

Diplomarbeit

mABHC

mobile Acid Base Homeostasis Calculator

eingereicht von

Christian Müllner

zur Erlangung des akademischen Grades

Doktor der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Klinischen Abteilung für Endokrinologie und Diabetologie

unter der Anleitung von

Dr. med. univ. Martin Grübler, B.Sc.

&

Assoc. Prof. Dr. med. univ. Stefan Pilz, Ph.D.

Graz, 04.05.2017

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 04.05.2017

Christian Müllner eh.

Foreword

Today everybody owns a smartphone or some similar kind of electronical device. Because of that many normal tasks got a lot easier and quicker. For example, you can scan a complicated formula und get the right answer in under a few seconds. But what about medicine? In Medicine, there can be complex formulas and equations and it takes some time to solve them. Time that is not always available.

Because of this fact, the idea of making an application for any android based smartphone seemed logical to me. So, when my supervisor Martin Grübler approached me with his idea of developing an app for the acid base disturbances I immediately became interested.

We would make an app that could be able to make the work of many residents and physicians a lot more comfortable and help them save time.

Before I started studying medicine I went to school in HTL Graz Gösting and there I learned the basics of JAVA programming, which is the programming language of any Android based app. So, it wasn't that complicated for me to design and develop a prototype to identify basic acid base homeostasis disturbances.

Within this thesis, I am going to first outline the physiologic basics of the human acid base homeostasis and second make a short introduction in JAVA coding, as well as explaining the different steps the application makes in interpreting an arterial blood gas analysis (ABG) result.

Acknowledgement

First, I want to thank Martin Grübler for giving me the opportunity to do my diploma thesis under his supervision. I always liked coding and thinking outside the box and making smart algorithms which use the minimal possible effort but getting the maximal possible output. I have been missing programming since I got out of school and the challenges it brings and so I got the possibility to do something I like while writing my diploma thesis.

Also, I want to thank Univ. Prof. Dr. Stefan Pilz for being my supervisor and helping me testing my application by providing me with the necessary examples of acid base disturbances.

Zusammenfassung

Hintergrund: Die heutige Hochleistungsmedizin verlangt von den meisten Ärzten und Ärztinnen in kürzester Zeit einen Patienten zu untersuchen und die bestmögliche Therapie festzulegen. Da durch den Mangel an Zeit nicht alle benötigten Untersuchungen immer von Hand durchgeführt werden können, greifen immer mehr Krankenhäuser auf elektronische Hilfeleistungen zurück. Die Auswertung einer Blutgasanalyse BGA erhielt bisher keine adäquate elektronische Lösung.

Aufgaben: Das Ziel dieser Diplomarbeit war es eine Applikation für das Betriebssystem Android zu entwerfen welches sich auf einer großen Anzahl von Smartphones befindet. Diese App soll in der Lage sein eine BGA auszuwerten indem sie alle notwendigen Berechnungen durchführt. Dann dem behandelten Arzt oder der behandelten Ärztin in aufgearbeiteter Form präsentiert, somit Zeit spart und dabei unterstützt den/die PatientenIn bestmöglich zu behandeln.

Methoden: Programmierung und Design einer App in der Programmiersprache JAVA in der Entwicklungsumgebung Android Studio. Testen der App mittels bekannter BGA Beispiele aus der Literatur.

Ergebnisse: Die App mABHC wurde entwickelt und programmiert. Nach Fertigstellung des Prototyps konnte die App BGA Beispiel richtig deuten.

Diskussion: Weitere Entwicklung sowie Testung der App sind noch notwendig aber zurzeit ermöglicht es ÄrztenInnen Säure Basen Haushalt Störungen zu identifizieren und dabei keine komplexeren Störungen zu übersehen.

Abstract

Introduction: Because contemporary medicine needs its physicians to examine and diagnose their patients in a short period, more hospitals tend to integrate electronic systems in their processes. For the evaluation of an arterial blood gas analysis (ABG) so far, no adequate electronic system exists.

Objectives: The main aim of this diploma thesis has been to develop an application (app) for the operating system android, which is currently used on a great number of smartphones. This app should be able to interpret and analyse a ABG and give the clinician a short and effective method to do the workaround on a patient.

Methods: Developing and designing an app for android in the programming language JAVA. Testing and operating the app with known cases derived from the scientific literature.

Results: The app mABHC was programmed and developed. Afterwards the app mABHC was tested and was able to correctly analyse several known cases from the literature.

Conclusion: The app mABHC is able to assist the physician by helping to interpret a ABG result which otherwise would take more time. mABHC needs more developing and testing but right now it is possible to get a quick overview and with that the diagnostic process can be easier.

Table of contents

FOREWORD	III
ACKNOWLEDGEMENT	IV
ZUSAMMENFASSUNG	V
ABSTRACT	VI
TABLE OF CONTENTS	VII
FIGURES	X
LIST OF TABLES	XI
LIST OF CODE SNIPPETS	XII
1 INTRODUCTION	1
1.1 “ACID AND BASE” THE BRØNSTED-LOWRY THEORY	2
1.2 PH	3
1.2.1 HISTORY	3
1.2.2 THE SCALE	3
1.2.3 HENDERSON-HASSELBALCH EQUATION	4
1.3 BUFFER SYSTEMS	5
1.4 ORGANS	6
1.4.1 LUNGS	6
1.4.2 KIDNEYS	7
1.4.3 LIVER	10
1.4.4 GASTROINTESTINAL TRACT	11
1.5 BLOOD	12
1.5.1 BICARBONATE BUFFER SYSTEM	12
1.5.2 PHOSPHATE & PROTEIN BUFFER SYSTEMS	13
1.6 DISTURBANCES	14
1.6.1 ACIDOSIS	14
1.6.2 ALKALOSIS	18
1.7 STEWART APPROACH – STRONG ION DIFFERENCE	22
1.8 INTERPRETATION OF A ABG RESULT	24
2 JAVA AND ANDROID STUDIO	26

2.1	JAVA PLATFORM AND LANGUAGE	26
2.2	ANDROID STUDIO	27
3	<u>THE APPLICATION - MABHC</u>	<u>28</u>
3.1	INTRODUCTION	28
3.2	LAYOUTS	28
3.2.1	MABHC_OPENING_SCREEN_LAYOUT	28
3.2.2	MABHC_NEW_CALC_PRIMARY_LAYOUT	29
3.2.3	MABHC_NEW_CALC_ANION_LAYOUT	29
3.2.4	MABHC_NEW_CALC_RESULTS_LAYOUT	30
3.2.5	MABHC_CALC_ONLY_ANG_LAYOUT	30
3.3	THE CODE STRUCTURE	31
3.3.1	LIBRARIES	31
3.3.2	INITIALIZATION	32
3.3.3	SETTING THE VIEW	33
3.3.4	START CALC	33
3.3.5	ONBTNCLICK	34
3.3.6	BTNCALCANGCLICK	35
3.3.7	THE METABOLIC DISORDER	38
3.3.8	CALCULATE THE EXPECTED PCO_2 AKA WINTER'S FORMULA	39
3.3.9	THE RESPIRATORY DISORDER	44
3.3.10	CALCULATE EXPECTED HCO_3^-	46
3.3.11	WHAT IF THE PH IS NORMAL?	49
3.3.12	WRITE RESULTS OUT	51
3.3.13	CALC ANG	53
4	<u>EXAMPLES WITH CASES FROM THE LITERATURE</u>	<u>55</u>
4.1	MANUAL WORKAROUND	55
4.1.1	CASE 1 – POSTOPERATIVE CARDIAC ARREST	55
4.1.2	CASE 2 - A WEAK OLD LADY	56
4.2	WORKAROUND DONE WITH MABHC	57
4.2.1	CASE 1 – RESPIRATORY FAILURE	57
4.2.2	CASE 2 – ACCIDENT	58
4.2.3	CASE 3 – DIARRHOEA	59
5	<u>DISCUSSION</u>	<u>60</u>
6	<u>LITERATURE</u>	<u>61</u>

Figures

Figure 1: Overview of the acid base physiology [13]	5
Figure 2: HCO ₃ transport along the nephron. Most of it is reabsorbed in the proximal tubule. In the normal acid base homeostasis nearly 0% of HCO ₃ ⁻ is excreted with the urine [17].	7
Figure 3: HCO ₃ reabsorption in the PCT [17]	8
Figure 4: Schematic of NH ₃ production in the PCT [17]	9
Figure 5: Acid secretion in the stomach [20]	11
Figure 6: step by step approach of a ABG result.....	24
Figure 7: mABHC - systematic approach of analysing a ABG result.....	25
Figure 8: Java Technology logo [57].....	26
Figure 9: Android Studio logo [58]	27
Figure 10: Screenshot of the project mABHC in Android Studio.....	27
Figure 11: mabhc_opening_screen_layout.....	28
Figure 12: mabhc_new_calc_primary_layout	29
Figure 13: mabhc_new_calc_anion_layout.....	29
Figure 14: mabhc_new_calc_results_layout	30
Figure 15: mabhc_calc_only_ang_layout.....	30
Figure 16: Results of Case 1 - Respiratory failure with the app mABHC	57
Figure 17: Result of Case 2 - Accident with the app mABHC	58
Figure 18: Results of Case 3 - Diarrhoea with the app mABHC	59

List of tables

Table 1: pH in different areas in the human body [9]	3
Table 2: Examples for causes which lead to respiratory alkalosis [34].....	19
Table 3: Interpretation of the results from Winter's formula [50].....	40
Table 4: if-query for the case tempPH = 2; tempCO2 = 2; tempHCO3 = 2.....	42
Table 5: formula for calculating the expected HCO3 in the respiratory alkalosis	45
Table 6: formula for calculating the expected HCO3 in the respiratory acidosis	45
Table 7: interpretation of the calculated HCO3 values in the respiratory alkalosis	47
Table 8: ABG results for Case 1 - Postoperative cardiac arrest	55
Table 9: ABG results for Case 2 - A weak old lady	56
Table 10: ABG results for Case 1 - Respiratory failure	57
Table 11: ABG Results for Case 2 - Accident [54].....	58
Table 12: ABG results for Case 3 - Diarrhoea [54].....	59

List of code snippets

Code snippet 1: importing the needed libarys	31
Code snippet 2: globally initialization of the variables	32
Code snippet 3: floatValuePH	32
Code snippet 4: onCreate.....	33
Code snippet 5: onBtnStartNewCalcClick	33
Code snippet 6: parsing the entered values in the variables	34
Code snippet 7: analysing the input of pH	34
Code snippet 8: depending if the user entered the value of Na, the program calculates the ANG or not	35
Code snippet 9: interpreting the variables	36
Code snippet 10: if-query of the pH, HCO ₃ ⁻ , pCO ₂	37
Code snippet 11: if-query for the case of temp _p H = 1; temp _p CO ₂ = 1; temp _p HCO ₃ = 1....	38
Code snippet 12: CalculateExpectedpCO ₂	39
Code snippet 13: Result of an interpretation done with the app mABHC including the ANG	41
Code snippet 14: if-queries for metabolic disorders with normal pCO ₂	43
Code snippet 15: if-query for the case of temp _p H = 2; temp _p CO ₂ = 1; temp _p HCO ₃ = 1 ...	44
Code snippet 16: function CalculateExpectedHCO ₃	46
Code snippet 17: if-query for the case temp _p H = 1; temp _p CO ₂ = 2; temp _p HCO ₃ =2.....	48
Code snippet 18: if-query in the case of temp _p H = 3.....	49
Code snippet 19: if-query in the case of temp _p H = 3; temp _p CO ₂ = 1; temp _p HCO ₃ = 1	50
Code snippet 20: WriteResultsOut().....	51
Code snippet 21: output of the function WriteResultsOut().....	52
Code snippet 22: CalculateANG().....	53
Code snippet 23: check if the user wants the ANG calculated including potassium	54

1 Introduction

Acid base homeostasis disturbances are a central issue in many medical departments. Especially disciplines such as emergency medicine, intensive care medicine and nephrology commonly rely on accurate identification of acid base disturbances in order to support a clinical diagnosis or to guide therapeutic interventions [1].

The acid base homeostasis is important for nearly any process in the human body. If an imbalance occurs many enzymes can't work correctly, proteins are being degraded and physiologic cell functions are impaired. In the worst case, death of the human individual is possible. [2] This homeostasis is achieved through various systems in our body like the Bicarbonate buffer (which is the biggest blood and acute buffer system), the more minor ones like the phosphate buffer, the protein buffer and for the long-term effect: the kidneys and the liver.

As mentioned before there are many ways this quite important homeostasis can be disturbed, for example through excessive vomiting, drug abuse, hyperglycaemia, but also by extreme sports, diet, certain medication etc. Because of the variety of the buffers that can be imbalanced there are sometimes quite a few calculations to make before someone is able to draw clear conclusions. Most of the times the blood gas analysis won't take long to interpret, but depending on the environment might be missed from a lesser experienced physician [3]. More so, today many physicians don't have time to make four or five complicated calculations by hand before starting the treatment, so it may happen that acid base homeostasis disturbances could be left unseen and untreated. To prevent this, some physicians may use computers to make the calculations for them [4]. But in an emergency, it is not always possible to leave the patient's bedside, so the next logical step is to use modern electronic devices like the smartphone for the interpretation's and calculations [5].

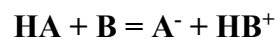
So I started the development of an application with the goal to save physician time, help them with interpreting ABG results and making the next treatment steps.

1.1 “Acid and base” the Brønsted-Lowry Theory

But first it is important to understand the meaning of the words acid and base. There are a few different traditional approaches to this question (also referred to as *descriptive* approaches), like the Brønsted-Lowry Theory, the Arrhenius Theory, the Lewis approach and the Usanovich approach. The most common used one is the Brønsted-Lowry Theory. In the year 1923 Johannes Nicolaus Brønsted and Thomas Martin Lowry introduced independently from each other a new concept of the acid base reaction [6] [7]. Till then the mostly used one was the Arrhenius Theory (1887). They both described an **acid** being a compound which is able to donate a proton H^+ to another compound which is then called conjugated **base**. The important new mechanism behind this theory was that a base can also be an acid by accepting a proton and an acid can also be a base by donating a proton and vice versa.



Or if you insert HA for the acid



In most books an acid is there by defined as a **H^+ donor** and a base as an **H^+ acceptor**.

The most important new finding of this theory was that an acid can only exist in relation with a base. They also defined water as a so called amphoteric substance, which means it can act as an acid and a base. Considering this theory, one important step towards understanding the human acid base homeostasis was possible:



With this formula it is possible to understand the balancing mechanism of the buffer system in the human body (see 1.3 Buffer systems).

1.2 PH

1.2.1 History

The term pH was originally introduced by a chemist named Søren Peder Lauritz Sørensen in 1909 and served the purpose of accommodating the definitions and measurements of the electrochemical cell. It is a numeric scale that displays the concentration of hydrogen ions. The exact meaning of the term pH is till today not fully clarified but it is assumed that it stands for “power of hydrogen” or “Potenz of hydrogen” [8].

1.2.2 The scale

Pure water is neutral which is corresponding to a pH of 7. If acid is added the pH will be less than 7 which is then called acidosis, if a base is added it will be greater than 7 which is called alkalosis. The blood in a human body obtains a pH of 7.4, if the acid base homeostasis is disturbed the pH will vary according to the disorder. In the human body not every area possesses the same pH, each cell or enzyme needs a different level to obtain its optimal function (for examples see Table 1 below).

