum bicarbonate will decline reciprocally in relation to an increase in serum chloride, leading to hyperchloremic metabolic acidosis(22,23).

When interpreting acid-base disorders, it is important to remember that there can be only one primary respiratory disturbance at a time. There is either alveolar hyperventilation (indicating respiratory alkalosis) or alveolar hypoventilation (indicating respiratory acidosis). However, one can have opposite metabolic disturbances at the same time.

More than one mechanism can produce metabolic acidosis at same time, as well as metabolic alkalosis. There is certainly no limit to the number of metabolic disturbances one particular patient may have.

Many different acids, pathologies and metabolic processes can contribute to the metabolic component of acid-base alterations.

MA is an emergency whether acute or chronic and requires prompt inventions as it may lead to complications such as cardiac arrhythmias,

hypotension, impaired oxygen delivery, increased muscle degradation. Hence meticulous correction of the imbalance and treatment of the cause may reduce morbidity(1,24,25)

From the above explanations it is clear that it is the bicarbonate that is chiefly decreased in metabolic acidosis. In metabolic acidosis, the decrease in bicarbonate leads to the failure of active sodium and water transport across the ciliary epithelium which causes a reduction in aqueous production there by reducing the intraocular pressure.

The main steps of aqueous humor production are

1. Accumulation of plasma by diffusion and ultra-filtration behind the tight junctions of non-pigmented epithelium of the ciliary body(CB)

2. Active transport across the blood aqueous barrier which involves trans cellular movement of Na(+), K(+)& HCO_3(-), Cl(-) across the non-pigmented epithelium of the CB.

Two main enzymes involved in this transport are

1. Na(+)-K(+) ATPase
2. Carbonic anhydrase

Carbonic anhydrase facilitates transport of bicarbonate by mediating rapid inter conversion b/w $HCO_3(-)$ & CO2. This bicarbonate further effect sodium and water transport by regulating the pH for optimum the active transport(26).

Hence bicarbonate reduction in metabolic acidosis leads to the failure of active sodium and water transport which causes a rapid fall in intraocular pressure.

Therefore we monitored the IOP prior to treatment of the metabolic acidosis as well as after correction of metabolic acidosis, in order to know the effects on the intraocular pressure (IOP) induced by metabolic acidosis.

The intraocular pressure was monitored using the perkins hand held applanation tonometer since it is portable and yields accurate results closer to the goldman applanation tonometer which is considered to be the gold-standard in ophthalmology(27).

This study was done to investigate the relationship between metabolic acidosis and the ocular hypotension, over a period of time in patients admitted in intensive care units.

AIM AND OBJECTIVES

To evaluate intra ocular pressure variation in patients diagnosed with metabolic acidosis and to compare it with Age matched controls at PSGIMSR during a time period of 18months.

REVIEW OF LITERATURE

Intraocular pressure (IOP), the hydrostatic pressure of the eye is a measure of the magnitude of force exerted by the aqueous humour on the internal surface of the anterior eye.

IOP is essentially maintained in dynamic equilibrium by the formation and drainage of aqueous humor (AH)(28)

The normal range for IOP was estimated to be 13.6 ± 3.4 mmHg among Indian population(29).

It is maintained at this level throughout life and between the sexes, though there is some variation with respect to age, ocular blood low and diurnally. Control of IOP within the correct physiological range is necessary to maintain the anatomical conditions necessary for optimal refraction and thus vision(30).

Normal regulation of IOP occurs chiefly through the regulation of the volume of the aqueous humour in the anterior chamber of the eye. Aqueous humor is a clear fluid that occupies and forms the anterior and posterior chambers of the eye. It provides a transparent and colourless medium

between the cornea and the lens in order to maintain the optical properties of the eye(31).

The cornea, along with sclera constitute the outer covering or coat of the eyeball. The main function of this coat is to protect structures inside the eye.

The cornea is a transparent avascular structure that acts as a structural barrier and protects the eye against infections. It contributes to about two-third of the refractive power of the eye.

The aqueous humor forms the main source of nutrients to the cornea. It flows from the posterior chamber to the anterior chamber via the pupil and drains at the angle of anterior chamber. The anterior chamber is present between the cornea and iris and posterior chamber between the iris and lens. Blood supply is by the branches of facial and ophthalmic arteries through the aqueous humor and the tear film(32).

The anatomy of human eye is shown in figure-1 and the flow of aqueous humor from posterior to anterior chamber in the fugure-2

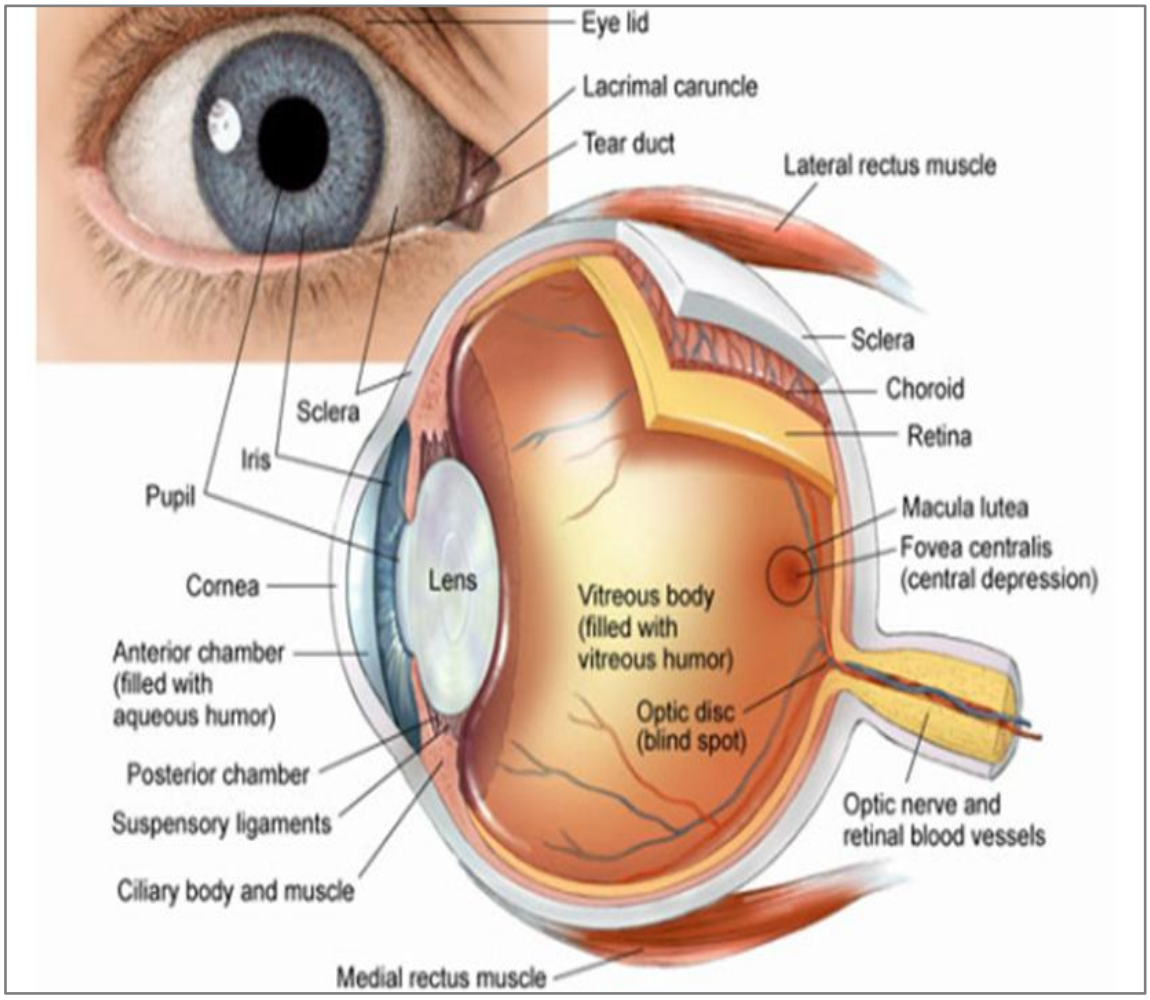

Eye lid
Lacrimal caruncle
Tear duct
Lateral rectus muscle
Sclera
Choroid
Retina
Sclera
Iris
Pupil
Macula lutea
Fovea centralis
(central depression)
Cornea
Lens
Vitreous body
(filled with
vitreous humor)
Anterior chamber
(filled with
aqueous humor)
Optic disc
(blind spot)
Posterior chamber
Suspensory ligaments
Optic nerve and
retinal blood vessels
Ciliary body and muscle
Medial rectus muscle

FIGURE-1

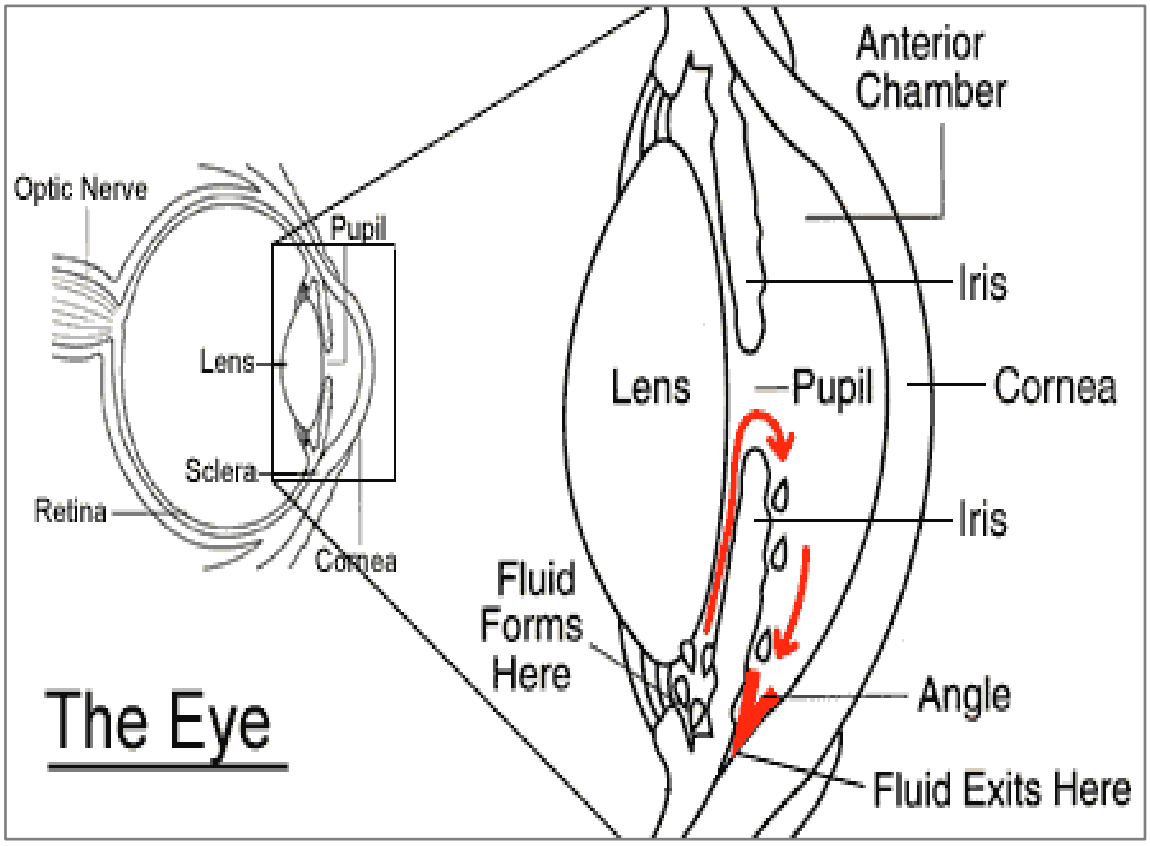


FIGURE-2

While approaching the intraocular pressure, it is essential to know the basic dynamics of aqueous humor as IOP regulation is dependent on the AH. The ciliary epithelium (CE) is widely accepted as the site of aqueous humor formation.

The CE is a double layer of cells covering the surface of the ciliary body. The inner layer which abuts to the aqueous side or vitreous body is called the non-pigmented epithelium (NPE), whereas the outer layer is heavily pigmented and is called the pigmented epithelium (PE) (figure-3).

The active transport of solutes across the CE has been accepted as the major driving force of aqueous humor formation(33).

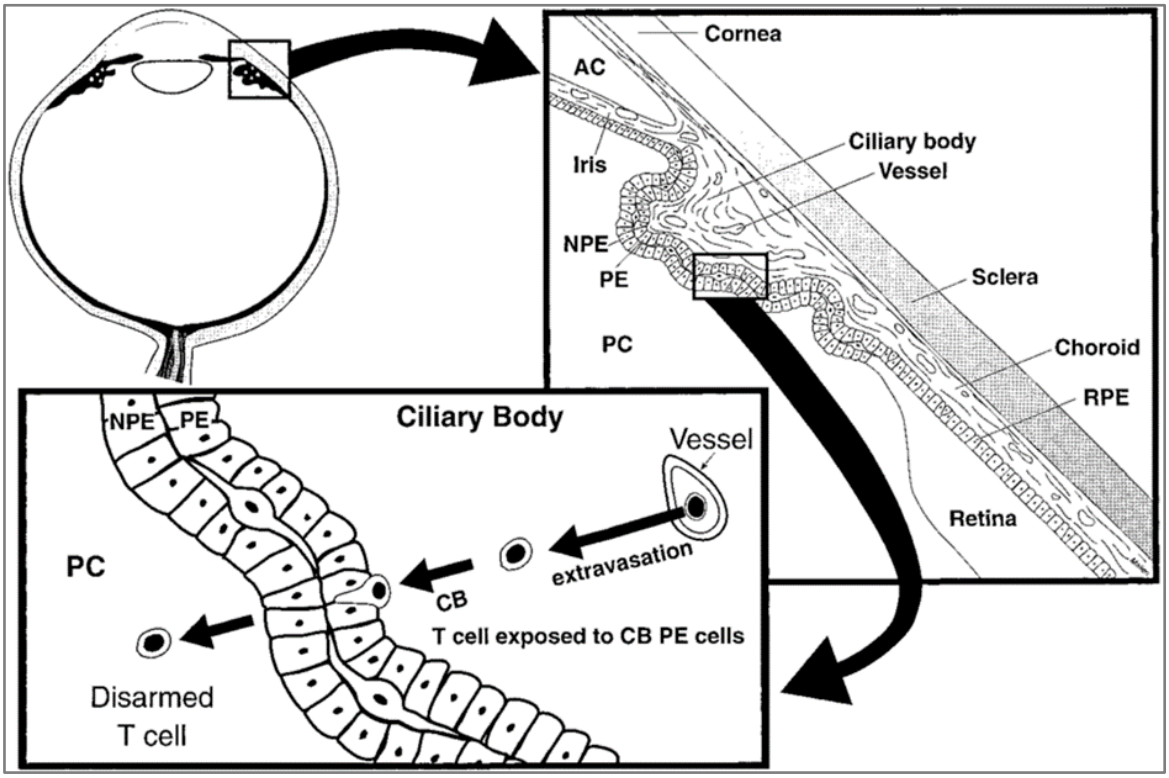


FIGURE-3

There are three mechanisms are involved in the formation of AQ:-

1. Diffusion,

2. Ultra filtration

3. Active secretion.

The first two processes are passive and does not involve active cellular participation (26).

1. Diffusion is defined as when lipid soluble substances (solutes), are transported via the lipid portions of the membrane of the tissues between the capillaries and the posterior chamber, along the concentration gradient across the membrane(34) (figure-4).

