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STUDY OF ACID BASE BALANCE IN CHRONIC SEVERE ANAEMIA

Medicine

Dr. Balbinder Kumar M.B.B.S, M.D. (Final Year), Junior Resident, Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Bihar.

Dr. [Prof.] Ganesh Narayan Jha* M.D. (Medicine), DTM&H, Ph.D. (Medicine), MRCP (UK), FRCP (Edin.), Professor, Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Bihar. *Corresponding Author

Dr. Debarshi Jana Young Scientist (DST), Institute of Post-Graduate Medical Education and Research, A.J.C. Bose Road, Kolkata-700020, West Bengal, India.

ABSTRACT

Aim of the study role of acid base balance in chronic severe anaemic patients admitted in Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Bihar. Study subject include 50 chronic and severe anaemic patients. All the fifty cases underwent detailed haematological, biochemical, electrocardiographic, roentgenographic studies followed by extensive analysis of blood for blood gases and acid base parameters at the onset. Some were further studied for venous blood lactate and the effect of intravenous frusemide on the acid base parameters and the clinical state of the patient. Twenty normal controls were also studied.

Work in future on the problem of chronic severe anaemia should include cases with cardiac failure and other complications like respiratory infections etc. and they should be studied for myocardial function, glomerular filtration rate and renal anion transport in addition to blood gases and acid base study as done by us. The role of ionotropic agents should be studied in such cases in isolation from that with diuretics. The administration of oxygen alone with a mask is also expected to improve almost all parameters quickly and should be studied.

KEYWORDS

Acid base balance, Cardiac failure, Respiratory infection.

INTRODUCTION

The body's balance between acidity and alkalinity is referred to as acid base balance. The blood's acid base balance is precisely controlled because even a minor deviation from the normal range can severely affect many organs. The body uses a variety of physiological mechanisms maintain pH of the ECF within narrow limits. The first is the action of blood and tissue buffers, of which the important involves reaction of H+ ions with bicarbonate to form carbonic acid, which, under the influence of enzyme carbonic anhydrase, dissociates to form CO_2 and water $CO_2+H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO^-_3$.

This buffer system is important because bicarbonate is present at a relatively high concentration in ECF (21--29mmol/lit), and two of its key component are under physiological control:CO_2 by the lungs and carbonate by the kidney.

Respiratory compensation of acid base disturbances can occur quickly. In response to accumulation, pH changes in the brainstem stimulate ventilatory drive, reduce pCO_2 and increase pH. Conversely, systemic alkalosis leads to inhibition of ventilation, causing a rise in pCO_2 and reduction in pH, although it should be noted that this mechanism has limited capacity to change pH because hypoxia provides an alternative stimulus to drive ventilation. The kidneys provide a third line of defence against disturbances of arterial pH. When acid accumulates due to chronic respiratory or metabolic (non renal) causes the kidneys have the long term capacity to enhance urinary excretion of acid, effectively in increasing the plasma bicarbonate.

Acid-base imbalance occurs when a significant insult causes the blood pH to shift out of the normal range (7.32 to 7.42).

HAEMOGLOBIN IN THE ACID BASE BALANCE

Anemia is condition in which the number of red blood cells or the haemoglobin concentration lower than normal. Haemoglobin is needed to carry oxygen and if you have too few or abnormal red blood cells, or not enough haemoglobin, there will be a decreased capacity of blood to carry oxygen to the body's tissues.

Intensive changes of blood gases occur in working tissues. CO_2 diffuses to erythrocytes. In the red blood cell CO_2 either (1)bind to haemoglobin (carbaminohemoglobin is formed), or (2)reacts with water.

This reaction is catalysed by H^++carbonic anhydrase $CO_2 + H_2O \leftrightarrow H_2CO_3$ Produced carbonic acid : $H_2CO_3 \leftrightarrow HCO_3$ More than 70% of produced HCO_3 leave erythrocyte using special HCO_3/CL antiport. That is bicarbonate is exchanged for Cl ion. This process is called Hamburger's effect(chloride shift). In carbonic acid dissociation H+ is produced. Generated protons are buffered by haemoglobin. Deoxygenated haemoglobin is stronger base than oxygenated thus Deoxygenated haemoglobin is more capable of taking up protons. In lungs HCO_3 is changed to CO_2, using enzyme CA. CO_2 is exhaled. Reaction $HCO_3 \rightarrow CO_2+H_2O$ demands H+. Protons for this process are taken from haemoglobin whose affinity to H+ is lowered just when it arrived to lungs where is high po2 and haemoglobin become oxygenated.