Compartment	pH
Gastric secretions (under conditions of maximal acidity)	0.7
Lysosome	5.5
Chromaffin granula	5.5
Neutral H ₂ O at 37°C	6.81
Cytosol of a typical cell	7.2
Cerebral fluid (CSF)	7.3
Arterial blood plasma	7.4
Mitochondrial inner matrix	7.5
Secreted pancreatic fluid	8.1

Table 1: pH in different areas in the human body [9]

1.2.3 Henderson-Hasselbalch equation

The Henderson-Hasselbalch equation is used to describe the correlation between HCO_3^- , CO_2 and the pH. Lawrence Joseph Henderson studied the acid-base homeostasis and discovered that the complex mechanism takes place in collaboration between the lungs, the kidneys, the liver and the red blood cells. He then described the first formula which later on Karl Albrecht Hasselbalch rewrote to the Henderson-Hasselbalch equation as known today:

$$pH = pK_a + \log_{10} \left(\frac{[A^-]}{[HA]} \right)$$

Formula 1: Henderson-Hasselbalch equation

Applied to the human bicarbonate puffer system it is possible to relate the pH according to the level of bicarbonate HCO_3^- and CO_2 (Formula 2: Henderson-Hasselbalch equation applied to the bicarbonate buffer system).

$$pH = pK_{a_{\text{H}_2\text{CO}_3}} + \log \left(\frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_2]} \right)$$

Formula 2: Henderson-Hasselbalch equation applied to the bicarbonate buffer system [10]

Because in modern medicine this equation is mostly used in the arterial blood gas analysis it is common to use the partial pressure of CO_2 ($p\text{CO}_2$) instead of H_2CO_2 (Formula 3: Henderson-Hasselbalch equation as used).

$$pH = 6.1 + \log_{10} \left(\frac{\text{HCO}_3^-}{0.0307 * p\text{CO}_2} \right)$$

Formula 3: Henderson-Hasselbalch equation as used [11]

1.3 Buffer systems

The buffer system of the body are very important parts. Without them, sustaining life as we know it would not be possible. For example, a simple gastroenteritis with loss of gastric acid could result in coma or seizures, because some enzymes cannot work correct anymore or even lose their function completely [12].

As mentioned before there are different buffer systems:

- I. The lungs
- II. The kidneys
- III. The liver
- IV. The blood (contains bicarbonate buffer, phosphate buffer,...)

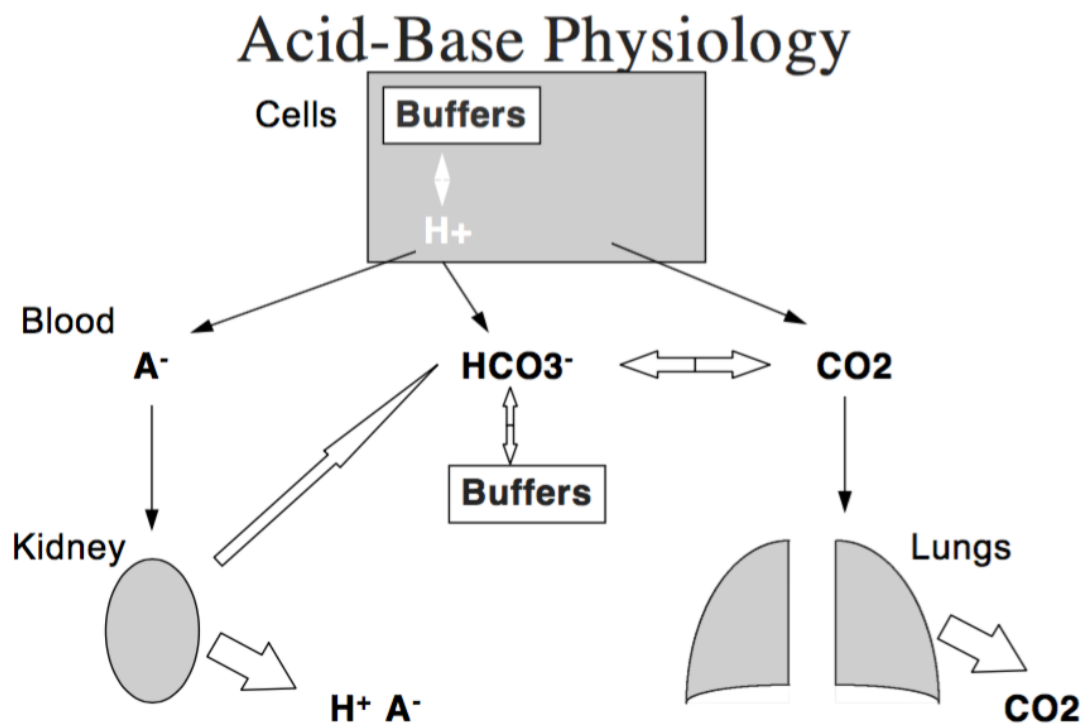


Figure 1: Overview of the acid base physiology [13]

1.4 Organs

1.4.1 Lungs

The lungs contain, in comparison with the other organs, the quickest organic method of compensating a (metabolic) acid base disorder. If the balance tilts towards an acidosis (the blood pH is lowered, too much free extracellular H^+ -ions (see 1.6.1 Acidosis)) the chemoreceptors in the Medulla oblongata are activated and the ventilation rate rises (hyperventilation) so that more CO_2 can be exhaled. Because more alveolar CO_2 is exhaled, more arterial CO_2 (aCO_2) is being transported to the lungs. Because the amount of aCO_2 is lowered the partial pressure of carbon dioxide pCO_2 is also lowered. According to the Henderson-Hasselbalch equation (see Formula 3: Henderson-Hasselbalch equation as used) and the fact that CO_2 counts as an acid, the pH rises towards a more balanced state [14].

Of course, this mechanism has its limits: If a severe metabolic acidosis is currently present it might not be possible to rise the ventilation rate high enough, so enough amount of CO_2 can be exhaled so that the acid base homeostasis can be balanced again. For example, it is not possible to maintain a respiratory rate of 40 over a long period, because of the rising respiratory work more energy is needed which usually the body can't offer [15].

Basically, it is possible that a metabolic alkalosis is compensated by hypoventilation, but because the lungs are also needed to maintain a certain oxygen level, this mechanism is rather limited.

The lungs may also be causes for an acid base disturbance as explained in

- 1.6.1.1 Respiratory Acidosis
- 1.6.2.1 Respiratory Alkalosis

1.4.2 Kidneys

In comparison, the kidneys are much less powerful in terms of excreting CO_2 out of the human body in comparison with the lungs (more specific: **kidneys 70-100 mmols/day vs lungs 12.000 to 13.000 mmols/day** [16]) but this is because these two organs have different tasks. As outlined previously, the lungs are the rapid acting mechanism in controlling the acid base balance (as mentioned in 1.4.1 Lungs) whereas the kidneys provide the long-term methods in holding the acid base homeostasis in a stable level. Of course, the kidneys are also able to act very fast if an imbalance occurs, but this is not a significant effect compared to the lungs.

If the pH is in the normal range (7.35-7.40 pH) the kidneys are excreting H^+ as well as ammonium (acid) and HCO_3^- . If an imbalance occurs for example an acidosis, the kidneys are now beginning to excrete more H^+ and ammonium and start reabsorbing HCO_3^- so that the pH can rise towards a normal level. If an alkalosis is present, the exact opposite is happening H^+ and ammonium are being reabsorbed (less excreted) and HCO_3^- is less reabsorbed [17].

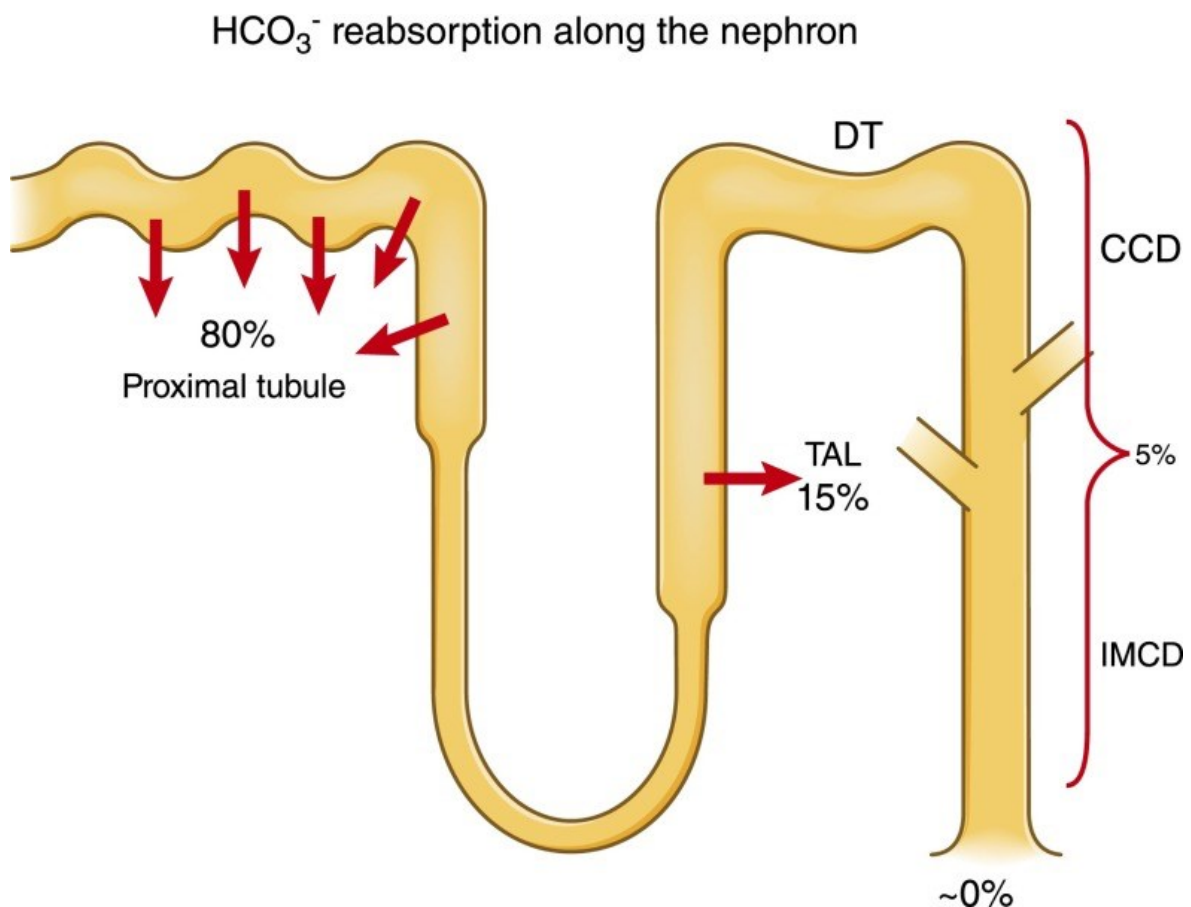


Figure 2: HCO_3^- transport along the nephron. Most of it is reabsorbed in the proximal tubule. In the normal acid base homeostasis nearly 0% of HCO_3^- is excreted with the urine [17].

Most of the filtered HCO_3^- (85%) is being reabsorbed in the proximal convoluted tubule (PCT). After HCO_3^- enters the PCT Lumen it cannot pass the membrane into the cell, so the body would lose all of it. Because this would result in a major acid base imbalance bicarbonate is combined with a free H^+ -ion and forms H_2CO_3 then diverts into $\text{H}_2\text{O} + \text{CO}_2$ which both can pass the membrane into the cell. In the cell, they both recombine to H_2CO_3 and finally back to HCO_3^- and H^+ . The free H^+ -ion can now be returned into the PCT Lumen and the HCO_3^- is transferred into the bloodstream via a Na^+ - HCO_3^- symporter (see Figure 3: HCO_3 reabsorption in the PCT).

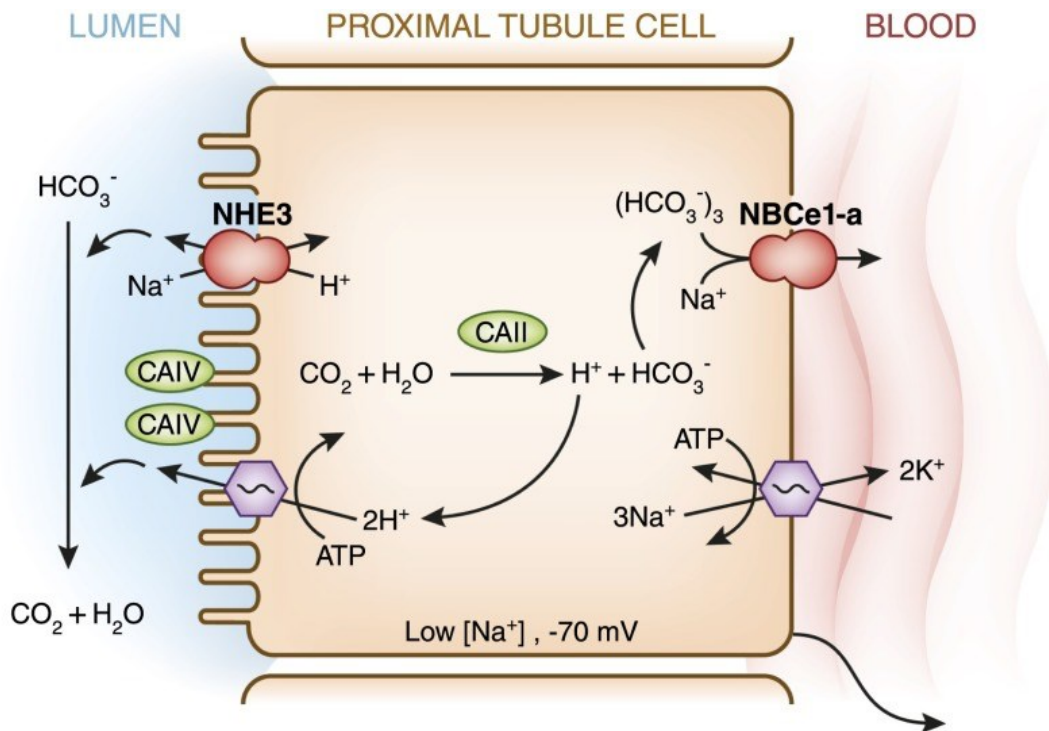


Figure 3: HCO_3 reabsorption in the PCT [17]

Ammonium NH_4^+ is a weak acid and therefore also important in the acid base homeostasis. Primarily it is formed out of glutamine in the proximal tubular cells. In the cell the enzyme glutaminase forms glutamate and NH_4 out of glutamine (see Figure 4: Schematic of NH_3 production in the PCT). The next step in this reaction makes out of the glutamate one NH_4 and alpha-ketoglutarate. The alpha-ketoglutarate is then metabolized into glucose (gluconeogenesis). For every glutamine which enters this cycle two HCO_3^- are also created this is a very important mechanism in compensating an acidosis. A defect in the ammonia excretion leads to the hyperkalaemia renal tubular acidosis (Typ IV renal tubular acidosis) [17].