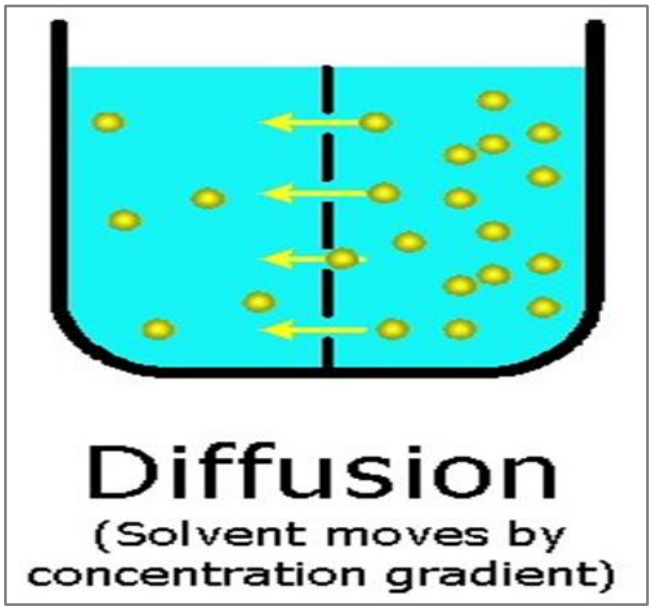


FIGURE-4

2. Ultrafiltration defined by the flow of water and water-soluble substances, across the fenestrated ciliary capillary endothelia into the ciliary stroma. This happens in response to an osmotic gradient or hydrostatic pressure, it is nothing but diffusion occurring under pressure(34)(figure-5).

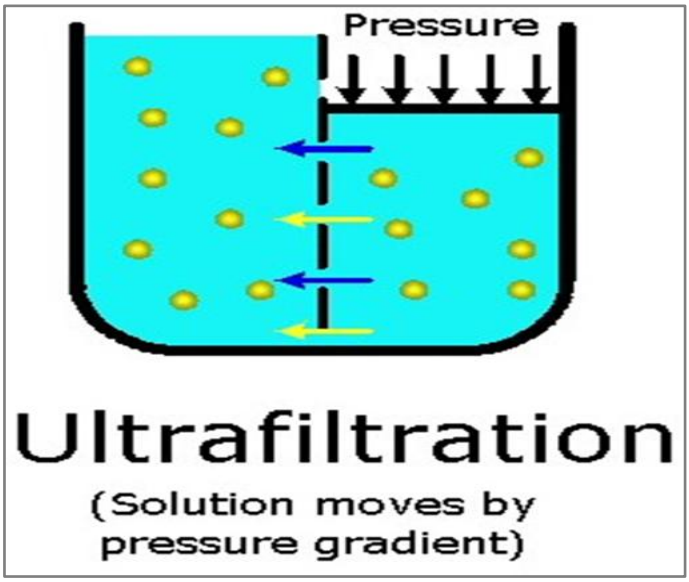


FIGURE-5

Both diffusion and ultrafiltration are responsible for the accumulation of plasma ultrafiltrate in the stroma (stromal pool formation), behind tight junctions of the non-pigmented ciliary epithelium. This process occurs within the posterior chamber(PC), from which aqueous humor is derived(26).

3.Active secretion is thought to contribute to nearly 80% to 90% of the total aqueous humor formation(33). The main site for active transport is believed to be the non-pigmented epithelial cells. Active transport takes place through selective trans-cellular movement of anions, cations, and other molecules across a concentration gradient in blood-aqueous barrier. This is mediated by protein transporters which are distributed in the cellular membrane.

Aquaporins (AQPs) are molecular water channels which aid with rapid bulk transport of fluid or transport of fluids against an insufficient osmotic pressure gap. There are two AQP's, AQP-1 and AQP-4, that have been shown to contribute to aqueous humor secretion(35).

The energy required for the transport is generated by hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), which is activated by Na+ and K+ mediated by the Na(+)-K(+)-ATPase.

This Na(+)-K(+)-ATPase(sodium-potassium ATPase) enzyme is found to be present in both non-pigmented and pigmented ciliary epithelium(26).

Thus the two critical Enzymes for Aqueous humor are

a) Na(+)-K(+) ATPase and

b) Carbonic Anhydrase

a) Na(+)-K(+) ATPase enzyme drives the Na(+)-K(+) exchange pump. This enzyme switches successively between two conformations within the cell membrane. The conformation presented to the cytoplasmic surface exhibits a high affinity for sodium and a low affinity for potassium. The affinities of the alternate conformation, presented to the extracellular surface under normal conditions, are opposite.

Thus by successively switching from one conformation to the other cyclically, 3 Na(+) are extruded and 2 K(+) are intruded per ATP molecule. The exchange is not electrically neutral and results in a net outward movement of a positive charge. Water moves along with sodium to produce aqueous humor. Sodium-potassium ATPase activity has been found to exists in the non-pigmented ciliary epithelium.

The presence Na(+)-K(+) ATPase in non-pigmented epithelium has been demonstrated by ‘ouabain’ which inhibits the enzyme and thereby reduces aqueous secretion. The localization of sodium potassium ATPase pump in the non-pigmented layer of the ciliary epithelium and its role in production of AH has been demonstrated by few studies(36–39)

b) Carbonic Anhydrase

This enzyme plays a key role in aqueous humor secretion by generating bicarbonate ions. The enzyme has been found to be present in non-pigmented layer at the tips of the ciliary processes. The carbonic anhydrase accelerates hydration of carbon dioxide to carbonic acid, which dissociates into hydrogen and bicarbonate ions(Equation-3)

Equation-3

$H_2O + CO_2 \longleftrightarrow H_2CO_3 \longleftrightarrow HCO_3^- + H^+$

Inhibition of carbonic anhydrase decreases not only the entry of bicarbonate ions into the posterior chamber, but also sodium ions. This function has been utilized in anti-glaucoma medicines which act by inhibiting the CA enzyme that causes consequent bicarbonate and AH reduction thereby lowering the IOP(40–44).

One postulated theory regarding the role of bicarbonate ions in aqueous humor production is that HCO3- is transported in parallel with Na+, primarily to offset the net outward movement of cations by the Na(+)-K(+) ATPase pump. Bicarbonate formation influences fluid transport by affecting the sodium ions, for optimal active ion transport probably by regulating the pH (26).

Chloride ion is an another major anion transported across the ciliary epithelium through the Cl(-) channels(45–47). Other molecules are also actively transported, that includes

- Ascorbic acid - secreted against a concentration gradient by the sodium-dependent vitamin C transporter-2 (SVCT2) and

- Amino acids - secreted by three different solute carriers(26).

The active transport creates an osmotic gradient across the ciliary epithelium, thereby promoting the movement of other plasma constituents by the process of ultrafiltration and diffusion(48)(figure-6).

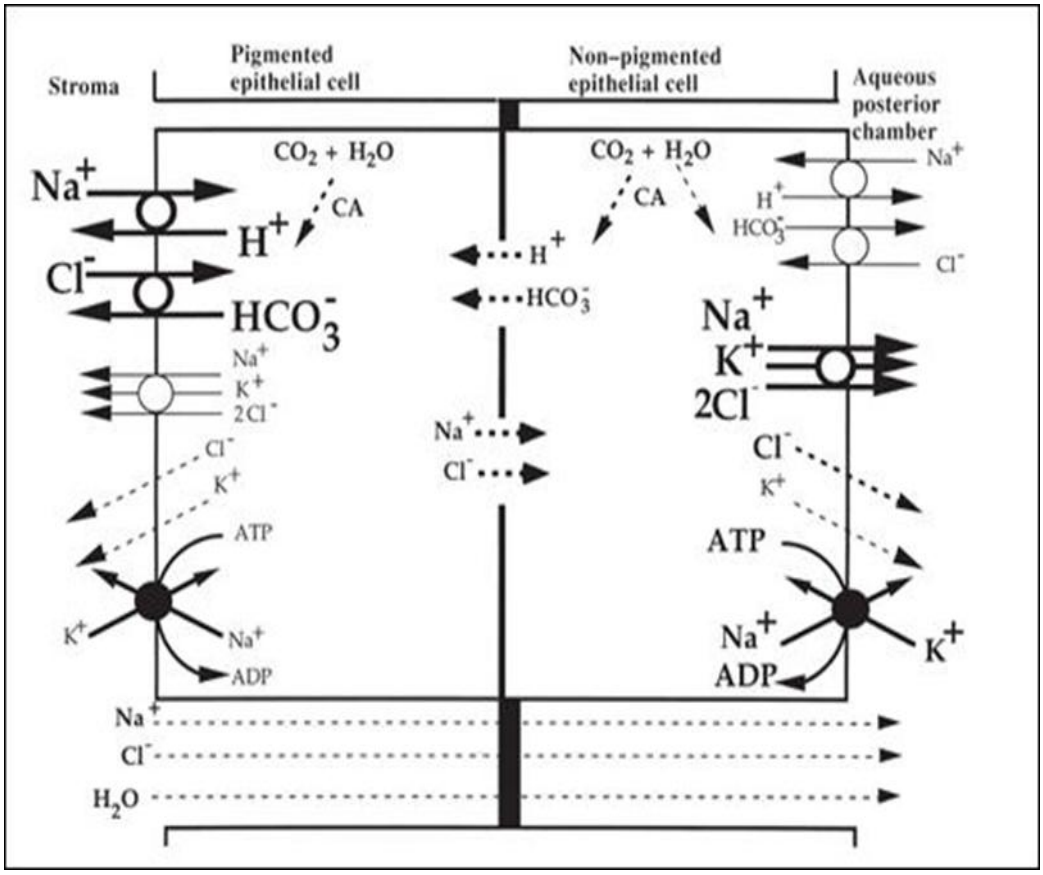


FIGURE-6

The aqueous humor turnover rate constitutes around 1.0% to 1.5% of the anterior chamber volume per minute , which is 2.4 ± 0.6µl/min (i.e.,mean ± SD, demonstrated in adults in 20–83 years, during daytime)(26).

Diurnal variations were observed in aqueous humor turnover rates, by using fluorophotometry, reflecting a pattern known as the circadian rhythm of aqueous humor flow in humans. Aqueous humor flow was found to be higher in the morning than at night(49–51).

AH flow is normally about 3.0µl/min in the morning, 2.4µl/min in the afternoon, and drops to about 1.5µl/min at night. This pattern of flow was stated to be due to the circulating steroids within the body(26).

The major components of the aqueous humor are:-

- organic and inorganic ions
- carbohydrates
- glutathione,
- urea
- amino acids and proteins
- oxygen and carbon dioxide
- water.

Aqueous humor is slightly hypertonic in comparison to plasma in a number of mammalian species, except from eyes of rhesus monkeys, in which no significant difference was observed.

There were no significant differences in osmolarity or ph or total concentration of dissolve substances in the AH between anterior and posterior chambers.

The Na+ concentration in plasma and aqueous humor are found to be similar. Most studies have shown that the difference between aqueous humor and plasma, are the concentrations of protein (200 times low) and ascorbate (20 to 50 times high).

With respect to the proteins, most AH proteins are intrinsic glycoproteins of the vitreous, which are secretory products of the inner epithelial layer of the ciliary body. Specific classes of immunoglobulins, such as IgG, were said to be higher as compared to IgM and IgA levels.

The relative concentrations of free amino acids differ, with ratios to plasma concentration ranging from 0.08 to 3.14. Glucose and urea in the aqueous humor are nearly 80% of the plasma levels.

Certain anti-oxidant substances are found in the aqueous humor are glutathione (formed the process of diffusion from blood) and ascorbate (which helps in protecting from light-induced oxidative damage).

Molecules such as collagenase, involved in the maintenance of the extracellular matrix (ECM), have been identified in human aqueous humor, that may influence TM outflow resistance and ultimately, the IOP.

In addition to it, growth factors have been identified in aqueous humor, along with its receptors on the target tissues, such as transferrin, transforming growth factors, endothelin-1 and indoleamine 2,3-dioxygenase(48,52,53).

The aqueous humor that is produced by the nonpigmented epithelium of the ciliary body, flows into the posterior chamber via the pupil and enters the anterior chamber (AC). Aqueous outflow through the angle of AC occurs through the following three probable routes:-

1. The ‘conventional pathway’ via the Trabecular meshwork(TM) and Schlemm’s canal (SC).
2. The ‘unconventional pathway’ via the ciliary muscle and suprachoroidal space.
3. Minor pathway via the iris surface and capillaries

The conventional route is the major site of aqueous outflow and the resistance produced in this area the maximum, which is responsible for the

changes occurring in primary open angle glaucoma (POAG)(54).The trabecular meshwork is shown in figure-7

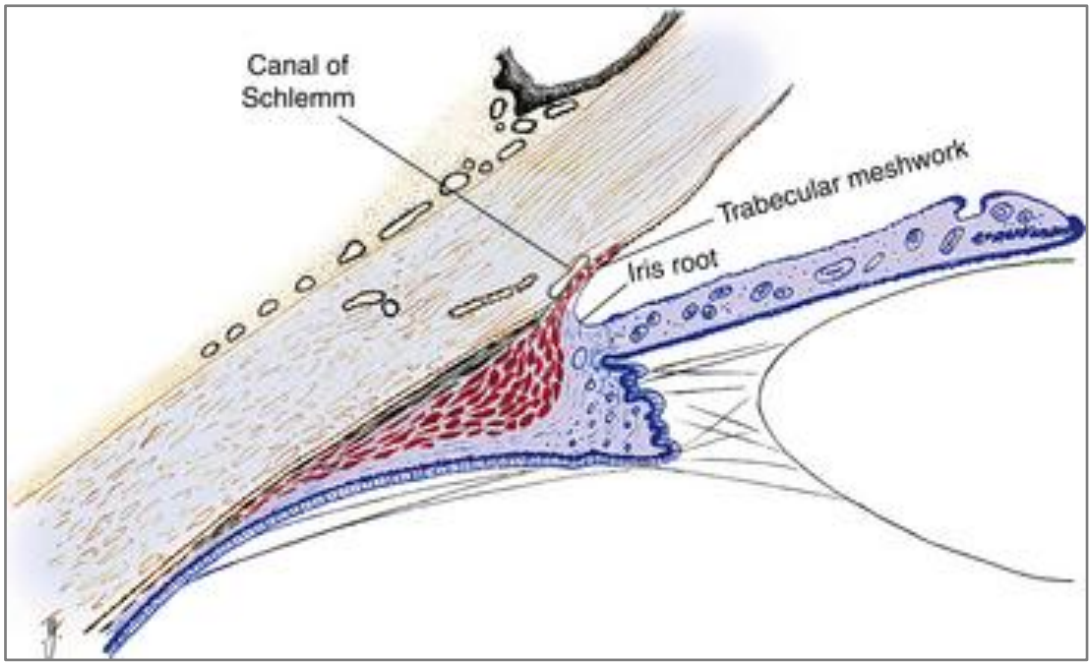


FIGURE-7

The trabecular meshwork can be divided into three separate regions, with differing functions as follows,

1. The innermost uveal meshwork.
2. The central corneoscleral meshwork.
3. The outer juxtacanalicular connective tissue (JCT) that is adjacent to the Schlemm's canal (SC).

1. The uveal meshwork is an irregular, netted, cord like structure connecting its different layers. These cords contain large spaces, that contribute little resistance to outflow. This part of the meshwork contains bands of connective tissue and irregular openings that measure about 25–75 microns.

2. The corneoscleral meshwork extends to about 100 microns in depth. It is contains a number of porous sheets, extending from the scleral spur posteriorly to the peripheral cornea anteriorly.

The size of openings in these sheets reduce progressively towards the deeper aspects of meshwork. These openings are oval in shape and have a diameter of 10 microns, with a lesser axis of 5microns. Near the Schlemm's canal, the lesser axis is further reduced to 1–2 microns, causing a tightening in this region.

The uveal and corneoscleral trabecular meshwork are organized into a network of trabecular beams / lamellae. Each lamella has a core, with a fibrillar extracellular matrix that is covered by endothelial-like flat trabecular cells.

The ECM is made up of type IV collagen, versican, ADAMTS4 - a metallopeptidase with thrombospondin motifs, laminin, fibronectin, matrix

metalloproteins 2 and 14 (MMP), glycosaminoglycans (GAGs), and matricellular proteins. The proteins within the cellular matrix are thrombospondins, the secreted protein acidic and rich in cysteine [SPARC], tenascin C, osteopontin, and hevin.