Reaction catalysed by carbonic anhydrase has reverse course in lungs in comparison to other tissues: $HCO_3 + H+ \leftrightarrow CO_2+H_2O$ The fall in plasma potassium after treatment has been suggested as a cause[2], and additional or alternative factor might be the presence of an acidosis, particularly lactic acidosis, as suggested by the report of corona and Cohen. They described a patient with severe pernicious anaemia and lactic acidosis, although the concentration of blood lactata(5.2 mmol/L) does not fully explain the degree of acidosis (arterial pH 7.25, anion gap 31.5 mmol/L), and other anions may have been involved. Because of compensatory mechanisms anemia has a minimal effect on blood lactate. In vitamin B12 deficiency, however, the metabolic defects might cause accumulation of lactate and methyl malonic acids and so contribute to an acidosis. Glutathione synthetase deficiency is a rare disorder of glutathione metabolism with varying clinical severity. Patients may present with hemolytic anemia alone or together with acidosis.

AIMS AND OBJECTIVES

The Aim Of The Study :

Role of Acid base balance in chronic severe anaemic patients admitted in Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Bihar.

MATERIAL AND METHODS

It is an observation, prospective study done at Darbhanga Medical College & Hospital (Bihar).

Newly diagnosed case of chronic & severe anaemic patients attending General Medicine Department in Darbhanga Medical College & Hospital from March 2019-February 2020.

Study subject include 50 chronic and severe anaemic patients attending Department of General Medicine in DMCH.

Arterial blood will be drawn from the patients for the first day in

hospital, treatment commencing on day 1 after sampling. A further sample will be obtained at least one month later. Haematological tests will be carried out using CMG methods. Plasma electrolytes, urea, creatinine, phosphate, calcium, aspartate aminotransferase will be measured by semi auto analyzer in the department of biochemistry. The plasma anion gap (mmol/I) will be calculated as (Na+K)-(CI+HCO_3). On day 0 only, arterial pH, PCO_2, and PO_2, will be measured using a AVANTOR pH/Blood Gas Analyzer.

Inclusion Criteria
- Severely anaemic patients

Exclusion Criteria:
- Patients in pediatric age group,
- Pregnant females,
- Severe congestive heart failure,
- Patients unwilling to giving informed consent for study.
- Chronic Renal Failure (CKD).

Parameters to be studied:
1. History and thorough clinical examination of the patients
2. Biochemistry: Urea, Creatinine, Glucose, Na+, K+, Ca++, CI-, HCO_3.
3. 2 ml of arterial blood will be collected by a heparin flushed syringe and sent (in ice pack) to central clinical laboratory immediately for ABG analysis.
4. Principle of Analysis : Principle is potentiometry and pH sensitive glass electrode for pH and Severinghaus CO_2 electrode for PCO_2 and amperometry and Clark oxygen electrode for Po_2

Above 3 parameters were measured by machine whereas bicarbonate (HCO_3-) BEf, (base excess of blood), percent SO_2 (percent saturation of available Hb at normal P50), etc were calculated by machine.

Study Techniques:
1. Clinical history : Name, age, sex, H/O present illness, Relevant past history etc.
2. Clinical examination (BP, HR)
3. Laboratory investigations
4. ECG
5. Statistical analysis of collected data

OBSERVATIONS
Fifty (50) patients of chronic severe anaemia with haemoglobin of 4 gms/100 ml of blood and less were taken up for the study after detailed clinical and biochemical examination to exclude conditions which are known to alter the acid base homeostasis, per se, regardless of anaemia.

All the fifty cases underwent detailed haematological, biochemical, electrocardiographic, roentgenographic studies followed by extensive analysis of blood for blood gases and acid base parameters at the onset. Some were further studied for venous blood lactate and the effect of intravenous frusemide on the acid base parameters and the clinical state of the patient. Twenty normal controls were also studied.

The patients were grouped for the study of blood gases and acid base parameters and the results are presented group wise below:
Group I : 20 normal control patients as defined in the previous chapter with haemoglobin 12.76 (± 0.947).
Group IIA : 21 patients with haemoglobin ≤ 2.5 gm/100 ml of blood.
Group IIB : 29 patients with haemoglobin 2.6 – 4.0 gm/100 ml of blood.
Group IIIA : 25 patients at the start of the study who were later evaluated after partial correction of anaemia.
Group IIIB: 25 above patients after partial correction of anaemia.
Group IVA : 10 normal patients taken as control for venous blood lactate estimation.
Group IVB : 20 anaemic patients studied for blood venous lactate levels.
Group V : For studying the effect of intravenous frusemide on the clinical and acid base status of 10 anaemic patients.