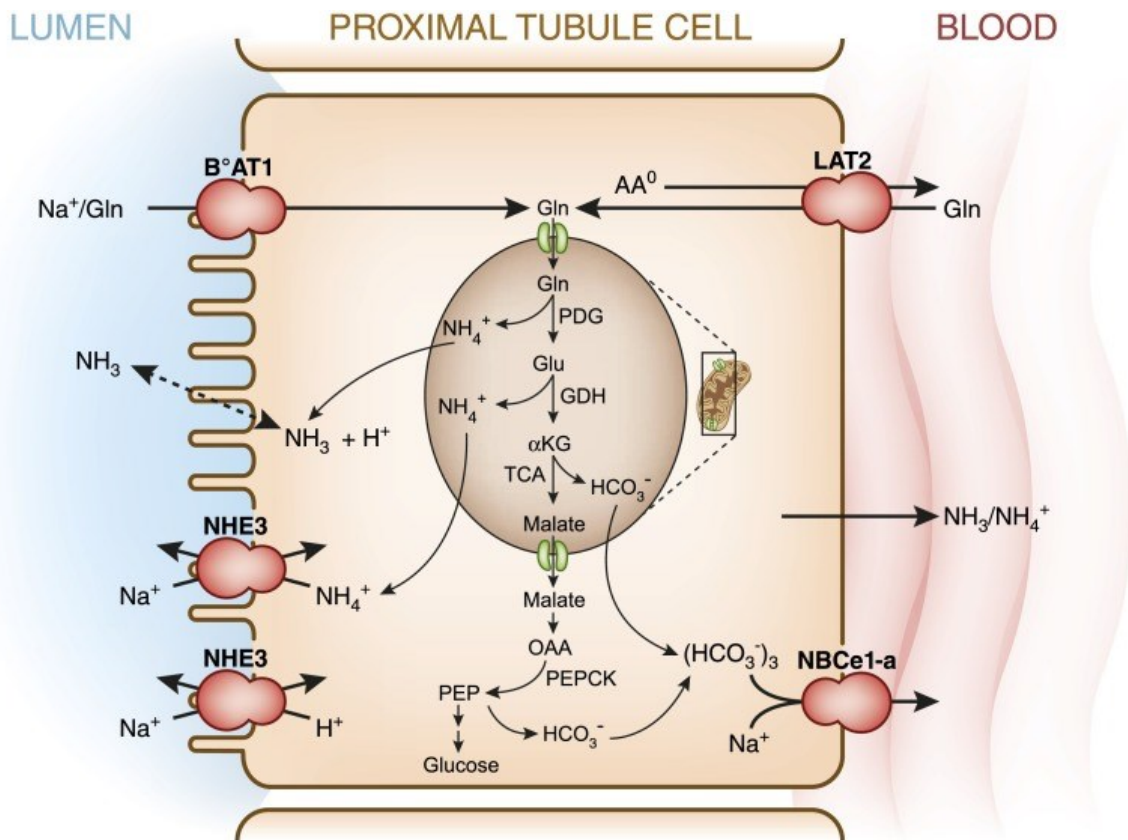
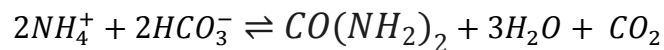


Figure 4: Schematic of NH_3 production in the PCT [17]

1.4.3 Liver

Discussing the acid base homeostasis mechanisms always leads to the two main organs in this system: the lungs and the kidneys. But according to new findings and studies the liver also plays a very important role in maintaining a constant pH level. The liver is able to produce urea $\text{CO}(\text{NH}_2)_2$ which is important for getting rid of the toxic ammonium. For this process NH_4^+ and HCO_3^- is needed (see Formula 4: Urea synthesis). Ammonium is a very toxic substance and is already at a slightly increased amount able to make neurological problems such as: cognitive impairment, reduction of efficiency of the central nervous system and in the worst case a toxic coma can occur. For the process of producing urea, the liver uses the same enzyme as the kidneys: glutaminase, to obtain NH_3 and glutamate. Urea, as a small neutral molecule, is able to pass cell membrane and can therefore be eliminated mostly through the kidneys and partially through the GI-tract. Because of that no free H^+ -ion can be removed out of the body via the kidneys [18].

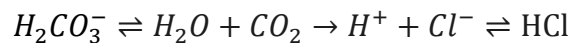


Formula 4: Urea synthesis

If an acidosis is present the liver reduces the production of urea, by slowing down the enzyme glutaminase, so that the kidneys can use the glutamine to get rid of the free H^+ -ions and thus compensate the acidosis. If an alkalosis occurs the liver produces more urea so that there is less free glutamine for the kidneys and therefore more free H^+ -ions. This explains the clinical observation that if a liver insufficiency is present a metabolic alkalosis may occur. As more free glutamine for the kidneys accumulate this results in less free H^+ -ions, because they are being removed with NH_4^+ via the urine. In the case of a kidney insufficiency a metabolic acidosis is present (kidney function is reduced and less H^+ -ions can be excreted).

1.4.4 Gastrointestinal tract

The GI-tract plays only a small active role in maintaining the acid base homeostasis but it is possible that a disorder has its origins there. For the acid milieu in the stomach, which is needed for digesting food and disassembling proteins etc., H^+ -ions are needed. The parietal cells are located in the fundus and the body of the stomach and produce hydrochloric acid **HCl** and the **intrinsic factor** (important for the Vitamin B12 absorption). For producing HCl CO_2 or $H_2CO_3^-$ is needed and in this process HCO_3^- is made:



Formula 5: production of HCl in the parietal cells

If the gastric acid reaches the duodenum the realising of HCO_3^- rich pancreatic juice is induced and the previously created HCO_3^- is used. This explains why vomiting leads to a disequilibrium of producing and reducing HCO_3^- . Therefore, excessive vomiting over some time can result in an alkalosis because of loss of H^+ ions and Chlorid.

On the other hand, diarrhoea commonly (although there are exceptions) induces the loss of HCO_3^- , an excessive loss of fluid and a relative increase in Chlorid, which – taken together – lead to a metabolic acidosis [19].

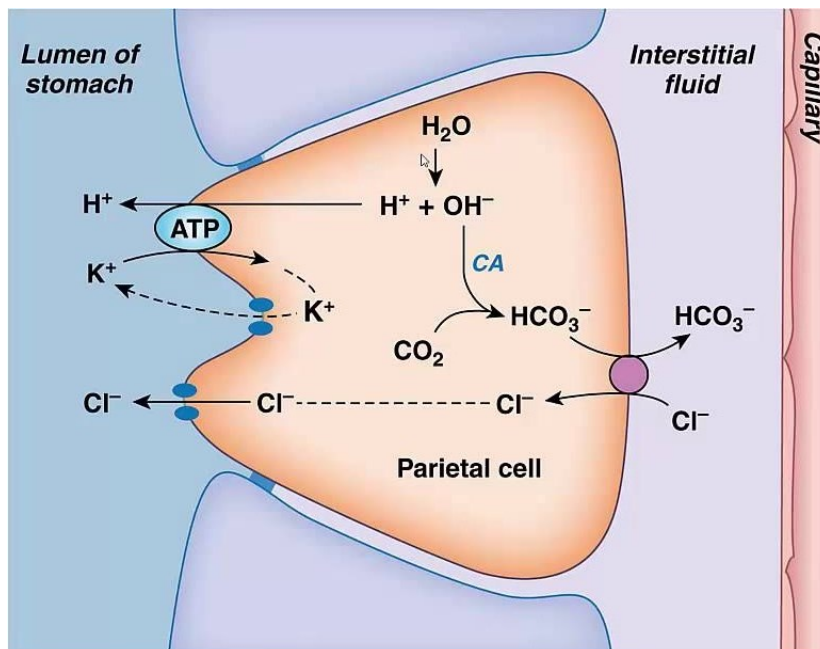


Figure 5: Acid secretion in the stomach [20]

1.5 Blood

The human body has possibilities of buffering in the blood. Erythrocytes are able to act as buffer by compensating small changes through the H⁺ accepting imidazole-ring of haemoglobin. This effect is under normal circumstances magnitudes more relevant than the total of plasma proteins. It bears mentioning that there are quite a number of different buffers, but only a few of were found to be of relevance in the clinical context. The main equation in this buffer system is the Henderson-Haselbalch equation as outlined before:



1.5.1 Bicarbonate buffer system

The bicarbonate buffer system is also part of the buffering system of the blood. Among others, the “Hamburger shift” leads to an exchange of Cl⁻ and HCO₃⁻ at the surface of the erythrocyte. This shift is crucial to enable the blood to adapt to acid-base disturbances before “reaching” the other buffer system, such as the lungs or the kidneys.

If too much free H⁺-ions are present they are bound to the bicarbonate and carbonic acid is formed (see below).

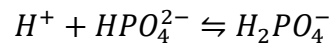


This new carbonic acid then dissociates in the CO₂ and H₂O and the CO₂ can be exhaled through the lungs. Obviously, without the correctly functioning lungs it is not possible to buffer this form of an acidosis over a longer period. If the blood is too acidic the carbonic acid rapidly dissociates into a H⁺-ion and HCO₃⁻, what further limits the blood buffer system to counter an acid base homeostasis disturbance. The bicarbonate buffer system of the blood is a very important first line defence against acid base disturbances, but as outline before it is limited in its options and depends on the function of the organs.

1.5.2 Phosphate & protein buffer systems

The phosphate & protein buffer systems also contribute their parts into keeping the acid base homeostasis within the normal range. But both are not quite as efficient as the lung-bicarbonate system. The phosphate buffer plays its role mainly in the cell and the protein buffer in the blood.

Phosphate buffer



Formula 6: phosphate buffer system

If there are too many free H^+ -ions and the homeostasis tilts to an acidosis, the phosphate buffer binds two H^+ -ions and forms dihydrogen phosphate $H_2PO_4^-$. $H_2PO_4^-$ can then be excreted through the kidneys [21].

Protein buffer

The protein buffer system is depending on the quantity the largest buffer system in the blood. Because albumin like haemoglobin also got a imidazole-ring, which can be ionized (protonated), they can serve as a buffer in the blood system. According to the Stewart approach (see 1.7 Stewart approach – Strong ion difference) the protein buffer plays a major role in the acid base homeostasis but with the normal uncorrected Schwartz-Bartter approach it is possible to miss an acid base homeostasis disturbance because it is not visible as a change in HCO_3^- or pCO_2 . It is possible that a nephrotic syndrome causes a Hypalbuminaemia and this may cause or aggravate some problems in the acid base homeostasis. This, however, is till today not fully understood and currently matter of debate [22].

1.6 Disturbances

1.6.1 Acidosis

„A metabolic state characterised by an increase in H⁺ concentration that occurs when the body can't buffer free H⁺ in the blood, which is due either to an accumulation of acid or depletion of the alkaline reserve bicarbonate, resulting in decreased pH in the blood.” [23]

The terms acidosis and acidemia are most of the times used interchangeably by physicians or general medicine personnel but the meaning of this two words is actually different. The term acidosis refers to all processes and chemical reactions which lead to a lowered pH. If the pH, which is measured most of the times in the arterial blood, is decreased under 7.35 an acidemia is present. The term means an abnormal low pH in the arterial blood, knowing that an acidemia cannot be present without an acidotic process. Based on the underlying mechanism acidosis is very broadly divided in metabolic and respiratory acidosis.

1.6.1.1 Respiratory Acidosis

Respiratory acidosis occurs because of alveolar hypoventilation. Because of the rapid production of new CO₂ and the disturbed clearance of the CO₂ in the lungs, the amount of aCO₂ (arterial CO₂; the amount of CO₂ in the arterial system) and therefore the PaCO₂ (Partial arterial pressure CO₂; the partial pressure which the amount of CO₂ in the arterial system generates) rises above its normal range (**PaCO₂ 35-45 mmHg**). The state of a PaCO₂ higher then 45 mmHg is called **hypercapnia**.

The effect can be approximated by the Henderson-Hasselbalch formula. The lower ratio of HCO₃⁻/PaCO₂ results in fall in pH (see below).

$$\downarrow pH = 6.1 + \log_{10} \left(\frac{HCO_3^-}{0.0307 * PaCO_2} \right)$$

There are in principle two different forms of a respiratory acidosis: an **acute** and a **chronic form**. The acute respiratory acidosis occurs because of a sudden change in the ventilation. This could be because of a drug or nervous system diseases induced respiratory depression, acute trauma to the thorax which lead to a reduced ventilation (e.g. rib fractures) and a variety of medical conditions such as those associated with bronchoconstriction [24]. The hallmark of respiratory acidosis is visible in the ABG with a rise of **PaCO₂ over 45 mmHg**. When the PaCO₂ rises (acutely), the pH falls and the human body needs to counter-regulate. An imbalance of the acid base homeostasis may aggravate the main diseases process (cell death, enzyme failure etc.). The first line compensatory mechanism is the bicarbonate buffer system which jumps into action in a few minutes. After that the kidneys and the liver also start their work, but this mechanism takes some time (hours till days [25]). Because **plasma HCO₃⁻ only rises 1 mmol/l for every 10 mmHg PaCO₂** the increase of the HCO₃⁻ amount is rather small [26].

If a pulmonary disease raises the amount of CO₂ slowly the body is most of the times able to maintain a static pH-level which then results in a chronic respiratory disorder. For example COPD [27], but there are other, non-pulmonary diseases, that can also lead to a chronic respiratory acidosis such as scoliosis, obstructive sleep apnoea, neuronal diseases (ALS, Myasthenia gravis) [28]. Most of the times these diseases result in a reduced ventilation (hypoventilation) for various reasons with CO₂ retention that is compensated metabolically. Nevertheless, it should be kept in mind that the diseases processes and their interaction with the acid base equilibrium are highly complex.

The chronic form of a respiratory acidosis lasts over a longer period and so the kidneys and the liver can reach their maximum of counter regulation. In this situation for every **10 mmHg PaCO₂** a **HCO₃⁻ rise of approximately 3.5 to 4 mmol/l** is possible. [29] On the other hand, an acute change of PaCO₂ from 50 to 60 mmHg results in a rise of HCO₃⁻ of 1 mmol/l. After a few days a new steady state would be reached with the same amount of PaCO₂ results in a rise of HCO₃⁻ of 4 mmol/l because of the kidneys and the liver [27].

1.6.1.2 Metabolic Acidosis

A metabolic acidosis can occur if there is a pathologic process that leads to an increase in free H⁺ ions in the body. This can either be by an increased acid concentration or a loss in HCO₃⁻. In words of the Brønsted–Lowry definition there is an increase in compounds that donate a proton. If the compound is not CO₂, then the clinical definition is metabolic acidosis.

One important marker for the metabolic acidosis is the anion-gap (ANG). The ANG refers to the unmeasured ions such as Na⁺, Cl⁻, K⁺ and others (Ca²⁺, Mg²⁺, etc.). But because these three are the most common to be measured they are used to calculate the ANG. With the ANG it is possible to divide the metabolic acidosis in three sub forms:

- High Anion-Gap Metabolic Acidosis (HAGMA):
 - o Ketoacidosis
 - o Lactic acidosis
 - o Renal failure
 - o Toxins
- Normal or Hyperchloremic Anion Gap Metabolic Acidosis (NAGMA):
 - o Renal failure
 - o Gastrointestinal causes (severe diarrhoea,...)
- Low Anion Gap Metabolic Acidosis (LAGMA)
 - o Most commonly because of hypalbuminaemia

This is important because these three different forms have different underlying diseases and therefore the anion-gap can be useful for differential diagnosing.

$$ANG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

Formula 7: ANG formula

Some clinicians don't include potassium (K⁺) in the calculation and therefore the adjusted ANG formula is used.

$$ANG = Na^+ - (Cl^- + HCO_3^-)$$

Formula 8: adjusted ANG formula

A hyperchloremic metabolic acidosis occurs for example in the setting of severe acute renal failure where massive losses of HCO_3^- may be present. This can be also approximated with the Henderson–Hasselbalch equation(see below).

$$\downarrow pH = 6.1 + \log_{10} \left(\frac{\downarrow \text{HCO}_3^-}{0.0307 * \text{PaCO}_2} \right)$$

If a massive gain of acid is present (e.g. diabetic ketoacidosis) the pH lowers because the acid base homeostasis is imbalanced towards the acids. The counter-regulation process is now mainly performed by the lungs and the bicarbonate buffer system. As soon as the chemo receptors detect the evaluated amount of arterial CO_2 hyperventilation starts to get rid of the unnecessary amount of carbon dioxide. This mechanism reaches its maximum approximately in a day [30]. With the **Winter's formula** [31] it is possible to calculate the amount of PaCO_2 which should be present after the lungs reach their full compensatory capacity. If the measured PaCO_2 is lower than the calculated/estimated one, then a respiratory acidosis is also present. On the other hand, if the estimated PaCO_2 is higher, then this would indicate that a respiratory alkalosis is also present. In other words, the Winters formula allows detection of combined (double) disturbances of the acid base balance. A common example is the metabolic compensation of a chronic respiratory acidosis. It is also possible to use it for the metabolic alkalosis.

$$\text{PaCO}_2 = (1.5 \times \text{HCO}_3^-) + 8 \pm 2$$

Formula 9: Winter's formula for metabolic acidosis

1.6.1.3 Delta Ratio

The Delta Ratio or Delta Delta Ratio is useful in differentiating the result of the calculated ANG to identify a potential mixed metabolic acidosis. The Delta Ratio is calculated with the increase in the ANG and the decrease of HCO_3^- . In the ketoacidosis for every mmol/l increase of the ANG a mmol/l decrease of HCO_3^- should be made. In lactat acidosis a 1:0.6 ratio is present (meaning for every mmol/l ANG increase 0.6 decrease of HCO_3^- should be present). If the Delta Ratio is 0 ± 5 mmol/l a HAGMA is present. If the Delta Ratio is above 5 mmol/l a HAGMA and a metabolic alkalosis is likely present. If it is lower than -5 mmol/l a combined HAG + NAG metabolic acidosis is possible [32].