These modulate the interactions between the trabecular cells and extracellular matrix, thereby helping in the tissue remodeling. The illustration of TM with its components is shown in figure-8

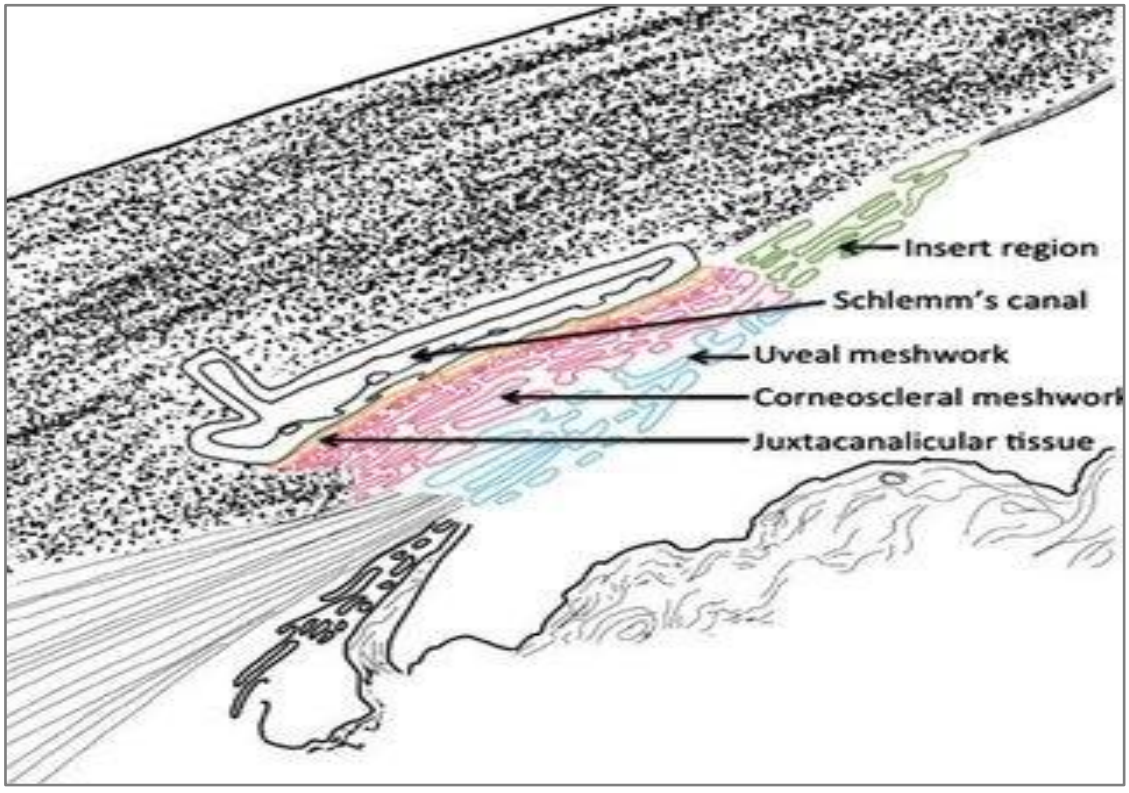


FIGURE-8

The Juxtacanalicular connective tissue has a loosely arranged extracellular matrix substance with a very few cells embedded in it.

Histologically, it can be divided into three layers:

1. The Trabecular endothelial layer - continuous along with the endothelium of corneoscleral meshwork.

2. The Central connective tissue layer- parallel and spindle cells are arranged loosely in a connective tissue ground substance that has type III collagen too. Connective tissue cells contain coated pits and vesicles within the plasma membrane, that modulates receptor-mediated endocytosis.

3. The Inner wall (IW) endothelium of SC - outermost part of Juxtaglomerular connective tissue. It is composed of elongated cells attached to each other by means of tight junctions upon a discontinuous basement membrane.

It is said to have a protruding surface with nuclei, cyst-like vacuoles, and finger-like projections, that protrude into the lumen of Schlemm's canal. This IW endothelium of the SC, its basement membrane, along with the adjacent JCT is collectively known as the 'IW region'.

The JCT contains a network of elastic fibers running tangentially to the IW endothelium, called as the ‘cribriform plexus’. As a response to fluctuating IOP, the JCT undergoes an expansion and recoil. The elastic fibers are said to contribute to this mechanism.

A sudden rise in IOP, as in rubbing of the eyes, is stabilized by changes in the JCT, that brings IOP back to the normal. Histology of elastic fibers shows an inner core of cross-linked elastin and an outer sheath of microfibrillar components.

Certain other proteins found to be associated with elastic fibers are the myocilin, fibronectin, versican,vitronectin, tenascin C, decorin, glycosaminoglycan (GAG) chains, fibrillin-1, microfibril-associated glycoprotein-1 (MAGP-1), laminin and collagens types III and VI

The IW cells also has few unique structures known as ‘giant vacuoles’. These range from 1-10 microns in width, 1-7 microns in height, and 20 microns in length. The giant vacuoles are an out-pouchings of the endothelium caused due to pressure drop across the inner wall endothelium.

The walls of these invaginations are very thin and contain unique pores. Whether giant vacuoles serve as passage for the aqueous humor into

the canal along with pores or function to sense pressure by mechanical stretching and thereby allow greater fluid flow in the adjacent intercellular junctions is unknown.

In humans, reduction in the formation of giant vacuoles in inner wall endothelium of the SC has been proposed to be responsible for the physiological age-related increase in outflow resistance.

T he IW of SC is found to have approximately 20,000 transcellular pores. The majority of them (about 75 %) are transcellular and serve as conduit for flow of AH into the SC. Others are said to exist at the border of neighboring cells.

The size of IW pores range from 0.1 microns to more than 3 microns, approximately with an average diameter of <1 micron. The density of pores in the IW endothelium is identified to be <1,000 pores/mm2.

The Schlemm's Canal

The SC is lined by the endothelium. It course around the eyeball concentrically at the corneoscleral junction, within the inner scleral sulcus. The SC is oval / triangular in cut-section with a diameter of about 180–250 microns. Posteriorly, it is related to the scleral spur, while the IW of

Schlemm's canal is related to the trabecular meshwork. Rarely, the SC may breakinto branches that coalesce once again. Figure-9 shows a schematic illustration of the SC.

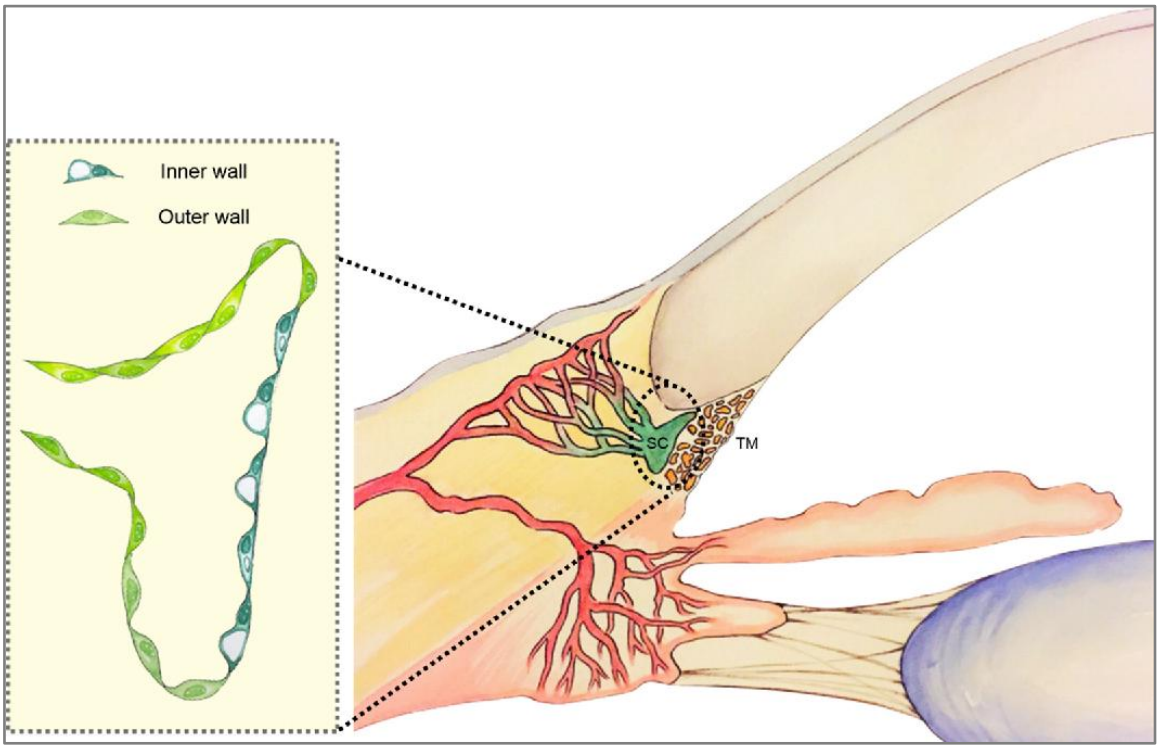


FIGURE-9

The lumen of the SC may collapse and reduce to a lesser size comparatively during raised IOPs which might contribute to the pathology of primary open angle glaucoma.

The aqueous humor from the SC drains into collector channels, which finally join with the deep scleral venous plexus. From here, AH drains

through the intra and episcleral-plexus into the anterior ciliary veins. Few collector channels bypass this deep scleral venous plexus and course directly via the sclera. These are termed as ‘aqueous veins of Ascher’, because they posses AH instead of blood. The aqueous veins drain finally into the conjunctival vessels close to the limbus.

The schlemm’s canal, collector vessels, and the aqueous veins are subdivided by means of septa. These septa are situated throughout the SC, but more at the collector channels. They function to bridge the inner and outer walls of the canal. The close approximation of these structures to collector channel openings might be to prevent the collapse of the canal lumen.

The collector channels and aqueous veins are relatively large vessels and therefore offer least flow resistance. Many studies support that these vessels are not likely to cause elevated flow resistance seen in glaucoma. Thus the 75 % of the resistance to aqueous humor outflow is localized within the TM and 25 % occurs further away from SC.

Increased intraocular pressure produces deformation of SC juxtacanalicular cells and trabecular lamellae with consequent enlargement of the juxtacanalicular space.

This makes cellular elements and ECM less compact and further suppresses the ability of the juxtacanalicular space, as a resistance element. With prolonged increase in IOP, the endothelium generates pressure and shear mediated signals that initiate responses at the cellular, molecular, and genetic levels thereby enabling adaptive changes which regulates pressure and flow.

A number of platelets or plaques have been demonstrated in the SC principally near the openings. It is not known whether these platelets or plaques block the AH outflow. But an increase in the number of plaques have been identified especially in elderly, patients with POAG, and in those with intermittent angle closure glaucoma(55–59).

Unconventional Pathway

The aqueous outflow through the uveoscleral or unconventional route vary from 4% - 60%. The outflow rate via this route tends to decline with age, allowing the conventional pathway to acquire more function of aqueous outflow.

The outflow via this route is also diminished during night-time, in exfoliation syndrome and ocular hypertension. However this outflow is said

to increase in certain conditions such as by prostaglandin analogs used to treat glaucoma, iridocyclitis, glaucomatocyclitic crisis.(60,61).

The uveoscleral pathway is not a perfect structural pathway unlike the trabecular meshwork or the schlemm's canal. Here, the AH enters the ciliary muscle and exits via the supraciliary space. It may also course along the anterior / posterior sclera and eventually pass via the emissarial canals around the vortex veins or into the choroidal vessels. The uveoscleral outflow operates under pressure gradients by the uvea, movements of the ciliary muscles and alterations in the ECM or in the cytoskeleton(34).The outflows of aqueous humor is shown in the figure-10

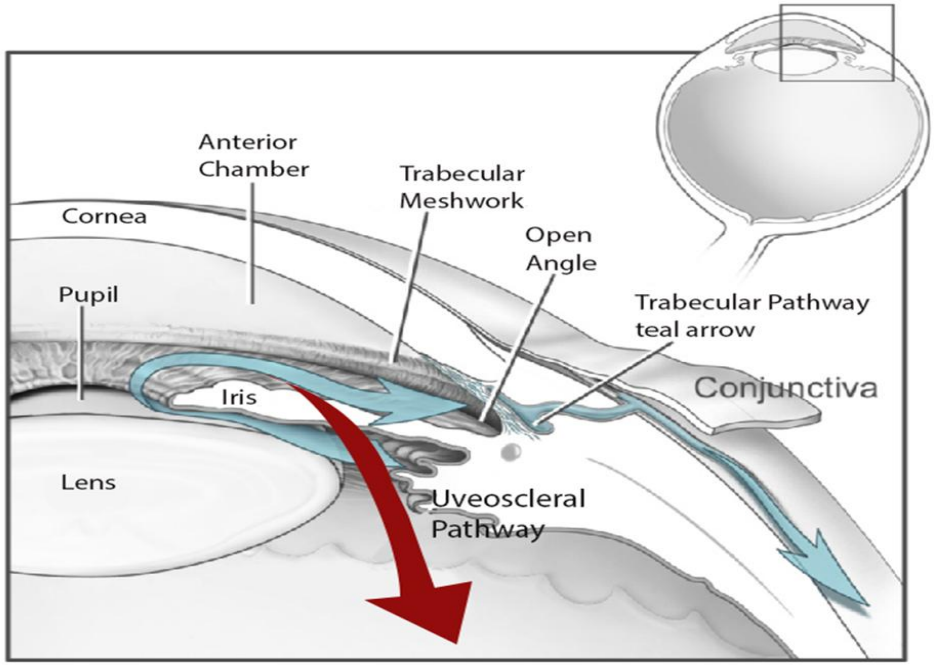


FIGURE-10

The chief functions of AQ include stabilization of the globe, providing nutrition to the eye, excreting the products of metabolism, transmitting inflammatory mediators and neurotransmitters, regulating homeostasis, permitting effective distribution of drugs during pathological conditions(26).

The acid base imbalance is primarily caused by change in the partial pressure of arterial carbon dioxide, in which case it is known as a respiratory disturbance or by change in the bicarbonate in which case it is known as a metabolic disturbance.

- If the primary disturbance is an increase in the Pco_2, it is termed as respiratory acidosis
- If the primary disturbance is a decrease in the Pco_2, it is termed as respiratory alkalosis
- If the primary disturbance is an increase in the $HCO_3(-)$, it is called as metabolic alkalosis
- If the primary disturbance is a decrease in the $HCO_3(-)$ it is known as metabolic acidosis (3-4).

Of the four acid-base disturbances, metabolic acidosis is discussed extensively in this study.

In metabolic acidosis, an acid base disorder, there is a primary reduction in the bicarbonate($HCO_3(-)$)(<22meq/L), typically with compensatory reduction in the arterial partial pressure of carbondioxide (Pco_2) and a marked reduction in the ph(2)(24).

PATHOPHYSIOLOGY IN METABOLIC ACIDOSIS:-

To maintain the ph within the physiological limits, the kidneys have to perform two major functions.

First is to reabsorb all the filtered bicarbonate, which occurs principally in the proximal tubule (PT).

The second is to excrete the daily hydrogen ion load which is done by the collecting duct(CD).

The PT absorbs nearly 80% of the filtered bicarbonate. Of the remaining filtered HCO3(-), the thick ascending limb of henle reabsorbs 10% , the distal nephron reabsorbs 10% of the HCO3(-) and no bicarbonate is left in the urine(1).This mechanism of reabsorption of filtered bicarbonate by PT of the kidney is described in figure-11.