Cause of anaemia: Of the 50 cases studied, all had microcytic hypochromic type of anaemia. Twenty two cases were due to hookworm infestation and the rest were due to malnourishment, iron deficiency, menorrhagia, repeated pregnancies and lactation or a combination thereof. One patient had bleeding piles with hookworm infestation and menorrhagia.

Socioeconomic status:
All the patients were poor with about seventy percent living in the villages with no access to sanitary latrines.

The important clinical characterisation of the case and the blood gas and acid base parameters have been tabulated in the succeeding tables along with statistical analysis and correlation as required between the groups.

Table I : Age And Sex Distribution (Total Material)

Age	Number	Male	Female	Percentage	
				Male	Female
12 – 20	20	12	8	60.0	40.0
21 – 40	24	15	9	35.7	64.3
above 40	6	5	1	83.3	16.7
Total	50	31	18	53.33	46.67

Table II :Haemoglobin Distribution Of The Patients

Group	Hb (gm%)	Number	Mean	SD	Range
IIA	≤ 2.5	21	2.009	± 0.367	1.2 – 2.4
IIB	2.6-4.0	29	3.489	± 0.365	2.6 - 4.0

Table III : Group I (Normal Controls) Acid Base Parameters

Acid Base Parameters	Number	Mean	SD	Range
Hb	20	12.76	± 0.947	11.0 – 14.1
pH	20	7.404	± 0.032	7.370 –7.432
PCO_2	20	39.82	± 1.725	37.2 – 42.2
PO_2	20	94.550	± 3.804	89.9 – 99.1
SB	20	24.650	± 1.116	23.1 – 26.6
BE	20	0.290	± 1.282	-1.6 to +2.4
Total CO_2	20	25.76	± 1.228	24.3 – 27.8
Anion gap	20	10.58	± 2.247	7.3 – 14.9

Table IV GROUP IIA (Heamoglobin ≤ 2.5 gm/100ml Of Blood) Acid Base Parameters

Acid base parameters	Number	Mean	SD	Range
pH	21	7.401	± 0.045	7.345 – 7.451
PCO_2	21	30.91	± 3.94	23.2 – 37.0
PO_2	21	78.31	± 7.94	66.4 – 92.4
SB	21	20.091	± 1.382	17.6 – 21.6
BE	21	-5.115	± 1.695	-8.4 to -3.4
Total CO_2	21	19.745	± 1.720	15.8 – 21.5
Anion gap	21	20.655	± 3.075	16.4 – 26.2

Table V Group IIB (Haemoglobin 2.6 TO 4.0 gm/100ml Of Blood) Acid Base Parameters

Acid base parameters	n	Mean	SD	Range
pH	29	7.444	± 0.032	7.358 – 7.531
PCO_2	29	33.258	± 4.501	24.6 – 41.3
PO_2	29	84.442	± 7.778	68.7 – 96.4
SB	29	23.284	± 1.412	21.8 – 27.1
BE	29	1.421	± 1.612	-3.2 to +2.8
Total CO_2	29	23.384	± 1.972	21.2 – 28.1
Anion gap	29	12.937	± 3.014	7.0 – 17.2

Table VI Comparison Of Acid Base Parameters Between Group IIA And Group IIB

Statistical correlation	Hb	pH	PCO_2	PO_2	SB	BE	Total CO_2	Anion gap
Df	28	28	28	28	28	28	28	28
t	10.609	3.067	1.438	2.066	6.011	5.934	5.092	6.709
P	<0.001	<0.01	>0.1	<0.05	<0.001	<0.001	<0.001	<0.001
Remarks	HS	S	NS	S	HS	HS	HS	HS

DISCUSSION
In the present study the arterial oxygen tension (PO_2) of the "very severely anaemic" group was 78.31 (±7.94) mmHg while in the "severly anaemic" group it was 84.442 (±7.778) and even this difference between the two groups was statistically significant (p less than 0.05). The $PO_2$of normal control was 94.550 (±3.804).

The PO_2 reported by Guleria et al. (1971) in the anaemic patients was 63.8 ± 12.5 mmHg and 76.1 ± 6.8 mmHg before and after correction of anaemia to about 11 gm/100 ml of blood respectively.