1.6.2 Alkalosis

“An abnormal condition of body fluids, characterized by a tendency toward a blood pH level greater than 7.45 caused by an excess of alkaline bicarbonate or a deficiency of acid. There are two types: respiratory alkalosis and metabolic alkalosis.” [33]

As for acidosis there are also two different terms: **alkalosis** describes the processes which decrease the amount of free H^+ -ions and therefore rising the pH-level. The term **alkalemia** is used to describe the state of a raised blood pH-level above 7.45. Although in clinical practice the terms are used interchangeably. Similar to acidosis, there are in principle two different pathological ways which can lead to a decrease in free H^+ -ions:

- A respiratory mechanism resulting in decreased $PaCO_2$
- A metabolic mechanism resulting in an increase in “proton accepting” compounds.

1.6.2.1 Respiratory Alkalosis

The respiratory alkalosis is a common issue, because many diseases cause pain and this results in an increased ventilation (hyperventilation) which then ends in a lowered CO₂ and therefore less free H⁺-ions. In fact, by definition every respiratory alkalosis is the result of hyperventilation. Although there are many different diseases which lead to or are associated with hyperventilating:

Causes:	
Central	<ul style="list-style-type: none"> - Head injury - Stroke - Psychogenic hyperventilation - Pain, fear, stress - Drugs (salicylate intoxication!,...)
Hypoxaemia	
Pulmonary	<ul style="list-style-type: none"> - Pulmonary embolism - Pneumonia - Asthma - Pulmonary oedema

Table 2: Examples for causes which lead to respiratory alkalosis [34]

Because of the hyperventilation the amount of alveolar CO₂ is reduced (normal amount PaCO₂ 35-45 mmHg) this leads to a reduction of the arterial CO₂ and PaCO₂ and therefore the amount of H⁺-ions is reduced. The HCO₃⁻/PaCO₂ ratio rises and according to the Henderson-Hasselbalch equation the pH is also elevated.

$$\uparrow pH = 6.1 + \log_{10} \left(\frac{HCO_3^-}{0.0307 \cdot \downarrow PaCO_2} \right)$$

As outlined before the first compensatory mechanism is the bicarbonate buffer system. Because of the loss of CO_2 through the lungs more CO_2 is produced intracellularly by the carboanhydrase enzyme, which combines HCO_3^- and H^+ to form H_2CO_3 . In a second step carbonic acid dissociates into CO_2 and H_2O what then results in the increase in H^+ -ions. Commonly the body can not compensate the full loss of CO_2 with this mechanism so the **pH will rise**. It is visible in the ABG results as an **acute respiratory alkalosis** (pH rises, pCO_2 is decreased, HCO_3^- is initially normal). The kidneys are the next step in fighting this disorder, but they need around two till three days before they reach full capacity. After this the **pH should be within or near the normal pH-level** if the underlying pathology persists. This is called a **chronic respiratory alkalosis**. The kidneys achieve this with a decreased reabsorption of bicarbonate. This mechanism is **limited** to a **minimum** of HCO_3^- of **12-20 mmol/l**. **Below that** the physician should also **think about a coexisting metabolic acidosis** (see also delta ratio and anion gap).

1.6.2.2 Metabolic Alkalosis

A **metabolic alkalosis** is based on either an **elevated HCO_3^-** or a **loss of free H^+ -ions**. There are many different ways in which one of these two problems can occur. Beside the causative pathologic mechanism, the initial cause and a maintenance process should be distinguished. Because the kidneys are able to hold the blood HCO_3^- concentration in a steady state around 24 mmol/l even in a large excess of bicarbonate, an initial cause without a maintenance process would not result in a sustained alkalosis.

Initial causes can be [35]:

- Any gain of alkalic substances (e.g. through infusions)
- Loss of H^+ -ions (e.g. gastric via vomiting through kidneys via diuretics (frusemide, thiazide), hypokalemia, hyperaldosteronism)

As outline before, a metabolic alkalosis alone without a maintenance mechanism would usually not be enough to be a serious health threatening problem.

Volume depletion (especially through aldosterone activation) can also contribute or cause a metabolic alkalosis. This observation is likely because volume depletion results in the increased secretion of H^+ -ions into the proximal tubule lumen so that a Na^+ -ion and H_2O can be reabsorbed in the nephron. But as for every excreted H^+ -ion a bicarbonate is created

beyond a certain point bicarbonate accumulates and shifts the pH upwards. The same problem occurs with chloride depletion. It has to be mentioned that this matter is currently matter of debate if the volume depletion or the chloride depletion is the trigger, although it is commonly impossible to differentiate the effects of these two. [36]

There are other mechanism which also maintain a metabolic alkalosis, but they intrinsically related to the pathophysiology already discussed. (taken from [37]):

- Primary hyperaldosteronism (Conn Syndrome)
- Cushing's diseases
- Secondary hyperaldosteronism
- Some drugs (e.g. carbenoxolone)
- Excessive licorice intake (glycyrrhizic acid)
- Bartter's syndrome (Syndrom of anti-diuretic hormone resistance or deficiency)
- Severe potassium depletion

Because HCO_3^- raises or the amount of free H^+ -ions are lowered (which means more HCO_3^- is produced) the pH-level is elevated what can again be estimated through the Henderson-Hasselbalch equation:

$$\uparrow pH = 6.1 + \log_{10} \left(\frac{\uparrow \text{HCO}_3^-}{0.0307 * PaCO_2} \right)$$

The compensatory process of the metabolic alkalosis includes to a certain degree hypoventilation, which can also lead to problems [38], [39] (e.g. respiratory acidosis see above). If the metabolic alkalosis is very severe and the response is a great reduction of the ventilation, a hypoxemia can occur. Therefore, it is important to maintain a high normal pO_2 level and depending on the level also to increase the fiO_2 . Note: A decrease of ventilation may not be present because of pain, stress or other stimuli that offset the chemoreceptor activation by the metabolic alkalosis.

1.7 Stewart approach – Strong ion difference

The Strong ion difference or Stewart approach was developed by Peter Stewart in 1981 as a method on approaching an acid base homeostasis disorder. It belongs to the so called *quantitative* approaches to the interpretation of acid base disorders. The difference between the common used Schwartz-Bartter approach (based on the Brønsted-Lowry Theory) and the Stewart approach is their definition of an acid and a base. Stewart defined an acid as a substance which shifts the equilibrium of water to a higher level of H⁺-ions and less OH⁻ ions. Because of this definition bicarbonate is not an independent variable but a depended one and can therefore not alter the blood pH by itself [40]. According to the approach there are a few variables which are responsible for the blood pH [41]:

- the strong ion difference SID which is basically calculated from the measured anions (Cl⁻ and lactate) and cations (Na⁺⁺, K⁺, Ca⁺⁺, Mg⁺⁺):

$$SID_{app} = Na^{++} + K^{+} + Ca^{++} + Mg^{++} - Cl^{-} - lactate^{-}$$

Formula 10: calculation of the apparent SID SID_{app} [42]

- the arterial pressure of carbon dioxide (PaCO₂)
- the plasma concentration of non-volatile weak acids (ATot); normally the ATot is formed by phosphate and the ion equivalence of albumin

According to these three variables he also defined six main disorder forms of the acid base homeostasis:

- respiratory acidosis
- respiratory alkalosis
- strong ion acidosis
- strong ion alkalosis
- non-volatile buffer ion acidosis
- non-volatile buffer ion alkalosis

For example, if the anion lactate is elevated the SID_{app} is lowered beneath its normal range of 40 mmol/l and the homeostasis tilts towards an acidosis. The effective strong ion difference (SID_{eff}) can be calculated based on the components of ATot and pH with this formula:

$$SID_{eff} = (12.2 * pCO_2 / 10^{-pH}) + 10 * [Albumin * (0.123 * pH - 0.631)] + [PO_4 * (0.309 * pH - 0.469)]$$

Formula 11: calculation of SID_{eff}

With the SID_{eff} and the SID_{app} the strong ion gap SIG can be calculated:

$$SIG = SID_{app} - SID_{eff}$$

Formula 12: calculation of SIG

The strong ion gap should be zero, if it is elevated an acidosis might be present.

Most of the physicians are using the more common approach based on the Brønsted-Lowry theory, but over the last decades the Stewart approach gained more and more attention because it includes albumin into its calculation process. Because the Stewart approach needs much more calculations and includes more different variables which are all open to measuring mistakes most physicians still tend to use the more established Schwartz-Batter approach. Also it is possible to recognize a hypalbuminaemia by calculating the anion gap and then by adjusting the calculation process a similar outcome to the Stewart approach can commonly be achieved. Nevertheless, even the Stewart approach has limitations and cannot be full model of the highly complex subject of acid base disturbances [43]. From a clinical point of view both the descriptive approaches (e.g. Brønsted-Lowry) and the quantitative approaches (e.g. Stewart) align in many cases. Newer approaches like the ion equilibrium theory may help to unify descriptive and quantitative interpretations of acid base chemistry, but they remain subject of ongoing research [44].

1.8 Interpretation of a ABG result

Knowing which form of an acid base homeostasis disorder is present a systematic approach should be done with every interpretation of a ABG result. There are many options on how to approach a blood gas analysis. Shown below is the approach which is used by mABHC [45]:

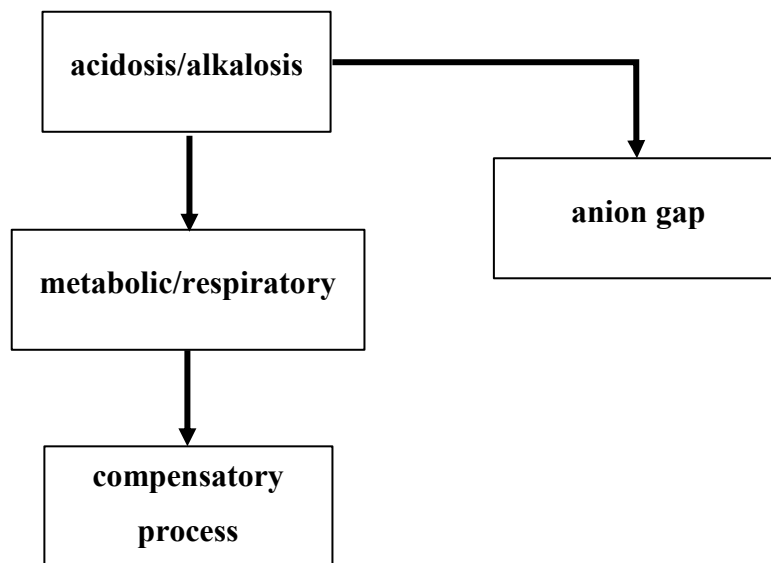


Figure 6: step by step approach of a ABG result

For a detailed systematic approach see Figure 7: mABHC - systematic approach of analysing a ABG result on the next page.

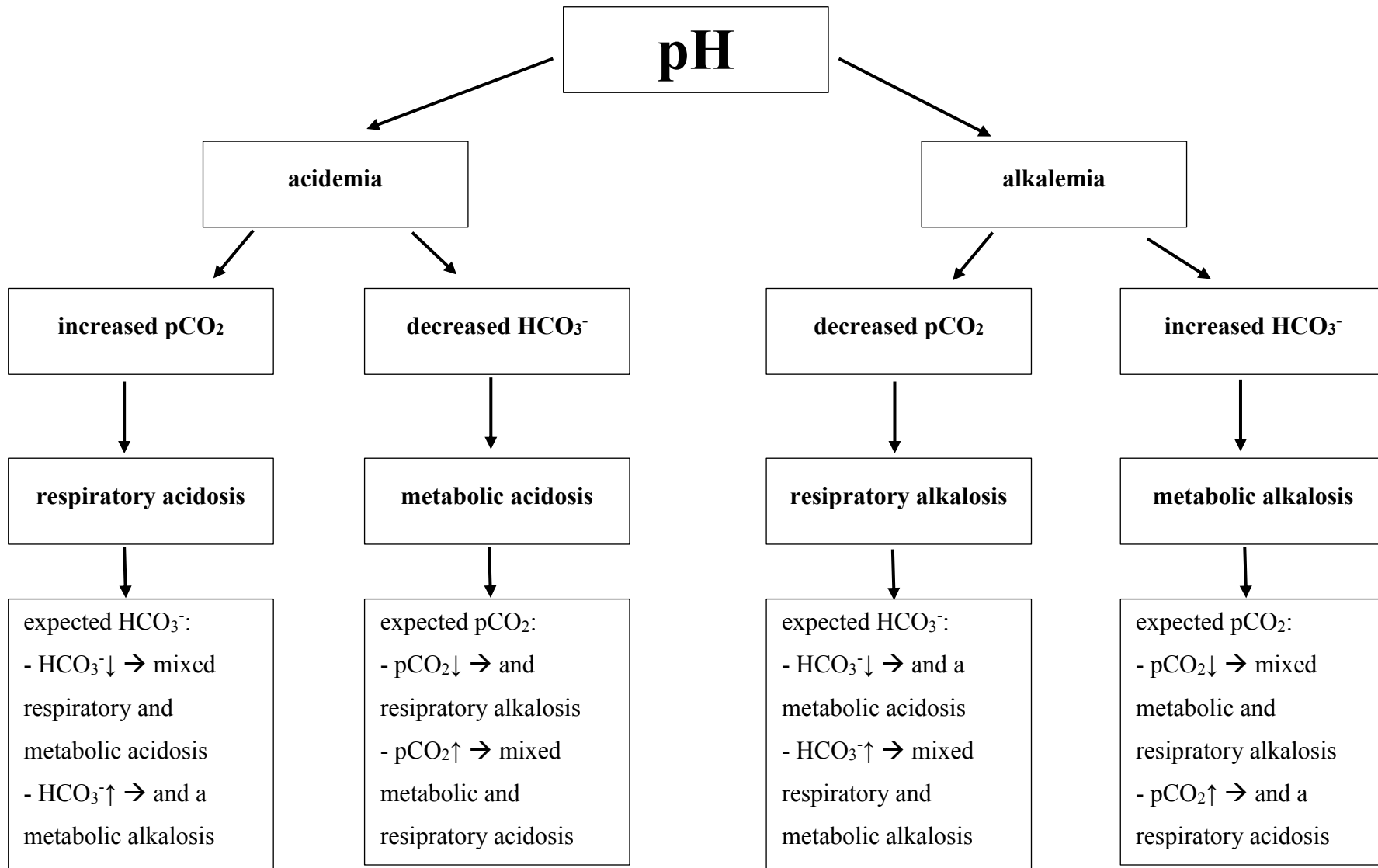


Figure 7: mABHC - systematic approach of analysing a ABG result

2 JAVA and Android Studio

2.1 Java platform and language

Java is a platform which contains many items for developing and coding, for instance it contains the java programming language which the mABHC is coded in. Not only it contains the programming language but also the java virtual machine (executes the code), many different programming languages, the java development kit (important for programming an android application).