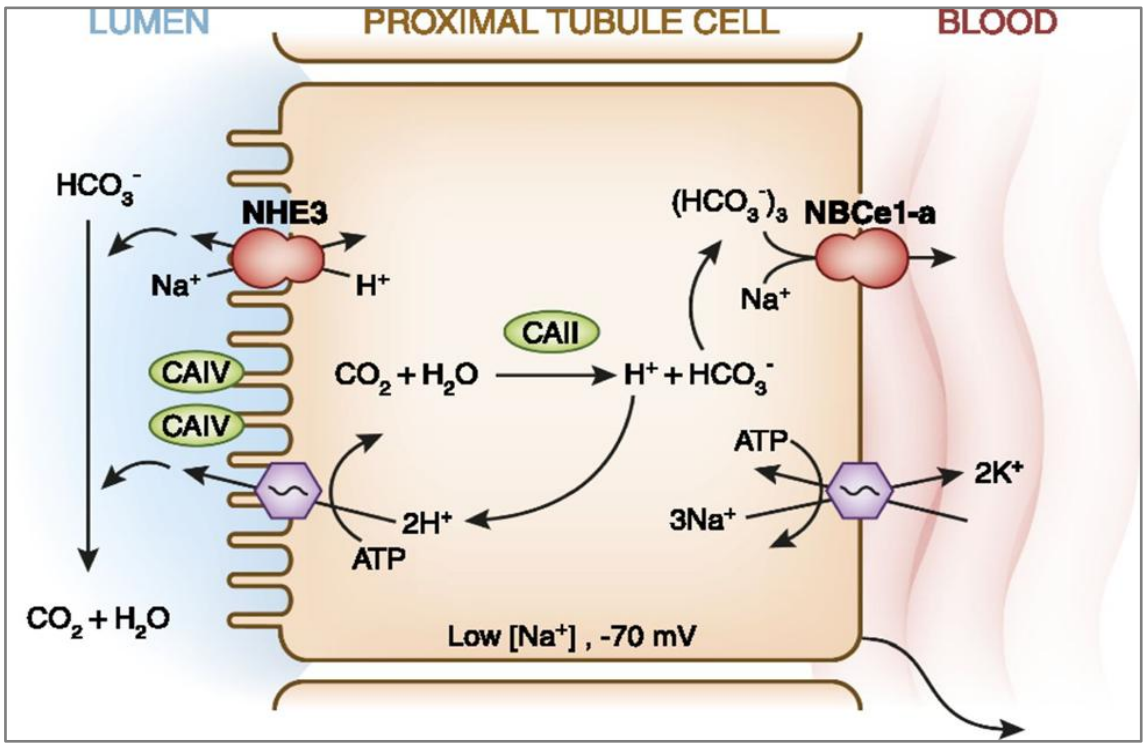


FIGURE-11

The proximal tubule of kidney reabsorbs HCO3- by secretion H+ through an apical sodium hydrogen exchanger (NHE-3) into the lumen. A small proportion of this apical membrane hydrogen ion secretion is mediated by H(+)ATPase. The H(+) secreted, reacts with the filtered Hco3- to form luminal H2co3, that dissociates into CO2 and H2O by the membrane bound carbonic anhydrase IV(CA IV).The luminal co2 diffuses across the apical membrane through a bifunctional water/gas AQP1 channel.

Once entering the cell, CO2 and H2O combine again through the carbonic anhydrase II(CA II) to form bicarbonate and hydrogen ions. The

bicarbonate that is produced within the cells now exists across the basolateral membrane through a Na(+)/3hco3(-) cotransporter(NBC-1)(62–64)

About 50-80meq of H(+) is produced in excess daily. This acid load is excreted via the three mechanisms- free H(+) excretion, titratable acidity and ammonium excretion. The ph of urine cannot be reduced below 5 since the gradient against which the H(+)ATPase required to pump the protons becomes too steep. ie.,the intracellular ph of 7.5 to a luminal ph of 5.

Therefore, a fully acidified urine even with a volume of about three liters would thus contain 0.03meq of hydrogen ions. Hence the free hydrogen ions excretion does not form a major role in the urinary acid secretion.

The major H+ excretion is predominantly through the titratable acidity and renal ammonium production. Titratable acidity is nothing but buffering of the secreted hydrogen ions by weak acids. The major filtered buffer here is the HPO4 2-/H2PO4(-). Thus the intercalated cells in the collecting duct(CD) are responsible for hydrogen and bicarbonate ions secretion whereas the principal cells are responsible for Na(+) reabsorption and K(+) secretion(figure-12).

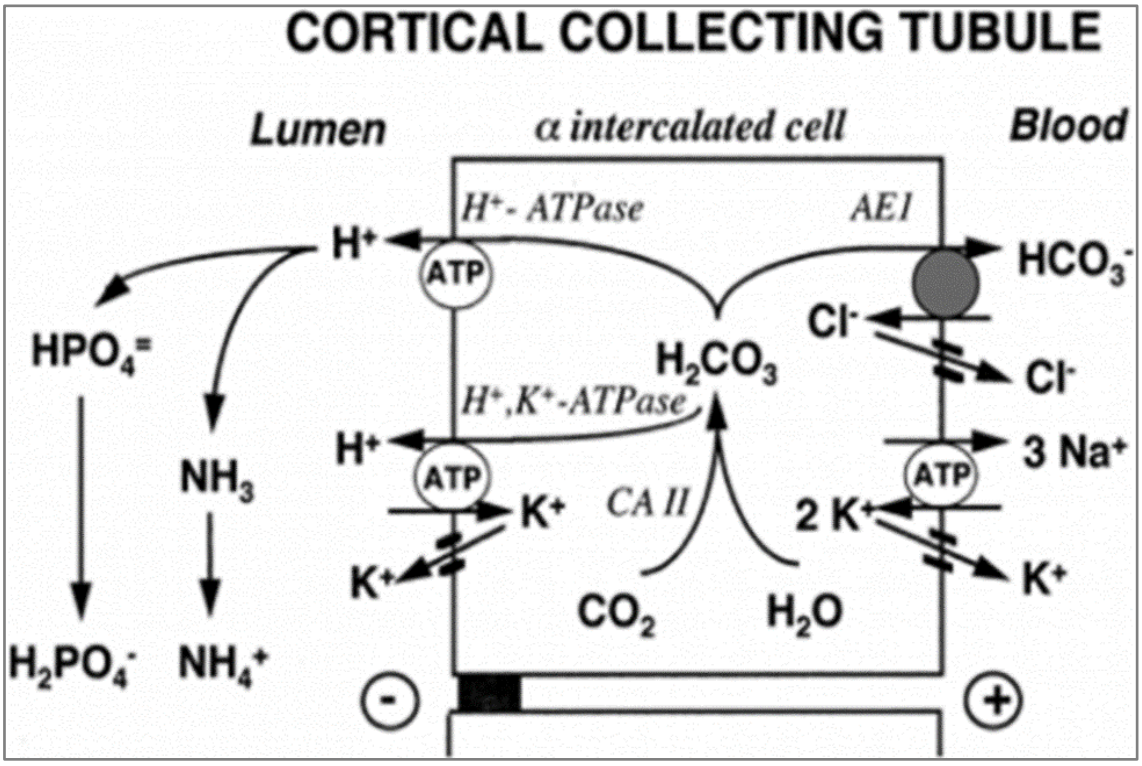


FIGURE-12

The alpha intercalated cell is primarily involved in the secretion of hydrogen ions. The main pump causing the luminal H+ secretion is an apical H(+)ATPase. A second ATPase known as H(+)/K(+)ATPase also causes secretion of the hydrogen ions.Thus the secreted luminal hydrogen ions titrate HPO4 2- to completely to H2PO4(-),that accounts for an excretion of 30-40meq of hydrogen ions per day.

The H+ is derived from the conversion of CO2 and H2O to H(+) and HCO3(-). This reaction is catalyzed by the cytoplasmic enzyme CA II.

Therefore, the intracellularly formed bicarbonate ions leave the cell by an electroneutral mechanism that involves abasolateral band 3 like CL(-)/HCO3(-) anion exchanger.

In comparison to the phosphate anions, the sulphate anions cannot be excreted with hydrogen ions because the pK of sulphuric acid is very low. Instead the sulphate anions are excreted as ammonium sulphate.

The concentration of the titratable acidity does not vary much from day to day. So, if there is a need to increase the renal acid excretion, titratable acidity is not the answer. At the time of metabolic acidosis, the kidney increases urinary hydrogen ions in the form of ammonium (NH4(+)).

The buffering of ammonia (NH3(+)) occurs via the following reaction (equation-4)

Equation-4

$$NH3(+) + H+ \longleftrightarrow NH4(+)$$

NH4(+) is produced in proximal tubule and secreted into the proximal tubular lumen by replacing hydrogen ions in the apical sodium potassium antiporter. Ammonium is then reabsorbed in the henles loop, where it replaces potassium in the Na(+)K(+)2CL(-)co transporter.

The ammonium dissociates back into ammonia and hydrogen ions in medullary interstitium of the thick ascending limb. Ammonia diffuses into the lumen of collecting duct, where it is available to buffer H(+) and becomes ammonium.NH4(+) is trapped within the lumen and is excreted as the chloride salt.

The kidney adjusts the quantity of ammonia synthesized to meet the demand, making it a powerful buffer system for the secreted hydrogen ions in urine. Thus for every molecule of H(+) that is buffered by ammonia, a molecule of HCO_3(-) is formed and released into the blood(1,2,2–4,6,8).

Metabolic acidosis is an emergency and needs immediate correction of the deficit ions as it leads to fatal complications. Therapy is addressed towards the underlying cause, independent of the ph. There are a few exceptions.

The primary problem with metabolic acidosis is myocardial suppression. Though alkali therapy seems to be the correcting treatment, it has limited value and potentiates the harm.

First, alkali is not an effective buffer under the physiological range of ph because at normal ph, it serves more as a transport role for CO2 in bold.

Second, $HCO_3(-)$ therapy can be harmful as it worsens the acidosis further by generating carbondoixide and lowering serum and cerebrospinal fluid(CSF) ph.

Also it causes calcium and potassium shifts, leading to cardiac arrhythmias, hypernatremia and volume expansion. In the setting of severe acidosis, i.e., ph<7, where the body's compensatory mechanisms are overwhelmed causing cardiac instability, bicarbonate therapy can be attempted with caution(1,24,25).

Regarding the intraocular pressure, it exists as a fine-tuned equilibrium between the production and drainage of aqueous humor.

The IOP increases with increased systemic blood pressure. Sudden increases in IOP induces mechanical stress and ischemic effects to the retinal nerve fiber layer, while sudden decreases can form micro-bubbles from dissolved gases within the microvasculature with consequent gas emboli and ischemic damage to tissues.

Homeostasis of intraocular pressure (IOP) is of vital importance in eye to maintain optical clarity for vision and function. Disruption of this fine equilibrium may have significant consequences, contributing to the

pathogenesis of diseases such as glaucoma, uveitis, and choroidal detachment(28).

It is well known that intraocular pressure is not a fixed value but fluctuates over time. This fluctuation can be categorized according to the period of time over which the IOP is monitored(65).

Instantaneous IOP fluctuation is defined as the IOP variation that occurs over a span of seconds, and is caused by blinks, saccades, eye rubbing, tight neckties, blood pressure, eye movements, caffeine, accommodation, wind instruments, head position, water drinking, body position.

Diurnal-nocturnal IOP fluctuation, refers to IOP variation that occurring over the course of a day. The diurnal IOP changes may be explained by bodily postural changes associated with blood pressure and episcleral venous pressure changes, by the cortisol levels, variations in AH production, environmental - light and dark cycles, and seasonal variations. This type of IOP fluctuation is also often referred to as central / humoral fluctuation.

Short-term IOP fluctuations are the ones that occur over days to weeks.

Long-term IOP fluctuation is the one that which occurs over months to years. A measure of long-term fluctuation can be obtained from repeated IOP measurements that occur during each examination(28).

Whenever the IOP is high above the normal range, there is an increased risk of development of POAG (primary open angle glaucoma).POAG is a chronic degeneration of the optic nerve characterized by optic disc abnormalities, retinal nerve fiber abnormalities with a corresponding visual field defects.

While the pathogenic relationship between IOP and glaucomatous optic neuropathy remains incompletely understood, elevated IOP is almost and always associated with the development of retinal ganglion cell death. It is postulated by several mechanisms that elevated IOP induces a direct mechanical damage to axons of retinal ganglion cell.

Alternatively, it has also been proposed that the elevated IOP produces a shearing of the attachments of the astrocytes from the optic nerve head, causing a loss of metabolic support to the optic nerve head.

Other mechanisms include an ischemic damage occurring due to compression of blood vessels that supply the optic nerve head.

Glaucoma is one of the worldwide leading cause of irreversible vision loss. Glaucomas are classified into two broad categories: open-angle glaucoma and angle-closure glaucoma. Open angle glaucoma is the most common. Reduction of IOP is the only proven method to arrest the progression of the disease.

Although treatment is usually initiated with topical hypotensive eyedrops, laser trabeculoplasty and surgery may also be advocated in resistant cases to slow disease progression(66–68).

Current management guidelines by the American Academy of Ophthalmology Preferred Practice Pattern recommend lowering the IOP to a sufficient target level, which is a value at which the treating ophthalmologist believes that the rate of disease progression will be lowered further to avoid functional impairment from the disease.

Target intraocular pressure levels for an eye are based on pretreatment pressure levels that were associated with retinal damage, the extent of

damage, associated risk factors for progression, expectancy of life, and potential for adverse effects from treatment.

In general, the initial target is a 20% - 50% reduction in pressure. The target pressure needs to be cyclically reassessed during follow-up, depending on the status of the disease. Eg, if there is a rapid disease progression (as evidenced by optic nerve changes / visual field loss) despite maintaining pressure levels at the target value, the target needs to be lowered further.

The target IOP should be achieved with the fewest medications possible and minimum side effects. Several classes of pressure-lowering medications are currently available. Medication choice are influenced by its cost, side effects, and dosing schedules.

In general, prostaglandin analogues are the first-line of medical therapy. These drugs reduce intraocular pressure by reducing outflow resistance by improving the aqueous humor out flow through the uveoscleral pathway. It is used as first line medication as it tends to produce fewer side effects which are tolerable by most of the patients. Of these adverse effects, majority were ocular side effects than systemic.

Other line of drugs are the beta blockers, alpha agonists, carbonic anhydrase inhibitors and neuroprotective agents.

The beta blockers work by reducing the aqueous production itself by inducing their effect directly in the ciliary epithelium. However they should be prescribed with caution especially in patients with bronchial asthma as it causes bronchospasm which is fatal in asthmatics. Also in cardiac failure as it may increase mortality in such patients by inducing heart block or sudden bradycardia.

Alpha agonists induces its effect mainly on alpha-2 receptors which decreases the aqueous production by its effect on ciliary epithelium and also by improving the uveoscleral outflow. Even these should be used with caution in children as it has a tendency to cross the blood-brain barrier and cause hypotension and depression.

The carbonic anhydrase inhibitors act by inhibiting the secretion of aqueous itself. But overall, the carbonic anhydrase inhibitors are found to be less effective than prostaglandin analogues, beta blockers and alpha agonists.

The neuroprotective agents are yet to be regularised and individualized and is gaining importance. All these medications are given

topically in divided doses and the patients need to be on drugs throughout his/her lifetime once diagnosed

There are other temporary medications for glaucoma such as miotics and osmotic agents. Therefore these medications are not prescribed in long term(69–72).

It was these topical medications (prostaglandin analogues, beta blockers, alpha agonist, carbonic anhydrase inhibitors) which glaucomatous patients would take life long, in whom usage of these eye drops might not be needed if critically ill. Sudden metabolic acidosis might itself lower the intraocular pressure in these patients .

On the contrary, in the setting of decreased intraocular pressure, serous choroidal detachment occurs. The increased transmural pressure secondary to decreased IOP causes transudation of serum into the suprachoroidal space (a space between the choroid and sclera) resulting in progressive detachment of the retina and choroid(28).

Ocular hypotony, is defined as IOP of above or equal to 5 mmHg at consecutive measurements in an individual eye. While clinical signs and symptoms are usually reversible in acute and transient stages, chronically

decreased IOP can have deleterious effects on intraocular tissue morphology and function, eventually leading to phthisis bulbi.

Although the underlying pathologies and mechanisms of ocular hypotony may be quite variable, they all work together, inducing an imbalance of aqueous production and outflow (trabecular, uveoscleral). Subsequent alterations of aqueous flow dynamics associated with compromised oxygen supply, nutrition, and metabolic exchange within the anterior chamber are the most important.

In particular, intraocular hypoxia has been shown to contribute to breakdown of the blood aqueous barrier (BAB), associated with invasion of serum components, i.e., proteins, growth factors, inflammatory cells, and tissue edema. Therefore, ocular hypotony is a sight threatening emergency and is best managed by treatment of underlying problem.

No clinically useful medications are available till date, to increase the IOP as primary action. The anterior chamber may be inflated with a viscoelastic or a pars plana injection of a viscoelastic/gas can be attempted as temporary measure. Few studies on topical ibopamine, a sympathomimetic that works by increasing the aqueous production and improving the IOP showed intolerance in the subjects.

Steroids may increase the IOP by increasing the aqueous production by lowering the ciliary body inflammation but it is found to efficacious only in steroid responders.ie., individuals who show a positive response to steroids. (73–75).

In order to prevent the complications of ocular hypotony, we attempted this study to make the treating physician aware of the fact that IOP decreases at the time of metabolic acidosis in critically ill patients in ICU set up, so that glaucoma medications may not be mandatory in such situations. The glaucoma medications advised topically in divided doses work by lowering the IOP sustainably.

The intraocular pressure is traditionally determined with an instrument called Tonometer and the method is described as tonometry.