The PO_2 figures reported by Guleria et al (1971) are surprising since

our patients were more anaemic (Hb being 2.01 ± 0.37 in the "very severely anaemic" group, and 3.489 ± 0.365 in the "severely anaemic" group) than theirs (being around 4 gms/100 ml of blood).

It is hard to explain this difference, since low PO_2 persists in their cases even after correction of anaemia to 11 gm%. Whether any pulmonary cause is responsible is not exactly known.

Our results are identical to that of Hickam who studied oxygen tension and alveolar – arterial pressure gradient in 10 patients with haemoglobin content between 2 – 8.9 gm/100 ml of blood. They observed an average resting arterial oxygen tension of 82 mmHg in the anaemic state as compared to 94 mmHg in the normal controls. The other authors (loccit) have not reported the actual data.

Arterial oxygen unsaturation has been observed in chronic anaemia by other workers (Brannon et al 1945; Bishop et al 1955 and Roy et al 1963) suggesting that anaemia affects gas exchange in the lungs. However, Whitaker (1956) and Ryan and Hickam (1963) have not observed arterial oxygen unsaturation. We have no data on saturation.

Our observations of PO_2 of 94.550 (± 3.804) in the normal controls and that of 95.233 (± 3.874) in the "partially corrected" group with haemoglobin 6.027 (± 0.725) and 84.442 (± 7.778) in the "severely anaemic" group suggests that even with moderate degrees of anaemia the PO_2 is maintained at normal and significant fall is noticed only in the "severly" and "very severly" anaemic groups.

The normal values of PO_2 obtained by Housely (1967) who used a Clark electrode which is known to give falsely high values, is understandable. Even though the correction factor (PCV – 45) × 0.097 = percentage error, was applied, the method is definitely less consistent and unreliable.

The aim of increased ventilation in anaemia is to raise the alveolar oxygen tension and oxygen delivery to the tissues. Thus the heamoglobin leaves the lungs almost fully saturated with oxygen, but this role seems to be limited because there is so little haemoglobin.

The fall in PO_2 may be due to the shift of the oxygen dissociation curve to the right along with a slight but significant increase in anatomical intrapulmonary shunts (Housley, 1967). Though no cardiorespiratory disease was detected in our patients on clinical grounds, incipient pulmonary oedema as detected at autopsy in asymptomatic cases (Tung, 1937 and Somers et al 1959) may be another cause of arterial hypoxaemia.

The carbondioxide tension in the "partially corrected" group (Hb 6.0 gm%) was 38.707 ± 2.90 in contrast to the "untreated group" (Hb 2.82 gm%) PO_2 30.72 ± 2.854, a highly significant difference (p less than 0.001). The PCO_2 levels in the normol controls was 39.82 (± 1.725) and this when compared to the partially treated group was not significantly different (p more than 0.3).

This implies that the PCO_2 levels start falling significantly when the haemoglobin levels falls below 6 gm%, probably around 4 gm/100 ml of blood.

Our PCO_2 values are comparable to those of Manfredi (1964), PCO_2 35 ± 3 mmHg (p less than 0.005) when compared with the controls. Our data also compares favourably before and after correction of anaemia. The mean values of PCO_2 in the present study were lower because of a severer degree of anaemia and a more sophisticated method for its determination.

The often reported finding of alveolar hyperventilation and uniform reports of low PCO_2, including our own study, are to be explained as a natural outcome of the body's effort at maintaining a higher alveolar PO_2, alveolo-arterial PO_2 gradient aimed at keeping up the required oxygenation in the face of low oxygen content of the arterial blood. It can be conjectured that the low PCO_2 may boomerang into shifting the haemoglobin dissociation curve to the left i.e. unfavourable side concerning oxygen delivery which, however, has not been shown and could perhaps not be quantitatively important.

In the present series all the 20 cases exhibited raised blood lactate levels. Their mean haemoglobin was 2.77 (± 0.823) gms/100 ml of blood with a mean blood lactate of 2.561 mEq/Litre (± 0.391). This was significantly higher than the blood lactate of the normal controls 1.060 (±0.205) mEq/L, (p being less than 0.001).

Friedman et al (1941) observed that L:P (Lactate : Pyruvate) ratio is dependent upon the proportion of oxidised to reduced diphosphopyridine nucleotide (NADH) in the reversible reaction:
Pyruvic acid + NADH Lactic acid + NAD

Seibert et al (1967) studied changes in the lactic acid to pyruvic acid (L/P) ratio in chronically anaemic patients in an endeavour to determine the haemoglobin at which compensatory mechanisms becomes inadequate and tissue hypoxia supervenes.