Figure 8: Java Technology logo [57]

The project java was started in 1990 by engineer Patrick Naughton at Sun Microsystems. First the project was called “oak” but due to copyright problems the developers came up with the name java (java is a strong coffee bean which is used to make a strong espresso the developers liked). The first intended use of this platform was for the television industry, but because it was too advanced they decided to develop in another direction [46].

There were five principles for the java language [47]:

- 1) It must be "simple, object-oriented, and familiar".
- 2) It must be "robust and secure".
- 3) It must be "architecture-neutral and portable".
- 4) It must execute with "high performance".
- 5) It must be "interpreted, threaded, and dynamic".

These five principles could be combined in one: developing a language which can be used by everyone and everywhere with high performance and maximum safety. Every developer should be able to code with this language and it is intended to be easy portable on different devices (computer, smartphone, smart TV etc.).

The today most broadly used smartphone operating system Android uses the java language and many applications are developed in android studio (see 2.2 Android Studio), which uses the java development kit. Broadly speaking the main limitations and disadvantages of Java relate to performance and architectural issues.

2.2 Android Studio

Android studio is an android software development tool developed and designed by google which also produces the operating system android. Android studio was first announced in 2013 at an IT-conference and the first version was released shortly after. It is also referred to as integrated development environment (IDE).

The current version which is used to develop the app mABHC is 2.2.3. Android Studio is a free IDE which allows those familiar to Java and HTML to design their apps. Also, it is possible to submit your developed app into the app store and sell it directly.



Figure 9: Android Studio logo [58]

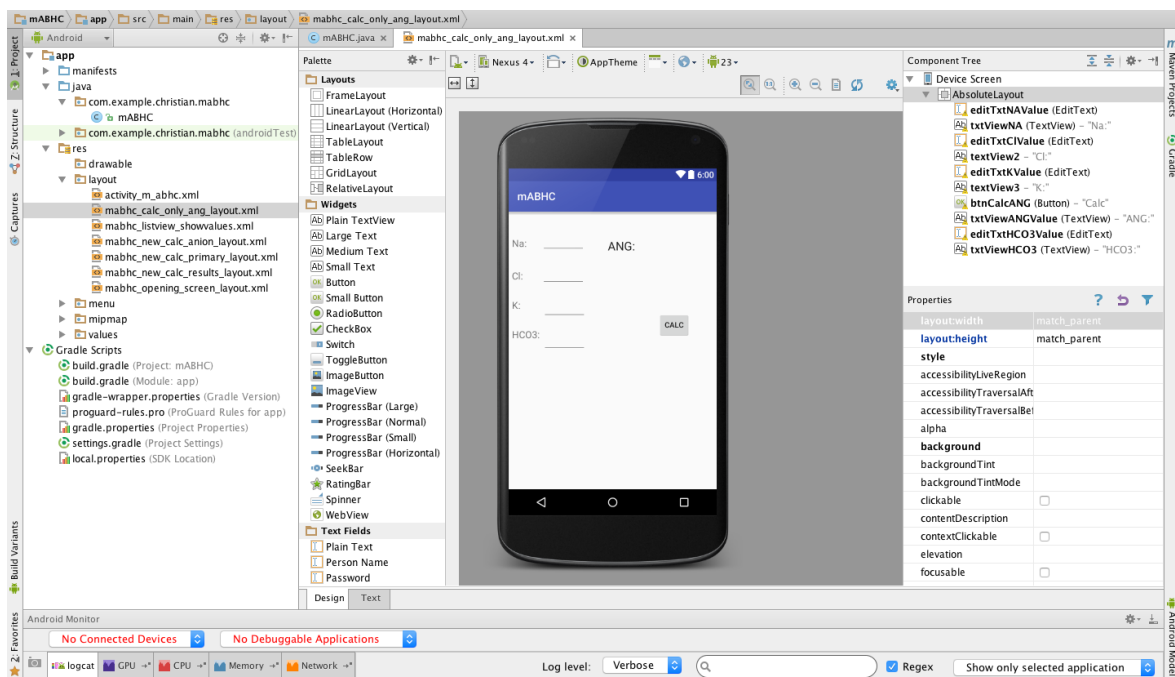


Figure 10: Screenshot of the project mABHC in Android Studio

3 The application - mABHC

3.1 Introduction

The following sides are explaining the function of the app mABHC. Describing the different steps which are made while interpreting the entered ABG result.

Fist a term explanation:

- layout – describing the current screen the user is seeing containing different components like textview, textedit, buttons etc.
- textview – displaying some text which the user cannot press or edit
- textedit – an editable text filed in which the user can enter something (values of Na⁺, K⁺, pH, etc.)
- Buttons – a button that can be pressed by the user and starting a process (go to the next screen, start the calculation, etc.)

3.2 Layouts

3.2.1 mabhc_opening_screen_layout

This layout contains two buttons which allow the user to choose between starting a new calculation and interpretation a ABG result (START CALC) or to only calculate the anion gap (CALC ANG).

Two text fields remind the user to always check the results of the calculation with the patient's history and clinic.

The button START CALC sets the view of the application to mabhc_new_calc_primary_layout.

The button CALC ANG sets the view to mabhc_calc_only_ang_layout.

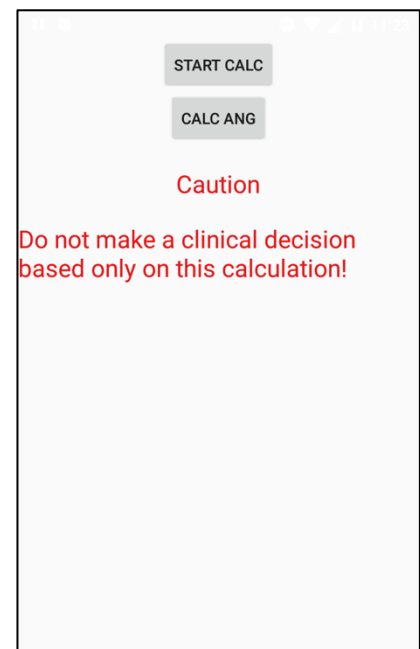


Figure 11:
mabhc_opening_screen_layout

3.2.2 mabhc_new_calc_primary_layout

On this layout, the three at least necessary values (pH, pCO₂, HCO₃⁻) for the interpretation are displayed and must be entered by the user.

Without entering all three variables the button NEXT is not working and the application reminds the user with a short explanation to enter the missing values.

If everything is entered correct a press on the button NEXT will bring up the next layout mabhc_new_calc_anion_layout.

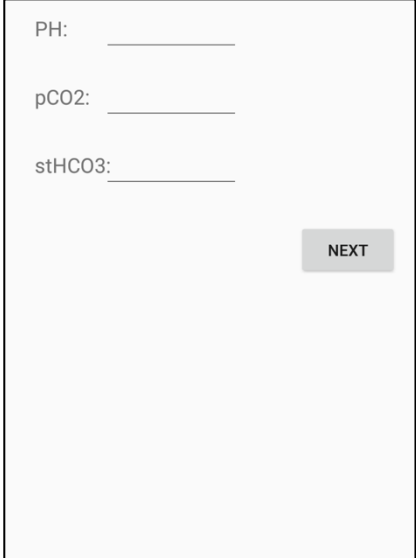


Figure 12:
mabhc_new_calc_primary_layout

3.2.3 mabhc_new_calc_anion_layout

This layout is completely optional. If the physician does not or cannot enter the anions the button CALCULATE can be pressed and the application will display the results.

However, if one anion, for example Na⁺, is entered Cl⁻ also needs to be fed to the program. The value of K⁺ is also optional because many physicians don't use potassium in the calculation of the anion gap.

There are two different formulas and reference ranges of the ANG depending if potassium has been entered or not (see below)

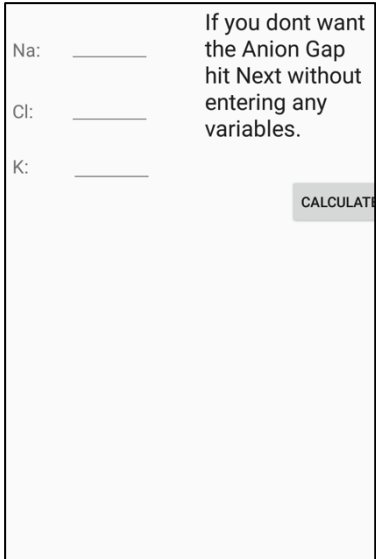


Figure 13:
mabhc_new_calc_anion_layout

With potassium:

$ANG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$ and reference range from **12 to 20 mmol/l**.

Without potassium (used most of the times in the clinical field):

$ANG = (Na^+) - (Cl^- + HCO_3^-)$ and referen range from **8 to 16 mmol/l**.

3.2.4 mabhc_new_calc_results_layout

After all the values are fed into the application the results of the entered ABG results are shown on this layout. Basically, it contains one listview, which is placed on the left site of the screen, that displays all the calculated values like ANG (if wanted), the expected CO₂ or HCO₃⁻ and also all entered values so the user can recheck if everything is correct.

On the right site is a bigger textview which contains the interpretation of the ABG. The first lines contain the basic information about the disturbance (acidosis, alkalosis, respiratory, metabolic), depending on the period of time the patient is sick it can be a different result.

As seen in Figure 14: mabhc_new_calc_results_layout depending on the time the patient has a combined (acute) alkalosis or a (chronic) respiratory alkalosis which persisted at least over 2 days with a compensatory process going on.

The last line contains, if wanted, the result of the anion analysis. In this case a metabolic acidosis is also present according to the calculated ANG.

PH: 7.58	-Respiratory Alkalosis
	and a metabolic
HCO3: 19.0 mmol/l	alkalosis (if > 2 days)
	-Respiratory Alkalosis
pCO2: 21.0 mmHg	with acut metabolic
	compensation
Na: 127.0 mmol/l	+ metabloic acidosis
	duo high ANG
Cl: 79.0 mmol/l	
K: 5.2 mmol/l	
ANG: 34.199997	
ExpectedaHCO3:	20.2 mmol/l
ExpectedcHCO3:	14.5 mmol/l
ExpectedCO2: 0.0	mmHg

Figure 14:
mabhc_new_calc_results_layout

3.2.5 mabhc_calc_only_ang_layout

If the user presses the button CALC ANG on the start layout (Figure 11: mabhc_opening_screen_layout) the view is set to mabhc_calc_only_ang_layout. Containing four textviews and four textedits the user must enter all values that are needed (except potassium if not wanted).

Pressing the button CALC will calculate the ANG and display it (see Figure 15: mabhc_calc_only_ang_layout).

Na: <input type="text" value="127"/>	ANG: 33.199997																
	Normal 8-16																
Cl: <input type="text" value="79"/>																	
K: <input type="text" value="5.2"/>																	
HCO3: <input type="text" value="20"/>	<input type="button" value="CALC"/>																
<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>-</td> </tr> <tr> <td>4</td> <td>5</td> <td>6</td> <td>←</td> </tr> <tr> <td>7</td> <td>8</td> <td>9</td> <td>✕</td> </tr> <tr> <td></td> <td>0</td> <td></td> <td>✓</td> </tr> </table>		1	2	3	-	4	5	6	←	7	8	9	✕		0		✓
1	2	3	-														
4	5	6	←														
7	8	9	✕														
	0		✓														

Figure 15:
mabhc_calc_only_ang_layout

3.3 The code structure

3.3.1 Libraries

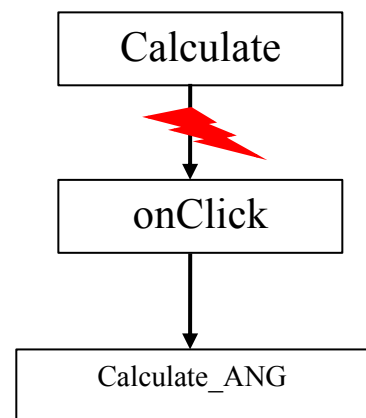
Upon opening the application, the first thing that is needed are the different libraries which contain the information for the android system how to visualize the different components, for example the Buttons. Without importing this library on the start, it would not be possible to use any buttons in the program.

```
import android.os.Bundle;  
import android.support.v7.app.AppCompatActivity;  
import android.support.v7.widget.Toolbar;  
import android.text.TextUtils;  
import android.view.View;  
import android.widget.ArrayAdapter;  
import android.widget.Button;  
import android.widget.EditText;  
import android.widget.ListView;  
import android.widget.TextView;  
import android.widget.Toast;
```

Code snippet 1: importing the needed libraries

There are many libraries containing all functions of the specific component, as illustration let's take the button library again: If this library is not present the android system would not know what to do with the command onClick.

onClick is a function of a button that starts a predefined process if the button is clicked, like the process of calculating the ANG. If now the button can't handle this event or even can't be placed, the process of calculating of the ANG can't be started.



3.3.2 Initialization

```
//Initializing all variables globally
private TextView txtViewPH;
private TextView txtViewHC03;
private TextView txtViewpCO2;
private TextView txtViewResultsofCalc;

private EditText edittxtPH;
private EditText edittxtHC03;
private EditText edittxtPCO2;
private EditText edittxtNA;
private EditText edittxtK;
private EditText edittxtCl;

private ListView listviewValues;

int tempPH = 0;
int tempHC03 = 0;
int tempPCO2 = 0;

boolean IfOnlyANGCalc = false;

Float floatvaluePH = (float) 0;
Float floatvalueHC03 = (float) 0;
Float floatvaluePCO2 = (float) 0;
Float floatvalueANG = (float) 0;
Float floatvalueNA = (float) 0;
Float floatvalueCl = (float) 0;
Float floatvalueK = (float) 0;
Float floatvalueexpectedPCO2 = (float) 0;
Float floatvalueexpectedacutHC03 = (float) 0;
Float floatvalueexpectedchronicHC03 = (float) 0;

String CalcResultsText = "";
String AgOrNormalMetabolic = "";
```

Code snippet 2: globally initialization of the variables

After the start, the different variables need to be initialized globally, so that they can be accessed from every subroutine of the program. There are different types of variables for example Boolean which can only be two states: false or true. Every variable is named after a specific pattern so no mixed-up mistakes could be made. Every TextView starts with the letters txtView as seen above, with this method it is not possible to mistake an EditText for an TextView.

For example, the EditText in which the user enters the pH, pCO₂, etc. are always named after the same principle and start with the term: “edittxt” and depending on which variable it is representing it contains the term K, Na, Cl, PH, pCO₂ etc. With that mechanism the purpose of this variable is always know and can’t be mistaken.

```
Float floatvaluePH = (float) 0;
```

Code snippet 3: floatvaluePH

The initialization of the variables is important so the program knows that they are existing and can access them at any time, also it is recommended to set them to zero or null so no calculation mistakes can be made.

3.3.3 Setting the view

After everything has been established and made ready the next thing the application needs to do is show the user the start screen so the he or she can press one of the two buttons. This is done by the routine **onCreate**. As the name says this routine is called when the program starts, without it the application can contain every possible function but the user never could press any button to use them.