There are different kinds of tonometers in practice and all of them are calibrated in millimeters of mercury and the IOP detected is expressed in terms of mmhg(28).

The properties of an ideal tonometer are:-

- Must give a reliable and accurate results
- Can be used in any position of the patient

- Must cause nil or least discomfort to patients
- Technically easier to use
- Must allow self-assessment by the patients
- affordable(76)

The Goldmann applanation tonometry (GAT) is considered to be the gold-standard since decades. It works on the principle of ‘Imbert-fick’ which is based on a fact the force needed to flatten a surface of an ideal dry, thin walled sphere divided by the area of flattening is equal to the pressure inside the sphere. It is an indirect method of measurement of IOP by flattening an area of 3.06mm of the central cornea (77,78).

In our study, we measured the IOP using Perkins hand held applanation tonometer mainly for two reasons. First, it is portable meaning it can be used at bedside. Second, is its accuracy which is found to be equivalent to the GAT standards.

The Perkins tonometer was devised as a handheld non-digital applanation tonometer that does not require a slit lamp unlike Goldmann applanation tonometer, (slit-lamp mounted).

Since it is not mounted on a slit lamp, it is portable and therefore can be used in supine and upright positions in recumbent and obese people to measure the intraocular pressure.

The Perkins tonometer is found to be easier in calibration, utilizes the biprism similar to that in GAT, uses blue light provided by a battery, easier to disinfect. The method of measuring the intraocular pressure of eyes are similar to the Goldmann applanation tonometer. The perkins tonometer consists of a doubling prism with holder, LEDs for illumination, a forehead rest with stem, locking screw, lens for viewing (eyepiece), a thumb wheel for rotating the scale and battery with a charging port. Moreover handling and maintenance of the instrument is not difficult. The cornea is anaesthetized and stained with flourescein prior to recording of IOP, similar to GAT.

The accuracy, compatibility and utility of the perkins applanation tonometer (PAT) in animals have been supported by few studies(77,78). The intraocular pressure measurement with PAT has been found to be comparable to that measured with GAT in animals.

A randomized study by arora et al involving hundred patients, the mean intraocular pressue with the tradional goldmann applanation tonometry was 21.65mmhg +/- 5.69 and the mean intraocular pressure with perkins tonometer was 21.40mmhg +/- 5.67. The mean difference between the two were 0.22mmhg +/- 0.44, which means that perkins tonometry gives results that are closest to the readings obtained by the goldmann applanation tonometry (27)

The advantages of PAT as compared to GAT are its portability, can be used in young children, uncooperative, anaesthetized and obese patients who has difficulty in maintaining upright posture in slit-lamp as well as bed ridden adults(27,76).

Therefore we attempted to know whether there was any MA induced variation in the intraocular pressure and this was assessed with the perkins tonometer in bedside patients.

Since there were no studies similar to ours in existing literature, this study might be helpful and informative.

FIGURE-13: PERKINS TONOMETER

MATERIALS AND METHODS

STUDY DESIGN

Prospective cross-sectional study

STUDY POPULATION

- Patients in ICU setup with metabolic acidosis (ph< 7.35; bicarbonate <22meq/L)
- Patients visiting PSG hospitals, Coimbatore under routine evaluation. (Age matched controls).

SAMPLE SIZE AND ITS JUSTIFICATION

A convenient sample size of 200 patients (400 eyes) which includes patients with metabolic acidosis and age matched controls satisfying the inclusion and exclusion criteria.

INCLUSION CRITERIA

- Age >20 years
- Both sexes
- Admitted in ICU with metabolic acidosis of any cause (cases)
- Patients visiting ophthalmology OPD (controls).

EXCLUSION CRITERIA

- Patients who had already been treated for Metabolic acidosis
- Patients who are being treated for Glaucoma.
- Patients who are terminally ill.

TOOLS USED

- Torch light/binocular loop
- Topical anaesthetic eye drops (0.5% proparacaine)
- Fluorescein strips (1mg of fluorescein sodium/strip)
- Perkins handheld Tonometer

POTENTIAL RISKS - Nil

METHODOLOGY

Informed consent from the study population (Patients's attenders, treating doctors and Patients)

⇓

Anterior segment evaluation using torch light and binocular loop

⇓

Topical anaesthesia with 0.5% proparacaine eye drops and staining of cornea with fluorescein (1mg fluorescein sodium/strip)

⇓

Intraocular pressure measured in patients diagnosed with metabolic acidosis and after treatment of metabolic acidosis (cases) and also in age-matched controls using Perkins tonometer

⇓

Readings documented were ABG (arterial blood gas analysis) report and IOP of cases and controls

⇓

Results were compared and analysed using appropriate statistical tests

JUSTIFICATION FOR STUDY

The fact that intraocular pressure is decreased in metabolic acidosis is to be known among the physicians as well as Ophthalmologists. This will enable them to stop using anti-glaucoma drugs in known Glaucomatous patients who develop metabolic acidosis due to various reasons.

RESULTS

A total of 200 patients were recruited into the study which includes 100 cases (patients diagnosed with metabolic acidosis) and 100 age-matched controls (patients without metabolic acidosis) respectively.

Table-1: Gender category

	Male	**Female**	**Total**
Cases	48	52	100
Controls	54	46	100
Total	102	98	200
	51%	49%	

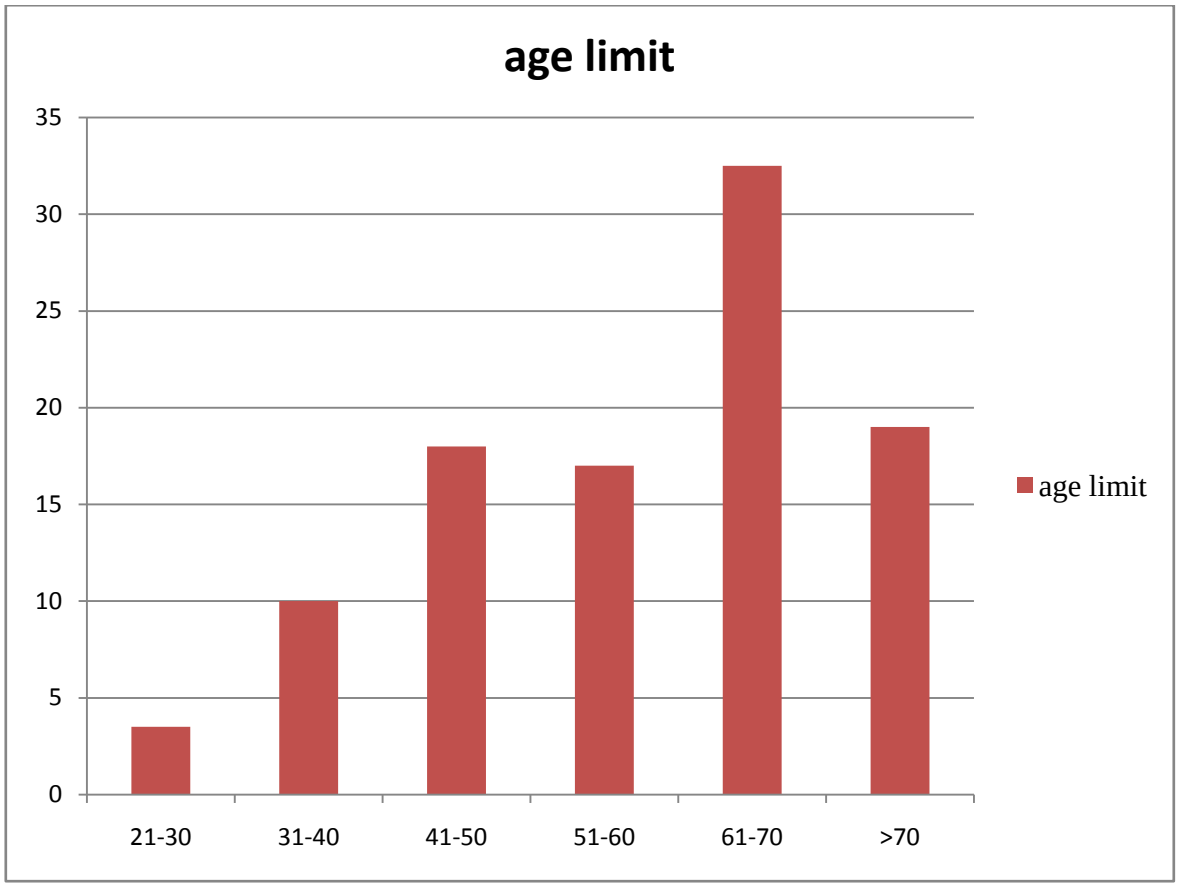
In our study, there were a total of 51% males among the cases and 49% females among controls according to the gender.

Table-2: Age group according to cases and controls

Age group	Cases	Controls	Total
21-30	5	2	7
31-40	12	8	20
41-50	16	20	36
51-60	15	19	34
61-70	31	34	65
>70	21	17	38
Total	100	100	200

Table-3: Overall age category in cases &controls

Age	Frequency	Percentage
21-30	7	3.5
31-40	20	10.0
41-50	36	18.0
51-60	34	17.0
61-70	65	32.5
>70	38	19.0
Total	200	100.0



There was a maximum of 65 patients constituting 32.5% between 61-70yeras of age among the cases and controls

1. Comparison between Pre and Post treatment IOP in both Right and Left eyes among cases

We monitored the intraocular pressure (IOP) in both eyes of patient at the time of metabolic acidosis and categorized it as **IOP-1** which is IOP (RE) -1 and IOP (LE)-1. The second readings taken after treating the metabolic acidosis was named as **IOP-2** which is IOP (RE)-2 and IOP (LE)-2.

Wilcoxon Signed Ranks Test and Mann-Whitney Test were the statistical analysis tests applied for the cases and controls.

Table-4: Wilcoxon Signed Ranks Test:-

	IOP_RE_1 - IOP_RE_2	**IOP_LE_1 - IOP_LE_2**
Z	-8.723b	-8.705b
Asymp. Sig. (2-tailed)	.000	.000
a. Wilcoxon Signed Ranks Test		
b. Based on negative ranks.		

There was a statistically significant difference in IOP between pre and post treatment in both the Eyes.

2. Comparison between Pre-treatment IOP in case and IOP in Control of both the eyes

We measured the IOP in control group as well, i.e, those without metabolic acidosis and assigned it as **IOP** which is IOP (RE) and IOP (LE) since it is a one-time recording.

Table-5: Mann-Whitney Test

	IOP_RE_1_IOP_RE_N	**IOP_LE_1_IOP_LE_N**
Mann-Whitney U	0.000	0.000
Wilcoxon W	5050.000	5050.000
Z	-12.287	-12.273
Asymp. Sig. (2-tailed)	.000	.000

There was statistically significant difference in IOP of Pre-treatment in case and Control IOP group in both the eyes

3. Comparison between post treatment IOP in case and IOP in Control of both the eyes.

Table-6: Mann-Whitney Test: -

	IOP_RE_2	**IOP_LE_2**
Mann-Whitney U	4997.000	4816.500
Wilcoxon W	10047.000	9866.500
Z	-.007	-.455
Asymp. Sig. (2-tailed)	.994	.649

There is no statistically significant difference in IOP of post treatment in case and Control IOP group in both the eyes.

Table-7: Mean IOP (mmhg) +/- SD:-

	IOP-1 (during MA in cases)	IOP-2 (after correction of MA in controls)	IOP (controls)
RE	6.9 +/-1.2	13.2 +/-1.8	13.2 +/-1.7
LE	7.29 +/-1.1	13.5 +/-1.7	13.4 +/-1.8

The IOP showed a significant reduction during metabolic acidosis in both eyes of cases and improved to normal levels as that of control group after treatment of the acidosis

Table-8: Descriptive for Metabolic Acidosis parameters among cases and controls:-

Parameters	**ABG(arterial blood gas analysis) among cases diagnosed with metabolic acidosis (Mean +/- SD)**	**ABG(arterial blood gas analysis) among cases after treatment of metabolic acidosis (Mean +/- SD)**	**ABG(arterial blood gas analysis) among controls (Mean +/- SD)**
FiO_2	41±13.7	39.1±10.5	39.3±10.8
pH	**7.1±0.08**	**7.4±0.04**	**7.4±0.04**
pCO_2	26.4±5.8	83.4±436.9	39.7±5.3
PaO_2	99.1±51.9	90.3±27.4	90.4±27.5
HCO_3	**12.8±3.1**	**25.2±2.2**	**25.1±2.2**
SaO_2	92.8±8.7	94.6±4.2	94.6±4.1
ABE	-9.4±6.5	0.7±2.4	0.69±2.6
Lactate	3.4±3.2	1.7±0.9	1.8±0.9

DISCUSSION

A total of 200 patients were involved in this study, conducted in a tertiary care hospital at Coimbatore. These patients were selected based on inclusion and exclusion criteria. It was a prospective cross sectional study.

Our study comprised of two broad groups:-

1. Cases- 100

2. Controls-100

Cases were those diagnosed with metabolic acidosis (ph <7.35 and bicarbonate <22meq/L)

Control group consisted of those without metabolic acidosis.

The mean age of cases were 56.94+/-2.97 (patients with metabolic acidosis) and controls were 57.57+/-2.63 (patients without metabolic acidosis).

There were 48 males and 52 females in cases and 54 males and 46 females in the control group, which summates to a total of 102 males and 98 females, constituting 51% and 49% respectively (Tabular column-1). Both the groups were comparable.

The age limit for our study was above 20years since adults were involved. Majority were between 60-70years of age. The age distribution among cases and controls is shown below and in Tabular column-2.

Age distribution as per cases and controls is shown in Tabular column-3.

We measured the intraocular pressure (IOP) in both eyes of cases twice. First at the time of metabolic acidosis (MA) and the second after correction of MA. The first reading was labeled as IOP-1 in (Right eye) RE and (Left eye) LE and second reading as IOP-2 in (RE) and (LE) respectively. Our goal was to know whether there was any variation in the IOP at the time of MA. So we recorded the IOP during MA and observed that IOP was reduced.

In order to know whether IOP decline was due to MA, we rechecked the IOP after correction of MA, i.e, after six hours. Post correction MA was interpreted using ABG (arterial blood gas analysis) report. Both IOP readings were compared with IOP of age-matched controls. Control group readings were labeled as IOP in RE and LE since it was a single time measurement.

Anterior segment of both eyes were examined with the help of torch light and IOP was monitored using Perkins tonometer after instillation of topical anesthetic drops (0.5% proparacaine) and staining of cornea with fluorescein strips (1mg of fluorecein sodium in each strip).The readings obtained were recorded.

Since the variables in our study did not follow normative data base, the Wilcoxon Signed Rank Test and Mann-Whitney Test were used for statistical analysis.

Tabular column – 4 shows comparison of results between Pre and Post treatment IOP in both Right and Left eyes.

It was observed that there is statistically significant difference on case group at the time of MA and after correction of MA. IOP in both eyes showed a decline at the time of MA and increased significantly (p = 001) after treating MA .ie, the IOP returned to normal levels after treatment of MA.

In Tabular column- 5 (Comparison between IOP-1: RE, LE in cases and IOP: RE, LE in controls), it was observed that there is statistically significant difference between pre-treatment IOP in case group and the

control group. The IOP was significantly less (p = 0.001) among case group at the time of metabolic acidosis (i.e, before treatment of MA) when compared to IOP in control group.

When IOP-2: RE, LE (second reading) in cases were compared with IOP in controls, (Tabular column- 6) there was no statistically significant difference (p = 0.649) between the IOP in the two groups. i.e., after correction of MA in cases and control group.

The mean IOP recorded among the cases was 6.9mmhg +/-1.2 Standard Deviation - SD in RE and 7.29mmhg +/-1.1 SD in LE at the time of MA. Mean IOP in the same group after treatment of MA was 13.2mmhg +/-1.8 SD in RE and 13.5mmhg +/-1.7 SD in the LE.

Mean IOP in control group was 13.2mmhg +/-1.7 SD in RE and 13.4mmhg +/-1.8 SD in LE respectively (Tabular column – 7).

The mean ph and bicarbonate among the cases (100) diagnosed with metabolic acidosis was 7.1±0.08 SD and 12.8±3.1 SD and after treating MA it was 7.4±0.04 SD and 25.2±2.2 SD respectively. Similarly the mean ph and bicarbonate among control group was 7.4±0.04 SD and 25.1±2.2 SD (Tabular column-8)

All the above observations suggest that IOP may decrease at the time of metabolic acidosis and returned to baseline following correction of MA.