Huckabee (1961) had demonstrated that surplus lactate is closely related with oxygen debt. A critical evaluation of excess lactate over pyruvate depends upon the assumptions as stated below:
i) The equilibrium constant between lactic and pyruvic acid has remained unaltered.
ii) The oxidative enzyme systems of the cells have not been appreciably affected.
iii) The red cell membrane diffusion characteristics have not been affected.

Even acidosis of whatever origin, chemical type, is known to decrease cardiac output and therby accelerate lactic acid production. Vogel and Sperelekis (1977) demonstrated impaired ventricular function in chicks by blocking the slow Ca^{++} current at an acid pH produced experimentally between 6.5 – 6.1 which is however, does not affect the faster Na^{+} current.

Severe anaemia could produce lactic acidosis at least through two mechanisms as a result of hypoxia and anaerobic metabolism or due to cardiac failure which is believed to be a complication of severe anaemia, the frequency being debatable. The latter produces low clearance and metabolism of lactates. The lactic acidosis by itself would impair cardiac function and maintain a vicious cycle. However, the only report and that too on experimental animals described very low pH before cardiac failure could not be an important factor in the lactic acidosis in anaemia which must of necessity be due to hypoxia.

In the present study significant negative correlation between lactate and haemoglobin levels was obtained in the anaemic subjects (r = 0.879 and p less than 0.001), as expected. This drives home the point that unmeasured anion concentration is accounted for primarily by the excess lactate production which suggests that hyperventilation and low PCO_2 have little or no role in lactate production in anaemic subjects.

Blood pH

Blood pH estimation, a measure of hydrogen ion concentration, was 7.404 (± 0.0.32) in the normol controls. In the "very severely anaemic" group it was 7.401 ± 0.045 and in the "severely anaemic group" it was 7.444 (± 0.032) i.e. on the upper limit of normal. Though these values are statistically significant (p less than 0.01) however, it is not clinically important because both the values are within the normal range of 7.36 to 7.44. However, this change indicates subtle adjustments within the physiological range.

Total CO_2, Standard bicarbonate, Base excess and Anion gap.

Total CO_2 of blood is the CO_2 released by acidification and it includes CO_2 from carbonic acid, HCO_3 ion and carbonate ion, dissolved CO_2 as well as carbamino Co_2.

Standard bicarbonate is the bicarbonate concentration in the plasama for whole blood equilibrated in-vitro with PCO_2 of 40 mmHg at 37^0C.

The total CO_2 was 19.745 (± 1.720) and 23.384 (± 1.972) in the "very severely anaemic" and "severely anaemic" groups respectively as compared to 25.76 (± 1.228) for the normal controls. The difference between the two anaemic groups is statistically highly significant (p less than 0.001).

Standard bicarbonate was 20.091 (± 1.382) an 23.284 (± 1.412) in the "very severely anaemic" and "severely anaemic" groups (p less than 0.001). The Base Excess was -5.115 (± 1.695) and 1.421 (± 1.612) respectively.

The anion gap was 20.655 (± 3.075) and 12.937 (± 3.014) in the "very

severely anaemic" and "severely anaemic" groups respectively.

The above results show a significant metabolic acidosis in the "very severely anaemic" group. The significant rise in blood lactate in the anaemic patients and its significant correlation with the anion gap suggests lactic acidosis to be the most important cause of metabolic acidosis in markedly anaemic patients due to peripheral tissue hypoxia.

No comparison can be drawn as no similar study is available in the literature.

Role Of Intravenous Frusemide On The Acid Base Parameters

As reffered to in the introduction, there is a widely held clinical impression that cardiac failure is a frequent complication of chronic severe anaemia. Cases are seen who are breathless and restless have raised JVP and enlarged, tender liver, oedema fof the feet and have pulmonary crepitations and rhonchi, often there is some fever.

We however, have an impression that true cardiac failure is rare and most of such patients are having what was described as "circulatory congested state" by Eichna. The breathlessness is largely because of hyperventilation, restlessness is due to cerebral hypoxia, the liver is enlarged due to fatty infiltration and tenderness is a highly subjective evaluation anyway. Oedema and raised JVP can be explained by renal retension of salt and water (ashraf et al 1975). The lung signs are often due to bronchial and alveolar infection as also the fever.

Diuretics often frusemide is promptly administered. Many such patients die before blood transfusion can be given or when being given.

We have felt that reduction in circulating blood volume, especially the central blood volume, due to the diuresis induced is responsible for the catastrophe.