In this routine the view (basically what's the user is seeing right now) is set to the opening layout which then shows the buttons and the information.

Simple but yet so important.

```
@Override
protected void onCreate(Bundle savedInstanceState) {
    super.onCreate(savedInstanceState);
    setContentView(R.layout.mabhc_opening_screen_layout);
}
```

Code snippet 4: onCreate

3.3.4 START CALC

onBtnStartNewCalcClick

Now let's say the user decides to start a complete new calculation process and presses the button START CALC. The program now needs to load up the layout

mabhc_new_calc_primary_layout.

```
public void onBtnStartNewCalcClick(View viewStartScreen) {
    setContentView(R.layout.activity_m_abhc);

    txtViewPH = (TextView) findViewById(R.id.txtViewPH);
    txtViewHC03 = (TextView) findViewById(R.id.txtViewHC03);
    txtViewPC02 = (TextView) findViewById(R.id.txtViewPC02);

    edittxtPH = (EditText) findViewById(R.id.edittxtPH);
    edittxtHC03 = (EditText) findViewById(R.id.edittxtHC03);
    edittxtPC02 = (EditText) findViewById(R.id.edittxtPC02);

    CalcResultsText = "";
}
```

Code snippet 5: onBtnStartNewCalcClick

The routine `onBtnStartNewCalcClick` links the field for pH, HCO_3^- and pCO_2 to their correct EditText fields and also sets the String (a variable which contains text characters) `CalcResultsText` that later on contains the interpretation of the calculations to "", which equals empty or null.

3.3.5 onBtnNextClick

After entering all the values and pressing the button NEXT, the routine onBtnNextClick is called and checks if every value has been entered. If any of the variables is missing the program will write an error message to the user so, he can correct the mistake and enter the value.

After everything is correct the next step that needs to be done is writing the numbers of pH, pCO₂ and HCO₃⁻ into their variables (see below).

```
floatvalueHCO3 = Float.parseFloat(edittxtHCO3.getText().toString());
floatvaluePH = Float.parseFloat(edittxtPH.getText().toString());
floatvaluepCO2 = Float.parseFloat(edittxtpCO2.getText().toString());
```

Code snippet 6: parsing the entered values in the variables

Because the EditText contains only characters but pH is a number there needs to be a transformation from one type of variable into another (string in float). This is done but using the command **parseFloat**.

Processing the input

After the program completed the transfer, the new variable needs to be analysed. This is shown on the example of the pH (see Code snippet 7):

```
//Check Value PH
if (floatvaluePH < 7.34) {
    tempPH = 1;
} else if (floatvaluePH > 7.45) {
    tempPH = 2;
} else {
    tempPH = 3;
}
```

Code snippet 7: analysing the input of pH

If the pH is under 7.34 an acidosis is present, if it is over 7.45 an alkalosis is present and if it is neither of them it is in the normal range. The application saves this information with a number in a variable called tempPH. Basically a **1** means that the value is too **low**, a **2** means too **high** and a **3** means it is in the **normal** range. This process is done with the other variables too.

After the three entered values are analysed and saved, the next routine is called: CalcANG(), which only loads the next screen and links the new EditText fields Na, K and Cl to their variables.

3.3.6 BtnCalcANGClick

Depending if the user just wants a quick interpretation of the three basic acid base homeostasis marker (pH, pCO₂ and HCO₃⁻) or wants to calculate the anion gap the next steps in the program are different.

```
if (TextUtils.isEmpty(edittxtNA.getText()))
```

Code snippet 8: depending if the user entered the value of Na, the program calculates the ANG or not

If the user just wants the basic information it is possible to click the button CALCULATE without entering any values of the electrolytes. The program will then start to analyse the given variables and write the results out.

If an interpretation of the anion gap is also wanted the EditText fields of Na and Cl need to be filled. Potassium (K⁺) is not necessary and most clinics don't use it in their routine of interpreting the ANG. Entering the potassium will result in a different reference range than without it: **with K 16±4, without K 12±4**. Because of the rapid development of more modern and more precisely measurement methods many hospitals also use the a reference range from 3-11 mmol/l [48].

Now the program starts to evaluate the previously saved variables (tempPH, tempCO₂, tempHCO₃⁻ and also if wanted calculates the ANG).

Basically the routine BtnCalcANGClick has subroutines covering every possible combination of these 3 variables:

Short reminder:

- pH =1 stands for acidosis, pH =2 alkalosis and pH =3 normal
- pCO₂ =1 stands for under 34 mmHg, =2 over 45 mmHg, =3 normal
- HCO₃⁻ =1 stands for under 20 mmol/l, =2 over 26 mmol/l, =3 normal

As mentioned in Figure 7 the application follows a strict approach system:

```
//PH = Azidose CO2 = Alkalose HCO3 = Azidose
if(tempPH == 1 && tempCO2 == 1 && tempHCO3 == 1)
```

Code snippet 9: interpreting the variables

The routine BtnClickCalcANG contains every possible combination of these three variables:

tempPH = 1 (acidosis)

	temppCO2 = 1	temppCO2 = 2	temppCO2 = 3
tempHCO3 = 1	metabolic acidosis with secondary process	mixed respiratory and metabolic acidosis	metabolic acidosis with normal pCO ₂ or secondary process
tempHCO3 = 2	unlikely (high ANG acidosis with secondary processes)	respiratory acidosis with secondary process	unlikely ((high ANG acidosis with secondary processes)
tempHCO3 = 3	unlikely (high ANG acidosis with secondary processes)	respiratory acidosis with normal HCO ₃ ⁻ or secondary process	unlikely ((high ANG acidosis with secondary processes)

tempPH = 2 (alkalosis)

	temppCO2 = 1	temppCO2 = 2	temppCO2 = 3
tempHCO3 = 1	respiratory alkalosis with secondary process	-	-
tempHCO3 = 2	mixed respiratory and metabolic alkalosis	metabolic alkalosis with secondary process	metabolic alkalosis with normal pCO ₂ or secondary process
tempHCO3 = 3	respiratory alkalosis with normal HCO ₃ ⁻ or secondary process	-	-

tempPH = 3 (normal)

	tempCO2 = 1	tempCO2 = 2	tempCO2 = 3
tempHCO3 = 1	metabolic acidosis or respiratory alkalosis with compensating process	-	acute metabolic process with/without compensation
tempHCO3 = 2	-	metabolic alkalosis or respiratory acidosis with compensating process	acute metabolic process with/without compensation
tempHCO3 = 3	acute respiratory process with/without compensation	acute respiratory process with/without compensation	normal blood gas analysis

For each of the above shown possible combinations the app contains a subroutine which then will calculate the expected pCO₂ according to the winters formula or the expected HCO₃⁻ depending on which disturbance is currently present.

```

//PH = Acidose CO2 = Alkalose HCO3 = Acidose
if(tempPH == 1 && tempCO2 == 1 && tempHCO3 == 1)
{...}

//PH = Alkalose CO2 = Acidose HCO3 = Alkalose
else if(tempPH == 2 && tempCO2 == 2 && tempHCO3 == 2)
{...}

//PH = Normal CO2 = Normal HCO3 = Normal
else if (tempPH == 3)
{...}

//PH=Alkalose CO2 = Alkalose HCO3 = Alkalose
else if(tempPH == 2 && tempCO2 == 1 && tempHCO3==1)
{...}

//PH = Acidosis CO2 = Acidosis HCO3 = Alkalosis
else if (tempPH == 1 && tempCO2 == 2 && tempHCO3 == 2)
{...}

//PH = Acidosis CO2 = Acidosis HCO3 = Acidosis
else if (tempPH == 1 && tempCO2 == 2 && tempHCO3 == 1)
{
    CalcResultsText = CalcResultsText + "-Combined respiratory and metabolic acidosis\n";
}
//PH = Alkalosis CO2 = Alkalosis HCO3 = Alkalosis
else if (tempPH == 2 && tempCO2 == 1 && tempHCO3 == 2)
{
    CalcResultsText = CalcResultsText + "-Combined respiratory and metabolic alkalosis\n";
}
//PH = Acidosis CO2 = Alkalosis HCO3 = Normal
else if (tempPH == 1 && tempCO2 == 2 && tempHCO3 == 3)
{...}
//PH = Alkalosis CO2 = Acidosis HCO3 = Normal
else if (tempPH == 2 && tempCO2 == 1 && tempHCO3 == 3)
{...}
//PH = Alkalosis CO2 = Normal HCO3 = Alkalosis
else if (tempPH == 2 && tempCO2 == 3 && tempHCO3 == 2)
{...}
//PH = Acidosis CO2 = Normal HCO3 = Acidosis
else if (tempPH == 1 && tempCO2 == 3 && tempHCO3 == 1)
{...}

```

Code snippet 10: if-query of the pH, HCO₃⁻, pCO₂

3.3.7 The metabolic disorder

Let's say the variables are tempPH = 1, tempCO2 = 1 and tempHCO3 = 1 which means that the pH is acidotic the pCO₂ is under the reference range which is alkalic and the HCO₃⁻ is also under the reference range which means acidotic.

```
//PH = Azidose CO2 = Alkalose HC03 = Azidose
if(tempPH == 1 && tempCO2 == 1 && tempHCO3 == 1)
{
    //Metabolic Acidosis
    CalculateExpectedpCO2(true);
    if((floatvaluepCO2 <= floatvalueexpectedpCO2 +2)
        && (floatvaluepCO2 >= floatvalueexpectedpCO2 -2))
    {
        CalcResultsText = CalcResultsText + Ag0rNormalMetabolic
            + " with appropriate respiratory compensation(if >24hours)\n";
    }
    if (floatvaluepCO2 > floatvalueexpectedpCO2 +2)
    {
        CalcResultsText = CalcResultsText + Ag0rNormalMetabolic
            + "and a respiratory acidosis(if >24hours)\n-"
            + Ag0rNormalMetabolic + " uncompensated (if <24hours)";
    }
    if(floatvaluepCO2 < floatvalueexpectedpCO2-2)
    {
        CalcResultsText = CalcResultsText + "-" + Ag0rNormalMetabolic
            + " and a respiratory alkalosis (if >24hours)\n-"
            + Ag0rNormalMetabolic + " uncompensated (if <24hours)\n";
    }
}
}
```

Code snippet 11: if-query for the case of tempPH = 1; tempCO2 = 1; tempHCO3 = 1

Because the pH is acidotic and pCO₂ is alkalic it cannot be a respiratory disturbance. But the metabolic component HCO₃⁻ is low which means a metabolic acidosis is present. Knowing that the next thing to do is use the Winter's formula to calculate the expected pCO₂ so that if there is a secondary process it won't be missed.

This is done by the routine CalculateExpectedpCO2(true). Because there are different approaches on the winter's formula with a metabolic acidosis than with a metabolic alkalosis the program needs to know which of these two disturbances is present. As before established a metabolic acidosis is present so we call the subroutine and send this including this information that a acidosis is present, which in this case is made by sending a "true".

3.3.8 Calculate the expected pCO₂ aka Winter's formula

```
public void CalculateExpectedpCO2(boolean tempmetabolAZDALK)
{
    //Metabolic Acidosis
    if(tempmetabolAZDALK)
    {
        floatvalueexpectedpCO2 = (float)1.5 *floatvalueHC03 + 8;
    }
    //Metabolic Alkalosis
    else
    {
        floatvalueexpectedpCO2 = (float) 0.7 * floatvalueHC03 + 20;
    }
}
```

Code snippet 12: CalculateExpectedpCO2

As mentioned before this routine needs one parameter to start with: the **Boolean tempmetabolAZDALK**. This Boolean basically tells the routine which formula it should use depending on the metabolic disturbance. If the variable is set **true** it jumps into the **metabolic acidosis** approach of the Winter's formula and if it is **false** the formula for **metabolic alkalosis** is used.

Winter's formula:

Acidosis	Alkalosis
$expectedpCO_2 = 1,5 * HCO_3^- + 8$	$expectedpCO_2 = 0,7 * HCO_3^- + 20$

Formula 13: Winter's formula for metabolic acidosis and alkalosis [49]

After the expected pCO₂ is calculated it is set into the variable **floatvalueexpectedpCO2**. Back to Code snippet 11: if-query for the case of temp_{pH} = 1; temp_{pCO2} = 1; temp_{HCO3} = 1.

The program now knows that a metabolic acidosis is present and it also knows the value of pCO₂ which should be present. The actual pCO₂ should be close to the calculated expected one. The range differs from author to author but in this approach a **±2 interval** is taken as reference. [50] For example if the measured pCO₂ is 30 mmHg and the calculated one is 36 mmHg this could be a hint that a second disturbance, a respiratory alkalosis, is also present (see table below).

measured $p\text{CO}_2 > \text{expected } p\text{CO}_2 + 2$	additional respiratory acidosis might be also present
measured $p\text{CO}_2 < \text{expected } p\text{CO}_2 - 2$	additional respiratory alkalosis might be also present
expected $p\text{CO}_2 + 2 < \text{measured } p\text{CO}_2 > \text{expected } p\text{CO}_2 - 2$	appropriate respiratory response to the metabolic disturbance (if enough time past (24 hours))

Table 3: Interpretation of the results from Winter's formula [50]

As seen in the table above there are three different ways in which the app can interpret this ABG result:

- Metabolic acidosis with appropriate respiratory response
- Metabolic acidosis and a respiratory acidosis
- Metabolic acidosis and a respiratory alkalosis

So it is possible to mistake the low $p\text{CO}_2$ for a normal response of the human body but is actually an additional respiratory disorder!

Depending on which if query is fulfilled the program writes the interpretation of the ABG into the string CalcResultsText and jumps to the next screen and displays the results to the user.

If the user entered the electrolytes the program will also calculate the ANG and includes this issue in the interpretation (Code snippet 13: Result of an interpretation done with the app mABHC including the ANG).

PH: 7.58	-Respiratory Alkalosis
HCO3: 19.0 mmol/l	and a metabolic alkalosis (if > 2 days)
	-Respiratory Alkalosis
pCO2: 21.0 mmHg	with acut metabolic compensation
Na: 127.0 mmol/l	+ metabloic acidosis
	duo high ANG
Cl: 79.0 mmol/l	
K: 5.2 mmol/l	
ANG: 34.199997	
ExpectedaHCO3: 20.2 mmol/l	
ExpectedcHCO3: 14.5 mmol/l	
ExpectedCO2: 0.0 mmHg	

Code snippet 13: Result of an interpretation done with the app mABHC including the ANG

If a metabolic alkalosis is present, the process of interpretation is the same expect for calculating the expected pCO₂:

```
//PH = Alkalose CO2 = Azidose HCO3 = Alkalose
else if(tempPH == 2 && tempCO2 == 2 && tempHCO3 ==2)
{
    //metabolic alkalosis
    CalculateExpectedpCO2(false);
    if((floatvaluepCO2 < floatvalueexpectedpCO2 +5)
        && (floatvaluepCO2 > floatvalueexpectedpCO2 -5))
    {
        CalcResultsText = CalcResultsText + "-Metabolic Alkalosis " +
            "with appropriate respiratory compensation(if >24hours)\n-";
    }
    if (floatvaluepCO2 > floatvalueexpectedpCO2 +5)
    {
        CalcResultsText = CalcResultsText + "-Metabolic Alkalosis " +
            "and a respiratory acidosis\n" +
            "-Metabolic Alkalosis uncompensated (if <24hours)\n";
    }
    if(floatvaluepCO2 < floatvalueexpectedpCO2 - 5)
    {
        CalcResultsText = CalcResultsText + "-Metabolic Alkalosis " +
            "and a respiratory alkalosis\n" +
            "-Metabolic Alkalosis uncompensated (if <24hours)\n";
    }
}
}
```

Table 4: if-query for the case tempPH = 2; tempCO2 = 2; tempHCO3 = 2

As explained above the function CalculateExpectedpCO2 needs to know if a metabolic alkalosis or acidosis is present. In this case a metabolic alkalosis is present so it is called with a false.