CONCLUSION

Our observation suggests that metabolic acidosis, a frequent acid-base imbalance may induce a decrease in the intraocular pressure and that the treating physician must be aware of this, so that usage of topical anti-glaucoma medications may not be compelled in such situations.

LIMITATIONS

We could not measure the central corneal thickness (CCT) in eyes prior to recording of intraocular pressure in patients since the measurements are taken using specular microscopy, an instrument that is not portable as our study participants were in ICU (intensive care units) patients.

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PROFOMA

HOSPITAL NUMBER:

AGE:

SEX:

IOP-1 (RE) :

IOP-1 (LE) :

ABG -1:

IOP -2 (RE) :

IOP -2 (RE) :

ABG - 2 :

IOP (RE) :

IOP (LE) :

ABG :

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS
(strike off items that are not applicable)

I , DR.K.SATHIYA , carrying out a study on the topic: EVALUATION OF INTRAOCULAR PRESSURE IN PATIENTS WITH METABOLIC ACIDOSIS AND COMPARING IT WITH AGE MATCHED CONTROLS USING PERKINS HAND HELD TONOMETER as part of my research project being carried out under the aegis of the Department of OPHTHALMOLOGY
(*Applicable to students only*): My research guide is: DR.JEEVA MALA MERCY JANAKI

The justification for this study is: THE FACT THAT INTRAOCULAR PRESSURE IS DECREASED IN METABOLIC ACIDOSIS IS TO BE KNOWN AMONG THE PHYSICIANS AS WELL AS OPHTHALMOLOGISTS. THIS WILL ENABLE THEM TO STOP USING ANTI-GLAUCOMA DRUGS IN KNOWN GLAUCOMATOUS PATIENTS WHO DEVELOP METABOLIC ACIDOSIS DUE TO VARIOUS REASONS.

The objectives of this study are:

Primary Objective: TO EVALUATE INTRAOCULAR PRESSURE IN PATIENTS DIAGNOSED METABOLIC ACIDOSIS

Secondary Objective: TO COMPARE THE IOP VARIATION WITH AGE MATCHED CONTROLS.

Sample size: 200 patients.

Study volunteers / participants are (specify population group & age group): PATIENTS OF 20 YEARS AND ABOVE ADMITTED IN ICU SETUP AND ALSO NORMAL PATIENTS VISITING OPHTHALMOLOGY OPD.

Location: PSG HOSPITALS PEELAMEDU COIMBATORE.

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Initial interview (specify approximate duration): 10 minutes.

Data collected will be stored for a period of 5 years. We will not use the data as part of another study.

Health education sessions: Number of sessions: NIL. Approximate **duration** of each session: ✓

___10_____ minutes.

Clinical examination (Specify details and purpose): ANTERIOR SEGMENT EXAMINATION

Blood sample collection: Specify quantity of blood being drawn: _____ml. (N/A)

No. of times it will be collected: _____. (N/A)

Whether blood sample collection is part of routine procedure or for research (study) purpose: (N/A)
1. Routine procedure 2. Research purpose

Specify **purpose**, discomfort likely to be felt and side effects, if any: NIL

Whether blood sample collected will be stored after study period: Yes / No, it will be destroyed

Whether blood sample collected will be sold: Yes / No - NO

Whether blood sample collected will be shared with persons from another institution: Yes / No-NO

Medication given, if any, duration, side effects, purpose, benefits: NIL

Whether medication given is part of routine procedure: Yes / No (If not, state reasons for giving this medication) YES

Whether alternatives are available for medication given: Yes / No (If not, state reasons for giving this particular medication) NO

Final interview (specify approximate duration):__10_____ mts. If **photograph** is taken, purpose:

Benefits from this study: The fact that knowing the IOP variation in metabolic acidosis helps avoiding anti glaucoma drugs in patients with glaucoma admitted in intensive care setup

Risks involved by participating in this study: NIL

How the **results** will be used: THE RESULTS WILL BE USEFUL FOR FUTURE STUDIES AND PUBLISHING IN JOURNALS.

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date: Witness:

Contact number of PI:
Contact number of Ethics Committee Office: 0422 4345818

பூ. சா. கோ மருத்துவக் கல்லூரி மற்றும் ஆராய்ச்சி நிறுவனம், கோவை

மனித நெறிமுறைக் குழு

ஒப்புதல் படிவம்

தேதி:

மரு. க. சத்யா ஆகிய நான் பூ. சா. கோ மருத்துவக் கல்லூரியின் / மருத்துவமனையின் கண் மருத்துவ துறையின் கீழ், **"வளர்சிதை மாற்றமடைந்த நோயாளிகளுக்கு ஏற்படும் உள்விழி அழுத்த மாற்றத்தினை பெர்கின்ஸ் டோநோமீட்டர் கருவியின் மூலம் கண்டறிந்து, அதனை நல்ல நிலையில் உள்ள நோயாளிகளின் வயதை பொருத்து ஒப்பிடுதல்"** என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி: மரு. ஜீவமாலா மெர்சி ஜானகி

ஆய்வு மேற்கொள்வதற்கான அடிப்படை:

உண்மையில் வளர்சிதை மாற்றமடைந்த நோயாளிகளுக்கு உள்விழி அழுத்தம் குறையும் என்பது அனைத்து மருத்துவர்களும் அறிந்ததே. எனவே அவர்களுக்கு உள்விழி அழுத்த நோய்க்கான மருந்துகளை தவிர்க்க வேண்டும்.

ஆய்வின் நோக்கம்:

1. வளர்சிதை மாற்றமடைந்த நிலையில் உள்ள நோயாளிகளின் உள்விழி அழுத்தத்தை கண்டறிந்து, அதனை நல்ல நிலையில் உள்ள நோயாளிகளின் வயதை பொருத்து நோக்கல்.

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை: 200

ஆய்வில் பங்கு பெறுவோர் மற்றும் வயது: இருபது வயதிற்கு மேற்பட்ட வளர்சிதை மாற்றமடைந்த நோயாளிகள் மற்றும் நல்ல நிலையில் உள்ள நோயாளிகள்.

ஆய்வு மேற்கொள்ளும் இடம்: தீவிர சிகிச்சை பிரிவு, இடைநிலை சிகிச்சை பிரிவு, கண் மருத்துவம், பூ. சா. கோ. மருத்துவக்கல்லூரி மருத்துவமனை, கோயம்புத்தூர்.

இந்த ஆய்வில் எங்களுடன் ஒத்துழைக்குமாறு கேட்டுக்கொள்கிறோம். நாங்கள் சில தகவல்களை இந்த ஆய்விற்காக சேகரிக்க உள்ளோம்.

ஆய்வு செய்யப்படும் முறை: பெர்கின்ஸ் டோநோமீட்டர் கருவியின் மூலம் ஆய்வு செய்யப்படும்

முதன்மை நேர்காணல்: 10 நிமிடங்கள்

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் **5 வருடங்கள்** பாதுகாக்கப்படும். இந்த தகவல்கள் வேறு ஆய்விற்குப் பயன்படுத்தப் பட மாட்டாது.

மருத்துவ பரிசோதனைகள்:

இரத்த மாதிரி சேகரிப்பு: ___மில்லி, _____முறை

இரத்த மாதிரி எடுப்பது வழக்கமான சிகிச்சைக்காகவோ அல்லது இந்த ஆய்விற்காகவோ: பொருந்தாது

இதனால் ஏற்படக் கூடிய அசௌகரியங்கள் / பக்க விளைவுகள்: இதனால் எந்த அசௌகரியமோ, பக்க விளைவுகளோ ஏற்படாது.

இரத்த மாதிரிகள் ஆய்விற்குப் பின் பாதுகாத்து வைக்கப்படுமா? ஆம் / இல்லை, அழிக்கப்படும்: **பொருந்தாது**

சேகரிக்கப்பட்ட இரத்தம் விற்கப்படுமா? ஆம் / இல்லை **பொருந்தாது**

சேகரிக்கப்பட்ட இரத்தம் வேறு நிறுவனத்துடன் பகிர்ந்து கொள்ளப்படுமா? ஆம் / இல்லை: **பொருந்தாது**

மருந்துகள் ஏதேனும் கொடுக்கப்படவிருந்தால் அவை பற்றிய விவரம் (கொடுக்கப்படும் காரணம், காலம், பக்க விளைவுகள், பயன்கள்): மேற்பூச்சு மயக்கமருந்து, ஆய்விற்கான பரிசோதனை, 2 நிமிடங்கள், பக்கவிளைவுகள் இல்லை, வலியற்ற பரிசோதனை.

மருந்துகள் கொடுக்கப்படுவது வழக்கமான சிகிச்சை முறையா?: ஆம்

கொடுக்கப்படும் மருந்துகளுக்கு மாற்று உள்ளதா?: இல்லை

ஆய்வில் பங்குபெறுவதால் ஏற்படும் பலன்கள்:
வளர்சிதை மாற்றமடைந்த நோயாளிகளின் உள்விழி அழுத்தத்தை அறிதல்.

ஆய்வில் பங்கேற்பதால் ஏற்படும் அசௌகரியங்கள் / பக்க விளைவுகள்: இந்த ஆய்வினால் தங்களுக்கு எந்த விதமான அபாயங்களும் அசௌகரியங்களும் ஏற்படாது.

ஆய்வின் முடிவுகள் எந்த முறையில் பயன்படுத்தப்படும்?
ஆய்வின் முடிவுகள், அடுத்தகட்ட ஆராய்ச்சிகளுக்கும், மருத்துவ ஆய்வு பத்திரிக்கைகளில் வெளியிடுவதற்கும் பயன்படுத்தப்படும்..

இந்த ஆய்வின் கேள்விகளுக்கு பதிலளிப்பதோ, இரத்த மாதிரிகள் அல்லது திசு மாதிரிகள் எடுப்பதிலோ உங்களுக்கு ஏதேனும் அசௌகரியங்கள் இருந்தால், எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சை முறையில் எந்த வித பாதிப்பும் இருக்காது என்று உங்களுக்கு உறுதியளிக்கிறோம். மருத்துவ மனையில் நோயாளிகளுக்கு அளிக்கப்படும் சேவைகளை நீங்கள் தொடர்ந்து பெறலாம். இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் வேறு எந்த விதமான

கூடுதலான பலனும் உங்களுக்குக் கிடைக்காது. நீங்கள் அளிக்கும் தகவல்கள் இரகசியமாக வைக்கப்படும். ஆய்வில் பங்கேற்பவர்கள் பற்றியோ அவர்கள் குடும்பத்தைப் பற்றியோ எந்தத் தகவலும் எக்காரணம் கொண்டும் வெளியிடப்படாது என்று உறுதியளிக்கிறோம். நீங்கள் அளிக்கும் தகவல்கள் / இரத்த மாதிரிகள் / திசு மாதிரிகள் அங்கீகரிக்கப்பட்ட ஆய்விற்கு மட்டுமே பயன்படுத்தப்படும். இந்த ஆய்வு நடைபெறும் காலத்தில் குறிப்பிடத்தகுந்த புதிய கண்டுபிடிப்புகள் அல்லது பக்க விளைவுகள் ஏதும் ஏற்பட்டால் உங்களுக்குத் தெரிவிக்கப்படும். இதனால் ஆய்வில் தொடர்ந்து பங்கு பெறுவது பற்றிய உங்கள் நிலைப்பாட்டை நீங்கள் தெரிவிக்க ஏதுவாகும்.

ஆய்வுக்குட்படுபவரின் ஒப்புதல்: இந்த ஆய்வைப் பற்றிய மேற்கூறிய தகவல்களை நான் படித்து அறிந்து கொண்டேன் / ஆய்வாளர் படிக்கக் கேட்டுத் தெரிந்து கொண்டேன். ஆய்வினைப் பற்றி நன்றாகப் புரிந்து கொண்டு இந்த ஆய்வில் பங்கு பெற ஒப்புக்கொள்கிறேன். இந்த ஆய்வில் பங்கேற்பதற்கான எனது ஒப்புதலை கீழே கையொப்பமிட்டு, கை ரேகை பதித்து நான் தெரிவித்துக் கொள்கிறேன்.

பங்கேற்பாளரின் பெயர், முகவரி:

பங்கேற்பாளரின் கையொப்பம் / கை ரேகை / சட்டப்பூர்வ பிரதிநிதியின் கையொப்பம்:

தேதி :

ஆய்வாளரின் கையொப்பம்:

தேதி :

ஆய்வாளரின் தொலைபேசி எண்:

மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி எண்: 0422-4345818

MASTER CODING SHEET

CASES							ABG- 1 (DURING METABOLIC ACIDOSIS)								ABG-2 (AFTER TREATMENT OF METABOLIC ACIDOSIS)							
HOSPITAL NO	AGE	GENDER	IOP (RE) - 1	IOP (LE) - 1	IOP (RE) - 2	IOP (LE) - 2	FiO_2	pH	pCO_2	PaO_2	HCO_3	SaO_2	ABE	Lactate	FiO_2	pH	pCO_2	PaO_2	HCO_3	SaO_2	ABE	Lactate
I18014477	22	1	8MMHG	8.5MMHG	12MMHG	13MMHG	50	7.258	28.9	83.7	15.9	96.1	7	5.62	31	7.318	4408	98	26	99.4	1	2
I18031088	79	1	6MMHG	8MMHG	13MMHG	13MMHG	80	7.197	33.4	204.4	12.7	99.2	-14.3	4.29	40	7.368	46.9	97.7	27	92.4	2	2.9
I18015310	33	2	4MMHG	5MMHG	11MMHG	12MMHG	35	7.188	9.9	191	3.7	99.1	-21.6	0.98	33	7.447	30.3	62.8	20.5	92.6	-1.4	2
I18017514	51	2	6MMHG	6MMHG	13MMHG	14MMHG	40	7.141	15	209.7	7.9	99.4	-14.7	1.01	38	7.44	43.2	58.6	29.8	91.9	3	1.1
I18035375	25	2	8MMHG	8MMHG	14MMHG	14MMHG	28	7.207	12.5	147.4	6.1	98.8	-18	1.3	37	7.349	45.3	76.3	30	94.2	4.1	1.3
I18017567	78	1	6MMHG	6MMHG	11MMHG	11MMHG	40	7.145	15	209.7	7.9	99.4	-14.7	1.01	28	7.356	43.2	58.6	29.8	91.9	2.3	1
I18020059	76	1	6MMHG	7MMHG	14MMHG	14MMHG	40	7.257	23	55.8	15.9	94.4	-5.7	1.63	40	7.338	44.5	60.4	27.1	92.3	4.4	1
I18020370	36	2	7MMHG	7MMHG	16MMHG	16MMHG	40	7.23	30.5	106	15.7	97.6	-8.8	2.34	40	7.4	36.6	78	22.7	95.5	-1.1	2.1
I18020358	73	1	7MMHG	7MMHG	17MMHG	17MMHG	40	7.128	31.6	93.7	16.2	96.8	-8.4	2.34	81	7.401	43.9	50	25.5	84.3	0.2	1.4
I18019828	26	2	6MMHG	6MMHG	12MMHG	12MMHG	50	7.203	24	197.9	14.6	99.4	8	6.06	37	7.399	37.4	75.9	22.4	94.8	-1.2	1.1
I18020093	33	1	8MMHG	8MMHG	11MMHG	11MMHG	50	7.183	22.7	217.6	16.6	99.8	-5.4	6	40	7.38	43.2	58.6	29.8	91.9	5.3	1.7
I18020170	62	1	8MMHG	8.5MMHG	12MMHG	12MMHG	40	7.081	27	68.7	7.7	92.7	-21.8	2	41	7.415	38.9	77.4	24.5	95.7	0.5	1
I18019620	75	2	6MMHG	7MMHG	16MMHG	16MMHG	40	7.185	34.8	143.6	16.2	98.6	-9.5	1.49	29	7.422	48	55.5	26.6	89.6	5.1	2.3
I18020715	29	1	8MMHG	8MMHG	14MMHG	14MMHG	40	7.047	19.7	73.5	10.6	94.5	-12.5	1.06	29	7.424	48.8	83.5	24.2	96.6	6	1.9
I18020615	68	1	7MMHG	7MMHG	15MMHG	15MMHG	40	7.177	25.2	107.2	11.5	97.4	-13.3	2.38	37	7.394	37.4	75.9	22.4	94.8	-2	1.1
I18020596	54	2	5MMHG	6MMHG	13MMHG	14MMHG	50	7.215	28.7	52.2	18	88	-5	6.77	37	7.4	47.3	113.6	23.4	97.8	-2.1	1
I18020638	64	1	7MMHG	7MMHG	14MMHG	14MMHG	21	7.217	23.2	70.6	14.6	93.9	-8	1.4	40	7.3	59.4	222.4	28.6	99.7	1.5	0.8
I18020231	76	1	7MMHG	7MMHG	16MMHG	16MMHG	40	7.201	25.3	190	12.2	99.2	-12.2	0.78	25	7.404	53	82.4	26.3	96.3	6.3	1.7
I18022485	62	2	6MMHG	6MMHG	13MMHG	13MMHG	21	7.187	23	86.2	13.5	96.7	-28.2	0.92	40	7.45	35.3	125	24.5	99	0.9	2
I18022601	44	1	8MMHG	8MMHG	15MMHG	15MMHG	40	7.158	22.1	54	7.7	79.7	-19.1	2.82	41	7.415	38.9	77.4	25	95.7	0.5	1
I18022154	61	1	8MMHG	8MMHG	17MMHG	17MMHG	37	6.947	25.8	118.9	5.5	93	-25	1	81	7.382	43.9	50	26	84.3	0.2	1.4
I18012560	58	2	7MMHG	8MMHG	17MMHG	17MMHG	50	7.239	28.4	221.2	11.8	99.5	-3.8	3.96	40	7.413	40.5	91	25.3	97.1	0.7	1.7
I18032959	69	1	6MMHG	6MMHG	13MMHG	14MMHG	40	6.958	23.6	172.1	5	97.5	-25.8	2.2	32	7.411	42.8	87.8	26.6	96.8	1.7	1
I18033328	26	2	6MMHG	7MMHG	12MMHG	13MMHG	40	7.023	33.1	84.5	8.4	86.6	-21.5	3.2	40	7.383	38.4	85.1	22.4	94.5	-1.4	1.6
I18031897	67	1	7MMHG	7MMHG	15MMHG	15MMHG	40	7.047	32.5	60.2	8.7	79.3	-20.8	2.07	29	7.416	36.7	83	24.3	96.3	-0.7	1
I18032968	57	1	8MMHG	8MMHG	16MMHG	17MMHG	35	7.197	23.6	77.2	11.3	94.4	-13.1	2.33	24	7.441	32.7	119.9	21.8	94.5	-2.1	0.8
I18033132	64	1	8MMHG	8MMHG	17MMHG	17MMHG	50	7.182	32	65.2	14.8	90.7	-10.6	2.48	28	7.352	41.9	135.8	22.7	92.3	-2.9	1
I18033179	57	1	6.5MMHG	6.5MMHG	11MMHG	12MMHG	100	7.205	24.7	341.9	13.4	99.9	-13.5	8.2	28	7.478	32.5	87.3	23.6	91.5	0	0.8
I18033058	73	1	6MMHG	8MMHG	16MMHG	16.5MMHG	45	7.208	14.9	166	11.1	99	-8.2	3.59	30	7.411	39	92	24.2	92.2	-0.4	1.1
I18033380	62	1	9MMHG	8.5MMHG	17MMHG	17MMHG	29	7.233	21.2	122	8.7	97.4	-17.1	2.5	30	7.413	35.9	113.8	22.4	93	-2.2	1.4
I18033356	52	1	9MMHG	9MMHG	16MMHG	16MMHG	24	7.202	27.8	96.1	13.4	96.8	-11.2	1.51	30	7.404	39	76	23.8	90	-0.9	1.3
I18033285	54	2	7MMHG	7MMHG	14MMHG	14MMHG	28	7.119	31.1	122.4	15.6	98.2	-9.1	1.22	30	7.411	39	92	24.2	93	-0.4	1.1
I18O33384	65	2	7MMHG	7MMHG	13MMHG	14MMHG	21	7.045	26.9	72	9.6	87.5	-19.2	6	40	7.44	37.3	75	24.7	95.5	0.8	1.2
I18031866	34	1	8MMHG	8MMHG	15MMHG	15MMHG	40	7.151	24.4	56.4	10.5	85.4	-14.7	1.18	21	7.383	30.3	71.4	22.2	95.4	-0.8	1.5
I18033344	69	1	8MMHG	9MMHG	15MMHG	16MMHG	40	7.072	29.2	64.8	12.7	90	-8.6	3.45	35	7.367	39.4	92.1	27.8	93.3	4.1	0.8
I18033104	59	2	8MMHG	8MMHG	16MMHG	16MMHG	50	7.183	29.7	80.5	13.3	95.9	-6.3	3.85	40	7.44	42.5	72.6	28.5	95.5	4.4	0.8
I18032890	61	2	6MMHG	6MMHG	12MMHG	13MMHG	28	7.229	12.5	146.5	6.4	98.8	-16.1	12.4	96	7.42	41.6	36.6	26.4	71.5	1.7	1.5

CASES							ABG- 1 (DURING METABOLIC ACIDOSIS)								ABG-2 (AFTER TREATMENT OF METABOLIC ACIDOSIS)							
HOSPITAL NO	**AGE**	**GENDER**	**IOP (RE) - 1**	**IOP (LE) - 1**	**IOP (RE) - 2**	**IOP (LE) - 2**	**FiO_2**	**pH**	**pCO_2**	**PaO_2**	**HCO_3**	**SaO_2**	**ABE**	**Lactate**	**FiO_2**	**pH**	**pCO_2**	**PaO_2**	**HCO_3**	**SaO_2**	**ABE**	**Lactate**
I18033304	44	2	7MMHG	7MMHG	14MMHG	14MMHG	29	7.152	39.1	93.7	11.2	96.5	-9.3	2.3	40	7.334	48.7	74	26.8	83	-0.5	0.6
I18033331	64	1	8MMHG	8MMHG	17MMHG	17MMHG	28	7.277	15.7	120.6	7.2	98	-16.8	16.02	40	7.305	50.4	72	24.5	87.4	-1.8	0.6
I18032817	51	2	5MMHG	5MMHG	13MMHG	13MMHG	29	7.079	38.9	90.1	12.8	90.1	-8.2	3.1	38	7.324	51.4	68	26.1	85.1	0.1	0.7
I18032359	65	1	6MMHG	6MMHG	14MMHG	14MMHG	60	7.31	35.4	64.6	14.5	91	-7.3	4.22	40	7.44	37.3	75	24.7	95.5	0.8	1.2
I18033329	41	1	8MMHG	8MMHG	15MMHG	15MMHG	50	7.141	39.6	80	16.6	93.9	-10.1	3.84	50	7.416	30.8	82.3	22.6	94	-1.9	2
I18030138	58	1	9MMHG	9MMHG	16MMHG	16MMHG	40	7.133	34.3	73.4	13.7	91.1	-6.9	6.4	35	7.392	35.1	150.3	22.9	96	-4.1	1.5
I18029009	62	1	8MMHG	9MMHG	15MMHG	15MMHG	21	7.036	30.6	57.5	16.9	87.5	-7.7	1.8	35	7.383	34.3	155.8	22	95	-2.1	1.5
I18028669	37	1	8MMHG	8MMHG	14MMHG	14MMHG	61	7.147	30.3	62.8	14.5	92.6	-2.7	3.9	40	7.405	30.5	73.4	23.9	96.8	0.5	1.4
I18029065	69	1	8MMHG	9MMHG	14MMHG	14MMHG	50	7.064	28	77.9	14.6	96.1	-2.8	2.6	37	7.42	43.3	91.1	29.4	94.1	2.9	1.8
I18029873	48	1	9MMHG	9MMHG	16MMHG	17MMHG	28	7.39	32.4	75.1	15.2	94.5	-5.2	1.3	35	7.408	36.3	90	22.4	91	-2.3	1.2
I19004060	77	2	6MMHG	6MMHG	12MMHG	12MMHG	32.7	7.088	32.7	38.3	13.3	66.4	-4.7	0.8	40	7.431	32.5	111	22.1	97	-3.2	1.6
I19013768	42	2	9MMHG	9MMHG	14MMHG	14MMHG	40	7.107	29.7	138.4	15.3	99.1	-4.8	1.7	22	7.333	49.2	101.6	27.1	97.3	-0.7	2.7
I19013810	67	1	6MMHG	7MMHG	12MMHG	13MMHG	50	7.164	28	77.9	15.6	96.1	-2.8	2.6	32	7.414	31.6	70.1	24.7	99.3	0.9	2.1
I19013786	59	2	6MMHG	6MMHG	13MMHG	13MMHG	28	7.19	32.4	75.1	16.2	94.5	-5.2	1.3	37	7.415	39	130	23.2	99.3	0.9	2.4
I19013887	64	1	7MMHG	8MMHG	12MMHG	13MMHG	32.7	7.088	32.7	38.3	11.3	66.4	-4.7	0.8	41	7.401	39.1	100.4	25.8	98.4	2.6	2.5
I19011038	45	1	8MMHG	8MMHG	14MMHG	14MMHG	40	7.147	19.7	73.5	10.6	94.5	-12.5	1.06	38	7.449	33.1	89.9	25.9	97.7	1.9	3.4
I19011454	65	1	8.5MMHG	9MMHG	13MMHG	13MMHG	40	7.101	25.3	190	12.2	99.2	-12.2	0.78	40	7.365	42	74.8	23.5	92	-1.9	3
I19011582	34	2	6MMHG	7MMHG	13MMHG	13MMHG	35	7.097	23.6	77.2	11.3	94.4	-13.1	2.33	37	7.441	34.7	73	23.1	95.1	-0.7	1.4
I19011249	76	2	6MMHG	6MMHG	11MMHG	11.5MMHG	29	7.052	29.1	93.7	15.2	96.5	-9.3	2.3	31	7.422	31.4	75.7	23.1	91.5	-2.8	1.6
I19011241	49	2	6MMHG	6MMHG	12MMHG	12MMHG	40	7.047	19.7	73.5	10.6	94.5	-12.5	1.06	41	7.447	33.2	98.8	25	97.5	1.1	1.4
I19011504	63	2	6MMHG	6MMHG	12MMHG	12.5MMHG	40	7.041	15	209.7	7.9	99.4	-14.7	1.01	41	7.45	38.3	102.6	26.2	98.2	2.2	1.4
I19011450	43	1	8MMHG	8MMHG	14MMHG	14MMHG	50	7.241	39.6	80	16.6	93.9	-10.1	3.84	28	7.42	38.8	96.1	29.6	97	1.1	1.3
I19002314	72	2	7MMHG	7MMHG	13MMHG	13MMHG	21	7.028	27.4	67	10.7	93.3	-5.8	1.6	40	7.428	39.2	117.8	28.9	93.1	1.3	1.7
I19010232	69	1	8MMHG	8MMHG	15MMHG	15MMHG	21	7.082	28.1	66.4	16.3	92	-7.7	3	50	7.416	44.5	87.3	28	92.5	1.9	2.5
I19011002	47	2	7.5MMHG	7.5MMHG	14MMHG	14MMHG	70	7.122	26.5	84	12.5	94.9	-6.9	8.4	37	7.41	35.8	101.1	22.9	99.7	-1.9	2
I19011212	68	2	6MMHG	6.5MMHG	12MMHG	13MMHG	45	7.171	28.7	76.8	10.4	93.2	-9.5	2.3	38	7.41	38.2	100	23.3	97.7	1	2.1
I19010896	44	2	5MMHG	6MMHG	11MMHG	11MMHG	40	7.084	33.9	89.2	14.8	96.5	-4.7	2.9	35	7.417	40.4	78.2	25.4	98	0.9	2.2
I19011087	67	2	6MMHG	7MMHG	13MMHG	13MMHG	70	7.122	26.5	84	11.5	94.6	-6.9	8.4	40	7.365	46.3	77.9	25.9	93.6	0.5	2.4
I19019027	64	2	4MMHG	5MMHG	10MMHG	10MMHG	81	6.891	28.7	178.7	7.3	97.3	-24.6	17	30	7.426	34.9	74.9	24.8	92	1.1	2.6
I19019020	39	1	7MMHG	8MMHG	11MMHG	12MMHG	21	7.039	25.8	41.9	13.1	78.6	-6.1	1.7	40	7.424	37.7	77.3	24.1	95.1	-0.3	3.1
I19018645	71	2	7MMHG	8MMHG	11MMHG	13MMHG	37	7.021	25	44.6	11.3	74.8	-19.7	5	40	7.374	34.7	78.5	22.9	91.3	-1.1	4.8
I19018963	79	1	8MMHG	8MMHG	12MMHG	12MMHG	37	7.113	20	28.4	14.7	79.9	-6.9	0.9	40	7.427	39.1	75.9	25.6	98	-2	4.5
I19019005	43	2	8MMHG	8.5MMHG	12MMHG	12MMHG	36	7.068	25	22.7	16.1	60.9	-7.6	1	40	7.345	36.8	85.3	27	95.6	-1	3.1
I19018740	66	2	7MMHG	7.5MMHG	11MMHG	11MMHG	21	7.088	29.7	25.5	14.5	42.1	-6.1	5.4	40	7.378	42.8	86.2	24	91.1	-2.1	3.7
I19020638	35	2	8MMHG	9MMHG	13MMHG	13.5MMHG	50	7.139	28.1	73.5	11.7	90.2	-14.2	11.7	50	7.36	35.2	119	26	97.1	-1	3.9
I19018590	62	2	7.5MMHG	7MMHG	15MMHG	15MMHG	40	7.097	24.4	68.1	10.4	93.1	-19.3	10.6	40	7.414	38	84.6	23.2	95	-1.6	4.5
I19009809	53	2	8MMHG	8MMHG	11MMHG	11MMHG	40	7.218	29	74.1	14.5	95.4	-10.1	7.8	40	7.311	40	99.2	22	97.7	1	2.4
I19020307	49	2	8MMHG	8MMHG	10MMHG	12MMHG	45	7.079	29.1	64.6	15.9	94.3	-4.6	4.5	40	7.358	38.1	111	24	98.9	0.8	3.1
I19020527	69	1	8MMHG	9MMHG	10MMHG	10MMHG	30	7.228	21.4	114.6	11.8	97.2	-6.3	1.4	41	7.366	38	101.9	23.5	94.6	-0.9	1.1
I19020655	78	2	8MMHG	8.5MMHG	11MMHG	11MMHG	44	7.076	24.1	43	11.3	95.2	-9.2	1.6	45	7.412	37	86.6	26.8	95.5	4.1	1.5