No means have been worked out and statistical comparison not attempted, the cases being too few.

However, the trend of changes are clear in a single direction and very revealing. It is obvious that cases with failure are far more anaemic (Hb 2.1 & 1.2 gm%) than those without (Hb 3.4, 3.4 & 4.0 gm%).

There was no selection on our part. All ten cases passed 680-1150 ml of urine over the two hours after receiving frusemide.

In those without CHF the CVP has fallen drastically (12.5 to 2.8 cm and 10.2 to 1.7 cm of saline in another).

The other changes are slight but easily noticeable. The heart and respiratory rate rising, the PCO_2, PO_2 and SB have fallen in all the 3 cases and the BE has become more negative. The conclusion is inescapable that frusemide has led to deterioration pushing them into a state chcracterising severer anaemia.

On the other hand in the cases with CHF and CVF which was initially in the pathological range has again fallen drastically (18.4 to 6.4 and 19.6 to 8.2 cm of saline). As a contrast, heart rate and respiratory rate has interestingly fallen and the PCO_2, PO_2 and the standard bicarbonate have improved and so also the base excess which has become less negative. Again a conclusion seems inescapable that these patients status has improved with the use of frusemide. What would happen if frusemide was repeated, we have not studied.

CONCLUSION

Finally we conclude the various parameters, only PCO_2 is not different between the most severe and the relatively less severely anaemic subjects and rising to normal with partial correction of anaemia to an average of 6 gm. Per 100 ml of blood. Thus the PCO_2 falls only when the haemoglobin is lower than 6 gm per 100 ml of blood and the fall levels off at a haemoglobin around 4 mg per 100 ml of blood with progressively worsening anaemia.

REFERENCES

1. Albert MS, Dell RB, Winters RW: Quantitative displacement of acid-base equilibrium in metabolic acidosis. Ann Intern Med 1967; 66:312–322.
2. Coronato A, Cohen AB. Lactic acidosis secondary to pernicious anaemia. Ann Intern Med 1969;70:77-80.
3. Diem, K; Lentner, C. (1970). "Blood – Inorganic substance". In: Scientific Tables (7th ed.). Basle, Switzerland: CIBA-GEIGY Ltd. P.527.
4. Galla JH: Metabolic alkalosis. J Am Soc Nephrol 2000; 11: 369–375.
5. Hesp R, Chanarin I, Tait CE. Potassium changes in megaloblastic anaemia. Clin Sci Mol Med 1975; 49:77-9.
6. Huckabee WE. Abnormal resting blood lactate. 1. The significance of hyperlactatemia in hospitalized patients. Am J Med 1961;30:833-9.
7. Johnson SK, Naidu RK, Ostopowicz RC, et al: Adolf Kussmaul: distinguished clinician and medical pioneer. Clin Med Res 2009; 7: 107–112.
8. Kiening KL, Hartl R, Unterberg AW, Schneider GH, Bardt T, Lanksch WR: Brain tissue pO 2 -monitoring in comatose patients: implications for therapy. Neurol Res 1997; 19: 233–240.
9. Krapf R, Beeler I, Hertner D, Hulter HN: Chronic respiratory alkalosis. The effect of sustained hyperventilation on renal regulation of acid-base equilibrium. N Engl J Med 1991; 324: 1394–1401.
10. Madias NE, Schwartz WB, Cohen JJ: The maladaptive renal response to secondary hypocapnia during chronic HCl acidosis in the dog. J Clin Invest 1977; 60: 1393–1401
11. Oliver J, Bourke E: Adaptations in urea ammonium excretion in metabolic acidosis in the rat: a reinterpretation. Clin Sci Mol Med Suppl 1975; 48: 515–510.
12. Santella RN, Maddox DA, Gennari FJ: Delivery dependence of early proximal bicarbonate reabsorption in the rat in respiratory acidosis and alkalosis. J Clin Invest 1991; 87: 631–638.
13. Seifter JL: Acid-base disorders; in Goldman L, Schafer AI (eds): Goldman's Cecil Medicine, ed 25. Philadelphia, Saunders Elsevier, 2016.
14. Shear L, Kleinerman J, Gabuzda GJ: Renal failure in patients with cirrhosis of the liver. I. Clinical and pathologic characteristics. Am J Med 1965; 39: 184–198.
15. Wanders RJ, Meijer AJ, Groen AK, Tager JM: Bicarbonate and the pathway of glutamate oxidation in isolated rat-liver mitochondria. Eur. J Biochem 1983; 133: 245–54.