Compared with the Winter's formula for acidosis the alkalosis case has different reference ranges: ± 5 mmHg [29].

After knowing the expected pCO₂ there are three different possibilities:

- Metabolic alkalosis with appropriate respiratory response
- Metabolic alkalosis and a respiratory acidosis
- Metabolic alkalosis and a respiratory alkalosis

These approaches are also done if the measured pCO₂ is within its normal range because as established before it could exist an additional respiratory disorder!

```
//PH = Alkalosis CO2 = Normal HCO3 = Alkalosis  
else if (tempPH == 2 && temppCO2 == 3 && tempHCO3 == 2)  
{...}  
//PH = Acidosis CO2 = Normal HCO3 = Acidosis  
else if (tempPH == 1 && temppCO2 == 3 && tempHCO3 == 1)  
{...}
```

Code snippet 14: if-queries for metabolic disorders with normal pCO₂

3.3.9 The respiratory disorder

```
//PH=Alkalose CO2 = Alkalose HCO3 = Azidose
else if(tempPH == 2 && tempPCO2 == 1 && tempHCO3==1)
{
    CalculateExpectedHCO3(false);
    if(floatvalueHCO3 > floatvalueexpectedacutHCO3+2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory Alkalosis " +
            "and a metabolic alkalosis (if < 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedacutHCO3-2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory Alkalosis " +
            "and a metabolic acidosis (if < 2 days)\n";
    }
    if(floatvalueHCO3 > floatvalueexpectedchronicHCO3+2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory Alkalosis " +
            "and a metabolic alkalosis (if > 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedchronicHCO3-2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory Alkalosis " +
            "and a metabolic acidosis (if > 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedacutHCO3 +2
        && floatvalueHCO3 > floatvalueexpectedacutHCO3 -2)
    {
        CalcResultsText = CalcResultsText + " -Respiratory Alkalosis " +
            "with appropriate compensation (if < 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedchronicHCO3 +2
        && floatvalueHCO3 > floatvalueexpectedchronicHCO3 -2)
    {
        CalcResultsText = CalcResultsText + " -Respiratory Alkalosis " +
            "with appropriate metabolic compensation (if > 2 days)\n";
    }
}
}
```

Code snippet 15: if-query for the case of tempPH = 2; tempPCO2 = 1; tempHCO3 = 1

The respiratory disorders are basically done with the same approach as the metabolic ones, with some short adjustments because for example the Winter's formula does not apply on the respiratory acid base disturbances.

Let's assume the tempPH = 2, tempPCO2 = 1 and tempHCO3 = 1. Following the systematic approach the app uses this equals a **respiratory alkalosis**.

As explained above, the body's answer on a respiratory disorder is established by the kidneys and the liver and takes some time to reach the full capacity.

For the acute phase a 10 mmHg drop of pCO₂ equals a 2 mmol/l decrease of HCO₃⁻ below a pCO₂ of 40 mmHg. The chronic phase equals a 5 mmol/l decrease of HCO₃⁻ for every 10 mmHg drop of pCO₂ below 40 mmHg.

Knowing that it is possible to establish a formula to calculate the expected HCO₃⁻ in the **respiratory alkalosis**:

acute phase (< 2 days):

$$\textit{expected HCO}_3^- = 24 - 2 * [(40 - \textit{measured pCO}_2)/10]$$

chronic phase (> 2 days):

$$\textit{expected HCO}_3^- = 24 - 5 * [(40 - \textit{measured pCO}_2)/10]$$

Table 5: formula for calculating the expected HCO₃ in the respiratory alkalosis

A very similar formula is used with the approach on a **respiratory acidosis**:

acute phase (< 2 days):

$$\textit{expected HCO}_3^- = 24 + [(\textit{measured pCO}_2 - 40)/10]$$

chronic phase (> 2 days):

$$\textit{expected HCO}_3^- = 24 + 4 * [(\textit{measured pCO}_2 - 40)/10]$$

Table 6: formula for calculating the expected HCO₃ in the respiratory acidosis

For every 10 mmHg increase of pCO₂ above 40 mmHg the HCO₃⁻ increases by 1 mmol/l in the acute phase. In the chronic phase after all organs reached their maximum power a 4 mmol/l HCO₃⁻ increase for every 10 mmHg increase of pCO₂ above 40 mmHg is achieved [29].

As seen in Code snippet 15 the routine calls the function **CalculateExpectedHCO3()** with the parameter false.

3.3.10 Calculate Expected HCO₃⁻

```
public void CalculateExpectedHCO3(boolean temprespiAZDALK)
{
    //Acut || chronic respiratory Acidosis
    if(temprespiAZDALK)
    {
        //acute
        floatvalueexpectedacutHCO3 = 24 + ((floatvaluepCO2-40)/10);

        //chronic
        floatvalueexpectedchronicHCO3 = 24 + 4*((floatvaluepCO2-40)/10);
    }
    //Acut || chronic respiratory Alkalosis
    else
    {
        //acute
        floatvalueexpectedacutHCO3 = 24 - 2*((40-floatvaluepCO2)/10);

        //chronic
        floatvalueexpectedchronicHCO3 = 24 - 5*((40-floatvaluepCO2)/10);
    }
}
```

Code snippet 16: function CalculateExpectedHCO3

Because there are two different formulas for the respiratory acidosis and the alkalosis the routine needs to know which one is present. This is accomplished by sending a true or false state upon calling the function. **True** equals an **acidosis** and false an **alkalosis**.

As explained in Table 5 & Table 6 on page 41 there are different formulas for the acute and the chronic phase of the respiratory disorder. Depending on which disorder is present the correct formula is used and the calculated values of the expected HCO₃⁻ are saved into the two variables **floatvaulexpectedacutHCO3** and **floatvalueexpectedchronicHCO3**.

After the calculating process is finished the interpretation of the numbers starts.

Back to the case of the respiratory alkalosis:

Now the app needs to check if the amount of bicarbonate is in the reference range of the normal metabolic compensation process. The reference range is ± 2 mmol/l for the calculated expected acute and chronic HCO_3^- [29]. Knowing that there are six different options, depending on the duration of the acid base disturbance:

<u>acute phase (< 2 days)</u>	
measured $\text{HCO}_3^- >$ expected acute $\text{HCO}_3^- + 2$	additional metabolic alkalosis might be also present
measured $\text{HCO}_3^- <$ expected acute $\text{HCO}_3^- - 2$	additional metabolic acidosis might be also present
expected acute $\text{HCO}_3^- + 2 <$ measured $\text{HCO}_3^- >$ expected acute $\text{HCO}_3^- - 2$	appropriate metabolic response to the metabolic disturbance
<u>chronic phase (> 2 days)</u>	
measured $\text{HCO}_3^- >$ expected chronic HCO_3^- $+ 2$	additional metabolic alkalosis might be also present
measured $\text{HCO}_3^- <$ expected chronic HCO_3^- $- 2$	additional metabolic acidosis might be also present
expected chronic $\text{HCO}_3^- + 2 <$ measured $\text{HCO}_3^- >$ expected chronic $\text{HCO}_3^- - 2$	appropriate metabolic response to the metabolic disturbance

Table 7: interpretation of the calculated HCO_3^- values in the respiratory alkalosis

The app will write out two of these six different options (for acute and chronic) and the physician then needs to establish how long the patient has been sick and if the change in bicarbonate is within the normal range.

The same principle mechanism is used in interpreting a **respiratory acidosis** with one exception the function **CalculateExpectedHCO3** is called with a **true**.

```
//PH = Acidosis CO2 = Acidosis HCO3 = Alkalosis
else if (tempPH == 1 && tempCO2 == 2 && tempHCO3 == 2)
{
    CalculateExpectedHCO3(true);
    if(floatvalueHCO3 > floatvalueexpectedacutHCO3+2)
    {
        CalcResultsText = CalcResultsText + "respiratory acidosis " +
            "and a metabolic alkalosis (if < 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedacutHCO3-2)
    {
        CalcResultsText = CalcResultsText + "respiratory acidosis " +
            "and a metabolic acidosis (if < 2 days)\n";
    }
    if(floatvalueHCO3 > floatvalueexpectedchronicHCO3+2)
    {
        CalcResultsText = CalcResultsText + "-respiratory acidosis " +
            "and a metabolic alkalosis (if > 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedchronicHCO3-2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory acidosis " +
            "and a metabolic acidosis (if > 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedacutHCO3 +2
        && floatvalueHCO3 > floatvalueexpectedacutHCO3 -2)
    {
        CalcResultsText = CalcResultsText + " -Respiratory Acidosis " +
            "with metabolic compensation (if < 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedchronicHCO3 +2
        && floatvalueHCO3 > floatvalueexpectedchronicHCO3 -2)
    {
        CalcResultsText = CalcResultsText + " -Respiratory Acidosis " +
            "with metabolic compensation(if > 2 days)\n";
    }
}
}
```

Code snippet 17: if-query for the case tempPH = 1; tempCO2 = 2; tempHCO3 = 2

3.3.11 What if the pH is normal?

The chapter before discussed the metabolic/respiratory acidosis and the metabolic/respiratory alkalosis. As explained in the Introduction chapter the human body has a variety of buffer systems which are able to hold the pH in a normal level if for example the disorder is not that strong or occurred a longer time ago. In this case the pH can seem normal but the metabolic and respiratory parameter (HCO_3^- , pCO_2) might already be out of their reference ranges. In this case of $\text{tempPH} = 3$ (which means normal range) the app check the two other variables if a disorder occurred and depending on this outcome which form of disorder is present.

```
//Ph = Normal CO2 = Normal HCO3 = Normal
else if (tempPH == 3)
{
    if(tempCO2 == 3 && tempHCO3 == 3)
    {
        CalcResultsText = "Normal BGA\n";
    }
    if(tempCO2 == 1 && tempHCO3 == 1)
    {...}
    if(tempCO2 == 2 && tempHCO3 == 2)
    {...}
    if(tempCO2 == 1 && tempHCO3 == 2)
    {...}
    if(tempCO2 == 1 && tempHCO3 == 3)
    {...}
    if(tempCO2 == 2 && tempHCO3 == 1)
    {...}
    if(tempCO2 == 3 && tempHCO3 == 1)
    {...}
    if(tempCO2 == 2 && tempHCO3 == 3)
    {...}
    if(tempCO2 == 3 && tempHCO3 == 2)
    {...}
}
```

Code snippet 18: if-query in the case of $\text{tempPH} = 3$

Every possible combination is checked in this if-query but because no azidemia or alkalemia is present it is a little bit more complicated because a decreased pCO_2 and HCO_3^- can mean a respiratory alkalosis or a metabolic acidosis.

```

if(tempCO2 == 1 && tempHCO3 == 1)
{
    CalculateExpectedHCO3(false);
    CalculateExpectedpCO2(true);

    if(floatvalueHCO3 > floatvalueexpectedacutHCO3+2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory Alkalosis " +
            "and a metabolic alkalosis (if < 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedacutHCO3-2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory Alkalosis " +
            "and a metabolic acidosis (if < 2 days)\n";
    }
    if(floatvalueHCO3 > floatvalueexpectedchronicHCO3+2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory Alkalosis " +
            "and a metabolic alkalosis (if > 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedchronicHCO3-2)
    {
        CalcResultsText = CalcResultsText + "-Respiratory Alkalosis " +
            "and a metabolic acidosis (if > 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedacutHCO3 +2
        && floatvalueHCO3 > floatvalueexpectedacutHCO3 -2)
    {
        CalcResultsText = CalcResultsText + " -Respiratory Alkalosis " +
            "with appropriate metabolic compensation (if < 2 days)\n";
    }
    if(floatvalueHCO3 < floatvalueexpectedchronicHCO3 +2
        && floatvalueHCO3 > floatvalueexpectedchronicHCO3 -2)
    {
        CalcResultsText = CalcResultsText + " -Respiratory Alkalosis " +
            "with appropriate metabolic compensation (if > 2 days)\n";
    }

    if((floatvaluepCO2 < floatvalueexpectedpCO2 +2)
        && (floatvaluepCO2 > floatvalueexpectedpCO2 -2))
    {
        CalcResultsText = CalcResultsText + AgOrNormalMetabolic
            + " with appropriate respiratory compensation\n";
    }
    if (floatvaluepCO2 > floatvalueexpectedpCO2 +2)
    {
        CalcResultsText = CalcResultsText + AgOrNormalMetabolic
            + " and a respiratory acidosis (if >24hours)\n" +
            "-Metabolic Acidosis uncompensated (if <24hours)\n";
    }
    if(floatvaluepCO2 < floatvalueexpectedpCO2-2)
    {
        CalcResultsText = CalcResultsText + AgOrNormalMetabolic
            + " and a respiratory alkalosis\n";
    }
}

```

Code snippet 19: if-query in the case of tempPH = 3; tempCO2 = 1; tempHCO3 = 1

As seen in Code snippet 19 the two combinations are checked if they are possible by calling both functions CalculateExpectedpCO2(true) and CalculateExpectedHCO3(false). After that it is possible to differentiate which disorder is present depending on the values of the calculated HCO₃⁻ and pCO₂.

This is done with every other possible combination of tempHCO3 and tempCO2.

3.3.12 Write Results Out

```
public void WriteResultsOut()
{
    setContentView(R.layout.mabhc_new_calc_results_layout);
    listviewValues = (ListView)findViewById(R.id.listviewValues);
    txtViewResultsofCalc = (TextView)findViewById(R.id.txtViewResultsofCalc);

    String[] values = new String[] { "PH: " + floatValuePH.toString(),
        "HCO3: " + floatValueHCO3.toString() + " mmol/l",
        "pCO2: " + floatValuepCO2.toString() + " mmHg",
        "Na: " + floatValueNA.toString() + " mmol/l",
        "Cl: " + floatValueCL.toString() + " mmol/l",
        "K: " + floatValueK.toString() + " mmol/l",
        "ANG: " + floatValueANG.toString(),
        "ExpectedaHCO3: " + floatValueexpectedacutHCO3 + " mmol/l",
        "ExpectedcHCO3: " + floatValueexpectedchronicHCO3 + " mmol/l",
        "ExpectedCO2: " + floatValueexpectedpCO2 + " mmHg"
    };

    ArrayAdapter<String> adapter = new ArrayAdapter
        <String>(this, R.layout.mabhc_listview_showvalues, values);

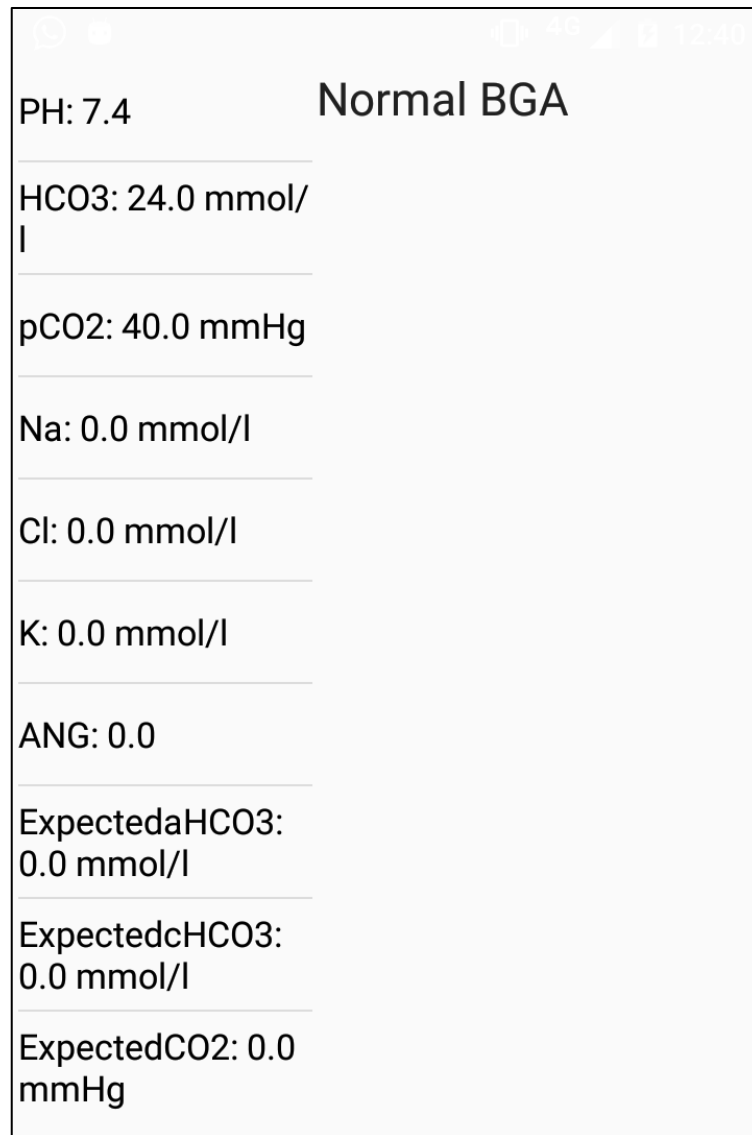
    listviewValues.setAdapter(adapter);

    txtViewResultsofCalc.setText( CalcResultsText );
}
```

Code snippet 20: WriteResultsOut()

All the above explained calculations and mechanism lead to this last important screen. The screen which presents the results to the user.