CASES							ABG- 1 (DURING METABOLIC ACIDOSIS)								ABG-2 (AFTER TREATMENT OF METABOLIC ACIDOSIS)							
HOSPITAL NO	AGE	GENDER	IOP (RE) - 1	IOP (LE) - 1	IOP (RE) - 2	IOP (LE) - 2	FiO_2	pH	pCO_2	PaO_2	HCO_3	SaO_2	ABE	Lactate	FiO_2	pH	pCO_2	PaO_2	HCO_3	SaO_2	ABE	Lactate
I19018741	37	1	8MMHG	9MMHG	12MMHG	12MMHG	40	7.094	21	89.1	13.5	92	-6.4	3.7	50	7.453	36.8	169.5	25.5	99.6	1.6	1.5
I19019019	73	2	7MMHG	7.5MMHG	14MMHG	14MMHG	40	7.226	23.4	83.4	16.1	90	-8.9	5.4	40	7.446	37	145	25	98.7	1.8	1.6
I19020628	68	2	6MMHG	7MMHG	12MMHG	12MMHG	40	7.223	25.7	84.1	10.5	95.1	-6.6	6.5	35	7.45	38	70.4	26.3	97.9	2.4	1.7
I19019561	46	2	8MMHG	8MMHG	13MMHG	13MMHG	40	7.082	22.4	75.8	15	94	-6.3	4.4	35	7.38	36.9	92.7	24.9	99.1	2.1	1.1
I19019260	79	1	7MMHG	8MMHG	12MMHG	13MMHG	40	7.229	29	76.9	16.1	93.6	-8.9	6.4	37	7.409	39.5	79.4	24.5	93.8	1.1	0.4
I19020335	32	2	6MMHG	6MMHG	11MMHG	11MMHG	50	7.202	18.5	79.3	14.8	91	-11.2	13.1	42	7.44	39.2	80	26	94.8	1.9	1.1
I19039725	73	1	8MMHG	7MMHG	10MMHG	11MMHG	50	7.251	26.2	72	15.5	95.3	-6.4	4.3	61	7.386	42.6	167	25	99.7	-2	1
I19026425	66	2	6MMHG	6MMHG	13MMHG	13MMHG	80	7.057	23.4	85.3	12.4	92.2	-4.8	1	40	7.45	36.6	79.4	24.9	98.7	0.9	0.8
I19026425	56	1	5MMHG	5MMHG	12MMHG	13MMHG	41	7.254	28.7	96.9	15.6	91.9	-8.4	2	37	7.426	40.2	70.1	25.8	94.3	1.4	1.7
I19027121	45	2	6MMHG	7MMHG	13MMHG	14MMHG	45	7.087	29.7	83.4	17	94	-6.3	1.1	43	7.45	39.2	75	23.6	92.4	0.8	1.1
I19027185	62	1	7MMHG	7MMHG	13MMHG	15MMHG	40	7.145	29	110	13.1	99.5	-2.4	1.6	50	7.376	38.7	79.4	28.3	91.3	4	0.9
I19027185	72	2	6MMHG	7MMHG	14MMHG	14MMHG	45	7.214	29.8	112	14.5	99.6	-2.8	2.1	40	7.437	38.5	96.3	28	98	7.6	1.1
I19027258	35	1	6MMHG	7MMHG	12MMHG	12MMHG	49	7.199	21	100.2	15.2	97	-2.1	1.1	45	7.423	43.3	86	24	96	4.6	1
I19028002	77	2	5MMHG	6MMHG	11MMHG	12MMHG	40	7.088	23.4	113.3	15.6	98.1	-1	2.8	50	7.337	39	82.9	28.3	93	3	1.1
I19028045	52	2	6MMHG	6MMHG	13MMHG	13MMHG	40	7.231	27.8	93.8	14.8	99	-4	3	45	7.365	42	72	24.6	95.5	6	1.7
I19027980	47	2	4MMHG	5MMHG	12MMHG	12MMHG	40	7.215	30	92	16	95	-3	2	40	7.362	48.2	96	26.7	94	0.7	2
I19027665	78	2	6MMHG	6MMHG	14MMHG	14MMHG	21	7.225	29.8	102.3	15.5	92.3	-6	1.03	37	7.422	45.4	103	29.1	95.8	4.4	1.8
I19027469	41	1	6.5MMHG	7MMHG	13MMHG	13.5MMHG	60	7.203	24.5	77	14.5	91.2	-3	1.3	37	7.385	37.7	82.9	23.9	94.3	-2.1	2.1
I19027591	76	2	6MMHG	6.5MMHG	13MMHG	13MMHG	21	7.145	27.4	77.4	14.4	94	-4	2.3	37	7.341	44.3	78.9	23.4	94.5	-1.4	1
I19027655	61	1	7MMHG	7MMHG	12MMHG	13MMHG	37	7.141	24.1	94	15.8	97	-2	1.6	37	7.387	38.6	138.1	23.7	99	-1.1	2.8
I19055533	38	2	5MMHG	6MMHG	12MMHG	13MMHG	37	7.122	28	83.5	11.9	96.4	-4.9	2.5	40	7.359	38.6	83.5	26.5	97	-1	3
I19023476	71	2	4MMHG	5MMHG	11MMHG	11MMHG	40	7.039	24	99	10	95	-2	4.4	30	7.412	36.3	70.6	28	98	2	2.1
I19088830	57	2	6MMHG	7MMHG	13MMHG	13MMHG	41	7.211	26.8	95.8	12.4	97.8	-1.7	2.6	39	7.365	41	80	25	97.9	-1.1	1.3

CONTROLS					ABG							
HOSPITAL NO	**AGE**	**GENDER**	**IOP- RE**	**IOP- LE**	**FiO_2**	**pH**	**pCO_2**	**PaO_2**	**HCO_3**	**SaO_2**	**ABE**	**Lactate**
I19001514	22	1	16MMHG	17MMHG	30	7.341	48.1	111	24.9	98.1	2	1.3
I19003138	79	2	14MMHG	14.5MMHG	21	7.378	46.9	97.7	27	92.4	1.5	2.9
I19004202	33	1	14MMHG	14MMHG	61	7.447	30.3	62.8	20.5	92.6	-2.7	3.9
I19002368	51	2	16MMHG	17MMHG	40	7.44	43.2	58.6	29.8	91.9	5.3	1.4
I18036108	25	2	15MMHG	16MMHG	40	7.349	45.3	76.3	30	94.2	6.6	1.2
I18036105	78	1	17MMHG	17MMHG	40	7.356	43.2	58.6	29.8	91.9	5.3	1.4
I18036116	76	2	14.5MMHG	14.5MMHG	40	7.348	44.5	60.4	27.1	92.3	5.4	1.5
I18036112	53	2	15MMHG	15MMHG	40	7.41	36.6	78	22.7	95.5	-1.4	2.1
I18036104	73	1	12MMHG	13MMHG	81	7.382	43.9	50	25.5	84.3	0.2	1.8
I18036110	26	2	13MMHG	13MMHG	37	7.394	37.4	75.9	22.4	94.8	-2.2	1.1
I19002345	55	2	14MMHG	13MMHG	40	7.356	43.2	58.6	29.8	91.9	5.3	1.4
I18065491	62	2	11MMHG	12MMHG	41	7.415	38.9	77.4	24.5	95.7	0.5	1
I19002548	75	2	14MMHG	14MMHG	29	7.422	48	55.5	26.6	89.6	5.1	3.3
I18036113	56	2	14MMHG	14MMHG	29	7.424	48.8	83.5	24.2	96.6	6	2.9
I18026771	68	2	12MMHG	12MMHG	37	7.394	37.4	75.9	22.4	94.8	-2.2	1.1
I18036122	54	2	15MMHG	16MMHG	37	7.4	47.3	113.6	23.4	97.8	-2.7	0.8
I18046107	64	1	17MMHG	17MMHG	40	7.3	59.4	222.4	28.6	99.7	1.5	0.8
I18026119	76	2	17MMHG	17MMHG	25	7.404	53	82.4	26.3	96.3	6.3	1.7
I18056118	62	1	12MMHG	12MMHG	40	7.45	35.3	125	24.5	99	0.9	1.4
I18036114	44	2	17MMHG	17MMHG	41	7.415	38.9	77.4	24.5	95.7	0.5	1
I19011017	61	1	13MMHG	14MMHG	81	7.382	43.9	50	25.5	84.3	0.2	1.8
I19013569	58	2	14MMHG	14MMHG	40	7.413	40.5	91	25.3	97.1	0.7	1.6
I19018243	69	2	13MMHG	13MMHG	32	7.411	42.8	87.8	26.6	96.8	1.7	1
I19018246	49	1	11MMHG	11MMHG	40	7.383	38.4	85.1	22.4	95.5	-2.7	1.6
I19017461	67	1	12MMHG	11MMHG	29	7.416	36.7	83	24.3	95.6	-0.6	1.3
I19009809	57	1	12MMHG	12MMHG	24	7.441	32.7	119.9	21.8	94.5	-2.4	0.8
I19018232	64	2	13MMHG	14MMHG	28	7.352	41.9	135.8	22.7	92.3	-2.9	1
I19017954	57	2	13MMHG	13MMHG	28	7.478	32.5	87.3	23.6	91.5	0	0.8
I19017963	64	1	11MMHG	12MMHG	30	7.411	39	92	24.2	92.2	-0.4	1.1
I19018305	62	2	11MMHG	11MMHG	30	7.413	35.9	113.8	22.4	93	-2.2	1.4
I19018235	52	2	12MMHG	12MMHG	30	7.404	39	76	23.8	90	-0.9	1.3
I19018590	54	1	14MMHG	14.5MMHG	30	7.411	39	92	24.2	93	-0.4	1.1
I19018660	65	1	14MMHG	14MMHG	40	7.44	37.3	75	24.7	95.5	0.8	1.2
I19019087	47	1	15MMHG	16MMHG	21	7.383	30.3	71.4	22.2	95.4	-0.8	1.5
I19016163	69	1	17MMHG	17MMHG	35	7.367	39.4	92.1	27.8	93.3	4.1	0.8
I19018901	59	1	13MMHG	13MMHG	40	7.44	42.5	72.6	28.5	95.5	4.4	0.8
I19017876	61	2	15MMHG	15MMHG	96	7.42	41.6	36.6	26.4	71.5	1.7	1.5
I19019045	44	1	14MMHG	14MMHG	40	7.334	48.7	74	26.8	83	-0.5	0.6
I19018523	64	2	12MMHG	13MMHG	40	7.305	50.4	72	24.5	87.4	-1.8	0.6
I19018796	51	1	12MMHG	12MMHG	38	7.324	51.4	68	26.1	85.1	0.1	0.7
I19024638	65	1	12MMHG	13MMHG	40	7.44	37.3	75	24.7	95.5	0.8	1.2
I18032855	41	1	14MMHG	14MMHG	50	7.416	30.8	82.3	22.6	94	-1.9	2
I19024221	58	1	13MMHG	13MMHG	35	7.392	35.1	150.3	22.9	96	-4.1	1.5
I19024612	62	2	12MMHG	13MMHG	35	7.383	34.3	155.8	22	95	-2.1	1.5
I19024438	46	1	11MMHG	12MMHG	40	7.405	30.5	73.4	23.9	96.8	0.5	1.4
I19024678	69	2	13MMHG	14MMHG	37	7.42	43.3	91.1	29.4	94.1	2.9	1.8
I19023651	48	1	12MMHG	11MMHG	35	7.408	36.3	90	22.4	91	-2.3	1.2
I19024743	58	1	15MMHG	16MMHG	40	7.431	32.5	111	22.1	97	-3.2	1.6
I19024710	42	1	13MMHG	13MMHG	22	7.333	49.2	101.6	27.1	97.3	-0.7	2.7
I19023571	67	1	16MMHG	16MMHG	32	7.414	31.6	70.1	24.7	99.3	0.9	2.1
I19033452	59	1	11MMHG	11MMHG	37	7.415	39	130	23.2	99.3	0.9	2.4
I18065289	64	2	11MMHG	10MMHG	41	7.401	39.1	100.4	25.8	98.4	2.6	2.5
I18065408	45	2	11MMHG	11MMHG	38	7.449	33.1	89.9	25.9	97.7	1.9	3.4
I19044436	65	2	11MMHG	12MMHG	40	7.365	42	74.8	23.5	92	-1.9	3
I17066543	34	1	12MMHG	12MMHG	37	7.441	34.7	73	23.1	95.1	-0.7	1.4
I18053247	76	2	13MMHG	13MMHG	31	7.422	31.4	75.7	23.1	91.5	-2.8	1.6
I19077745	49	1	16MMHG	16MMHG	41	7.447	33.2	98.8	25	97.5	1.1	1.4
I19055543	63	1	15MMHG	16MMHG	41	7.45	38.3	102.6	26.2	98.2	2.2	1.4
I19044438	43	1	14MMHG	13MMHG	28	7.42	38.8	96.1	29.6	97	1.1	1.3
I18043290	63	2	12MMHG	12MMHG	40	7.428	39.2	117.8	28.9	93.1	1.3	1.7
I19024462	69	2	11MMHG	11MMHG	50	7.416	44.5	87.3	28	92.5	1.9	2.5
I19033256	47	1	10MMHG	10MMHG	37	7.41	35.8	101.1	22.9	99.7	-1.9	2
I19025565	68	1	10MMHG	10MMHG	38	7.41	38.2	100	23.3	97.7	1	2.1
I19023173	44	1	11MMHG	12MMHG	35	7.417	40.4	78.2	25.4	98	0.9	2.2

CONTROLS					ABG							
HOSPITAL NO	**AGE**	**GENDER**	**IOP- RE**	**IOP- LE**	**FiO_2**	**pH**	**pCO_2**	**PaO_2**	**HCO_3**	**SaO_2**	**ABE**	**Lactate**
I19025255	67	2	13MMHG	15MMHG	40	7.365	46.3	77.9	25.9	93.6	0.5	2.4
I19025694	64	1	13MMHG	13MMHG	30	7.426	34.9	74.9	24.8	92	1.1	2.6
I19025455	39	2	14MMHG	14MMHG	40	7.424	37.7	77.3	24.1	95.1	-0.3	3.1
I19023799	71	2	14MMHG	13MMHG	40	7.374	34.7	78.5	22.9	91.3	-1.1	4.8
I19023651	79	1	12.5MMHG	14MMHG	40	7.427	39.1	75.9	25.6	98	-2	4.5
I19025398	43	1	13MMHG	14MMHG	40	7.345	36.8	85.3	27	95.6	-1	3.1
I19025734	66	1	15MMHG	14.5MMHG	40	7.378	42.8	86.2	24	91.1	-2.1	3.7
I19025591	35	1	12MMHG	12MMHG	50	7.36	35.2	119	26	97.1	-1	3.9
I19025384	62	2	12MMHG	11MMHG	40	7.414	38	84.6	23.2	95	-1.6	4.5
I19025447	53	1	15MMHG	15MMHG	40	7.311	40	99.2	22	97.7	1	2.4
I19025400	49	2	17MMHG	16MMHG	40	7.358	38.1	111	24	98.9	0.8	3.1
I19027355	69	2	11MMHG	11MMHG	41	7.366	38	101.9	23.5	94.6	-0.9	1.1
I19026500	61	2	12MMHG	13MMHG	45	7.412	37	86.6	26.8	95.5	4.1	1.5
I19026834	43	2	12MMHG	13MMHG	50	7.453	36.8	169.5	25.5	99.6	1.6	1.5
I19027073	73	1	13MMHG	13MMHG	40	7.446	37	145	25	98.7	1.8	1.6
I19027404	68	2	12MMHG	13MMHG	35	7.45	38	70.4	26.3	97.9	2.4	1.7
I19027220	46	1	12MMHG	12MMHG	35	7.38	36.9	92.7	24.9	99.1	2.1	1.1
I19026344	79	1	12.5MMHG	11MMHG	37	7.409	39.5	79.4	24.5	93.8	1.1	0.4
I19033345	32	1	14MMHG	14MMHG	42	7.44	39.2	80	26	94.8	1.9	1.1
I19066152	73	1	11MMHG	12MMHG	61	7.386	42.6	167	25	99.7	-2	1.3
I19045222	66	2	11MMHG	11MMHG	40	7.45	36.6	79.4	24.9	98.7	0.9	0.8
I19066642	56	1	11.5MMHG	11MMHG	37	7.426	40.2	70.1	25.8	94.3	1.4	1.7
I19026268	45	1	14MMHG	14MMHG	43	7.45	39.2	75	23.6	92.4	0.8	1.2
I19028079	62	2	14MMHG	14MMHG	50	7.376	38.7	79.4	28.3	91.3	4	0.9
I19028005	72	2	13MMHG	14MMHG	40	7.437	38.5	96.3	28	98	7.6	1.1
I19027741	35	1	14MMHG	15MMHG	45	7.423	43.3	86	24	96	4.6	1
I19028184	77	1	12.5MMHG	13MMHG	50	7.337	39	82.9	28.3	93	3	1.1
I19027635	52	1	13MMHG	13MMHG	45	7.365	42	72	24.6	95.5	6	1.7
I19028054	47	1	12MMHG	12MMHG	40	7.362	48.2	96	26.7	94	0.7	4
I19028130	78	1	14MMHG	14MMHG	37	7.422	45.4	103	29.1	95.8	4.4	1.8
I19028009	41	2	15MMHG	14MMHG	37	7.385	37.7	82.9	23.9	94.3	-2.1	3
I19028160	76	1	14MMHG	14MMHG	37	7.341	44.3	78.9	23.4	94.5	-2.4	3.7
I19027710	61	2	13MMHG	13MMHG	37	7.387	38.6	138.1	23.7	99	-2.1	3.6
I19028105	38	1	14MMHG	14MMHG	40	7.348	38.6	83.5	26.5	97	-1	3.8
I19028087	71	2	13MMHG	13MMHG	30	7.412	36.3	70.6	28	98	1	1.1
I19066480	57	2	14MMHG	15MMHG	40	7.417	36	78.7	24.6	97	-1.9	1.7