On the left side of the screen a so called ListView is visible. A ListView is a container for many different strings, like a table. In this case it contains all the entered values as well as the calculated ones (see above), so that the user can check if the values are valid and/or if he/she made an input error. On the right side of the screen a TextView txtViewResultsofCalc is placed which shows the interpretation of the ABG.



Code snippet 21: output of the function WriteResultsOut()

3.3.13 CALC ANG

```
public void CalculateANG(View btnCalculateANGClick)
{
    TextView txtViewANGValue = (TextView)(findViewById(R.id.txtViewANGValue));

    try {
        try {
            floatvalueNA = Float.parseFloat(edittxtNA.getText().toString());
        } catch (NumberFormatException e) {
            e.printStackTrace();
        }

        try {
            floatvalueCL = Float.parseFloat(edittxtCL.getText().toString());
        } catch (NumberFormatException e) {
            e.printStackTrace();
        }

        try {
            floatvalueK = Float.parseFloat(edittxtK.getText().toString());
        } catch (NumberFormatException e) {
            e.printStackTrace();
        }

        if(IfOnlyANGCalc)
        {
            floatvalueHCO3 = Float.parseFloat(edittxtHCO3.getText().toString());
            IfOnlyANGCalc = false;
        }

        if (TextUtils.isEmpty(edittxtK.getText())) {
            floatvalueANG = floatvalueNA - floatvalueCL - floatvalueHCO3;
        } else {
            floatvalueANG = floatvalueNA + floatvalueK - floatvalueCL - floatvalueHCO3;
        }

    } catch (NumberFormatException e) {
        e.printStackTrace();
        Toast.makeText(getApplicationContext(), "Hier is da Error", Toast.LENGTH_LONG).show();
    }

    txtViewANGValue.setText("ANG: " + floatvalueANG.toString() + "\nNormal 8-16");
}
```

Code snippet 22: CalculateANG()

The function CalculateANG() is used in two different forms:

- calculating the ANG in a complete interpretation of a ABG result
- only calculating the ANG

Depending on which case is present there are a few things different but the basic calculation process still stays the same. Also, there are two different layouts for the two options, because if the user only wants to calculate the ANG he needs to enter the HCO_3^- additionally.

The first step is to link the existing variables to their corresponding EditText. After that the program checks if the user wants to calculate the ANG with potassium or without:

```
if (TextUtils.isEmpty(edittxtK.getText())) {  
    floatvalueANG = floatvalueNA - floatvalueCL - floatvalueHC03;  
} else {  
    floatvalueANG = floatvalueNA + floatvalueK - floatvalueCL - floatvalueHC03;  
}
```

Code snippet 23: check if the user wants the ANG calculated including potassium

If the EditText of K⁺ is empty the app knows that the user does not want the potassium included in the calculation otherwise it is included in the formula.

After this is done the result is saved into the variable floatvalueANG and can be accessed from every other function and if the user only wanted the ANG it is displayed including the normal reference range.

4 Examples with cases from the literature

4.1 Manual workaround

4.1.1 Case 1 – Postoperative cardiac arrest

Patient after postoperative cardiac arrest. ABG results [51]:

pH	7.27
pCO ₂	55.4 mmHg
HCO ₃ ⁻	24,3 mmol/l
Na ⁺	138 mmol/l
Cl ⁻	103 mmol/l
K ⁺	4,7 mmol/l

Table 8: ABG results for Case 1 - Postoperative cardiac arrest

The pH is decreased under 7.35, the pCO₂ is elevated above 45 mmHg and the HCO₃⁻ is within the normal range.

pCO₂ is decreases which means this is an acidotic process which is also seen in the pH. The HCO₃⁻ is within its normal range so a respiratory acidosis is present.

Now it is necessary to confirm that no an additionally acid base disorder is present by calculating the expected HCO₃⁻. For every 10 mmHg rise in pCO₂ in the acute period (< 2 days) a rise of 1 mmol/l of HCO₃⁻ would be normal.

$$\text{expected } HCO_3^- = 24 + [(\text{measured } pCO_2 - 40)/10]$$

The expected HCO₃⁻ is 25,5 which is very close to the actual HCO₃⁻ so no additionally metabolic disorder is present.

The ANG is 10,7 (without K⁺) which is also within the normal range.

Result:

A respiratory acidosis with appropriate (beginning) metabolic compensation is present.

4.1.2 Case 2 - A weak old lady

A weak old lady is being admitted to the emergency ambulance. Weakening since a few days [34].

pH	7.58
pCO ₂	49 mmHg
HCO ₃ ⁻	44,4 mmol/l
Na ⁺	145 mmol/l
Cl ⁻	86 mmol/l
K ⁺	1,9 mmol/l

Table 9: ABG results for Case 2 - A weak old lady

The pH is elevated as well as the pCO₂ and the HCO₃⁻. There are two options how this combination is explainable:

- a metabolic alkalosis
- a respiratory acidosis

Because the pH is also elevated a metabolic alkalosis must be the main disorder. To confirm this first diagnosis the expected pCO₂ needs to be calculated using the Winter's formula:

$$expectedpCO_2 = 0,7 * HCO_3^- + 20$$

The expected pCO₂ in this case would be 51 mmHg, which is very close to the measured pCO₂ of 49 mmHg. With this it is established that currently no additionally respiratory disorder is present. After calculating the ANG, which is 14 mmol/l also no high anion gap acidosis is observable.

Result:

A metabolic alkalosis with appropriate (but insufficient) respiratory compensation is present.

4.2 Workaround done with mABHC

4.2.1 Case 1 – Respiratory failure

A 68-year-old woman with chronic obstructive airway disease presents with a since two-hour existing worsening dyspnoea. ABG results [52]:

pH	7.28
pCO ₂	67 mmHg
HCO ₃ ⁻	26.2 mmol/l
Na ⁺	-
Cl ⁻	-
K ⁺	-

Table 10: ABG results for Case 1 - Respiratory failure

Results with mABHC:

PH: 7.28	-Respiratory acidosis and a metabolic acidosis (if > 2 days)
HCO ₃ : 26.2 mmol/l	-Respiratory Acidosis with metabolic compensation (if < 2 days)
pCO ₂ : 67.0 mmHg	
Na: 0.0 mmol/l	
Cl: 0.0 mmol/l	
K: 0.0 mmol/l	
ANG: 0.0	
ExpectedaHCO ₃ : 26.7 mmol/l	
ExpectedcHCO ₃ : 34.8 mmol/l	
ExpectedCO ₂ : 0.0 mmHg	

Figure 16: Results of Case 1 - Respiratory failure with the app mABHC

4.2.2 Case 2 – Accident

A 22-year-old woman had an accident and received 6-litres of isotonic saline. Her initial ABG results [36]:

Excerpt: Hyperchloremia is a rise of blood chloride above 107 mmol/l. Most of the times a Hyperchloremia does not result in severe symptoms (e.g. thirst, cerebral oedema, etc.). Some causes for Hyperchloremia are excessive chloride administration, net water loss (e.g. fever), renal tubular acidosis etc. [53]

pH	7.28
pCO ₂	39 mmHg
HCO ₃ ⁻	18 mmol/l
Na ⁺	135 mmol/l
Cl ⁻	115 mmol/l
K ⁺	3.8 mmol/l

Table 11: ABG Results for Case 2 - Accident [54]

Result with mABHC:

PH: 7.28	-Low Anion Gap Acidosis with a respiratory acidosis+ low ANG
HCO ₃ : 18.0 mmol/l	
pCO ₂ : 39.0 mmHg	
Na: 135.0 mmol/l	
Cl: 115.0 mmol/l	
K: 3.8 mmol/l	
ANG: 5.800003	
ExpectedaHCO ₃ : 0.0 mmol/l	
ExpectedcHCO ₃ : 0.0 mmol/l	
ExpectedCO ₂ : 35.0 mmHg	

Figure 17: Result of Case 2 - Accident with the app mABHC

4.2.3 Case 3 – Diarrhoea

A 22-year-old patient developed a massive volume loss because of watery diarrhoea.

ABG results [54]:

pH	7.6
pCO ₂	40 mmHg
HCO ₃ ⁻	38 mmol/l
Na ⁺	140 mmol/l
Cl ⁻	86 mmol/l
K ⁺	3 mmol/l

Table 12: ABG results for Case 3 - Diarrhoea [54]

Results with mABHC:

PH: 7.6	-Metabolic alkalosis and a respiratory alkalosis
HCO ₃ : 38.0 mmol/ l	-normal ANG
pCO ₂ : 40.0 mmHg	
Na: 140.0 mmol/l	
Cl: 86.0 mmol/l	
K: 0.0 mmol/l	
ANG: 16.0	
Expected aHCO ₃ : 0.0 mmol/l	
Expected cHCO ₃ : 0.0 mmol/l	
Expected CO ₂ : 46.6 mmHg	

Figure 18: Results of Case 3 - Diarrhoea with the app mABHC

5 Discussion

This first version of the mobile Acid Base Homeostasis Calculator demonstrates the feasibility of developing such a solution. More development and testing is needed to make sure the app enables the input of different combinations of gases, fluids and the electrolytes and reports reliable results. But knowing that nearly every year a new formula or adaption of an existing approach on an acid base homeostasis disorder is published it may become essential to rely on electronic support systems. Currently the app offers just a basic interpretation process with the anion gap and the calculation of the expected values of bicarbonate and the partial pressure of carbon dioxide. More functions need to be added, like the Stewart approach. Shown on the cases it is possible to mistake a low $p\text{CO}_2$ for an additionally respiratory alkalosis but it can be just the respiratory compensation. More so, a normal HCO_3^- alone does not mean that no metabolic process is currently active. Every acid base homeostasis disorder needs to be determined completely including the expected $p\text{CO}_2$ and HCO_3^- so that no additionally disorder is missed. The anion gap is also a very specific parameter in the acid base homeostasis and is able to provide critical information about the origin of the acidosis, like a salicylate poisoning or a lactate acidosis.

6 Literature

1. Smolle KH, Funk GC. Wasser-Elektrolyt- und Säuren-Basen-Störungen in der Intensiv- und Notfallmedizin. 1st ed. Bremen: Uni-Med; 2010.
2. Dhondup T, Quian Q. Electrolyte and Acid-Base Disorders in Chronic Kidney Disease and End-Stage Kidney Failure. *Blood Purif.* 2017;(43): p. 179-188.
3. Gordon D, Schiff M, Omar Hasan M, Seijeoung Kim RP, Richard Abrams M, Karen Cosby M, Bruce L, Lambert P, et al. Diagnostic Error in Medicine Analysis of 583 Physician-Reported Errors. *Arch Intern Med.* 2009; 169(20): p. 1881-1887.
4. Wolf MB, Land EC. A comprehensive, computer-model-based approach for diagnosis and treatment of complex acid–base disorders in critically-ill patients. *Journal of Clinical Monitoring and Computing.* 2011 December; 25(6): p. 353-364.
5. Thomairy NAM, Mummaneni MM, Alsalamah SM, Moussa NM, Coustasse A. Use of Smartphones in Hospitals. *Health Care Manager.* 2015 October/December; 34(4).
6. Brönsted JN. Einige Bemerkungen über den Begriff der Säuren und Basen. *Recueil des Travaux Chimiques des Pays-Bas.* 1923: p. 718-728.
7. Lowry TM. The uniqueness of hydrogen. *Journal of the Society of Chemical Industry.* 1923 January: p. 43-47.
8. Harper D. Online Etymology Dictionary - pH. [Online].; 2001 [cited 2017 January 21]. Available from: <http://www.etymonline.com/index.php?term=pH>.
9. Walter F, Boron ELB. *Medical physiology.* 3rd ed. Philadelphia: Elsevier; 2017.
10. Michael Lieberman ADM. Marks' Basic Medical Biochemistry: A Clinical Approach. In Michael Lieberman ADM. *Marks' Basic Medical Biochemistry: A Clinical Approach.*: Lippincott Williams & Wilkins; 2009. p. 50.
11. Angus S. Acid Base Online Tutorial. [Online].; 2006 [cited 2017 February 25]. Available from: http://fitsweb.uhc.edu/student/selectives/TimurGraham/Introduction_to_Acid_Base_disorders.html.
12. Apurv Khanna NAK. Metabolic alkalosis. *Journal of Nephrology.* 2006 March-April: p. 86-96.
13. Lauren I. Acid base homeostasis [PDF]. [http://pedscm.org/FILE-CABINET/Practical/Akron_pdfs/8FLUIDS.PDF].

14. Blüher S, Schulz M, Bierbach U, Meixensberger J, Tröbs RB, Hirsch W, et al. Central lactic acidosis, hyperventilation, and respiratory alkalosis: leading clinical features in a 3-year-old boy with malignant meningeal melanoma. *European Journal of Pediatrics*. 2008 April: p. 483-485.
15. Zając A, Chalimoniuk M, Maszczyk A, Gołaś A, Lngfort J. Central and Peripheral Fatigue During Resistance Exercise – A Critical Review. *Journal of Human Kinetics*. 2015 December: p. 159-169.
16. Brandis K. anaesthesiaMCQ - 2.4 Renal Regulation of Acid-Base Balance. [Online].; 2015 [cited 2017 February 24. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/ab2_4.php.
17. Hamm LL, Nakhoul N, Hering-Smith KS. Acid-Base Homeostasis. *Clinical Journal of the American Society of Nephrology*. 2015 December: p. 2232-2242.
18. SM M, LR S, J M, M D, L T, RA M. Acidosis-induced downregulation of hepatocyte mitochondrial aquaporin-8 and ureagenesis from ammonia. *Biochemistry and cell biology*. 2015 August: p. 417-420.
19. Gennari FJ, Weise WJ. Acid-Base Disturbances in Gastrointestinal Disease. *Clinical Journal of the American Society of Nephrology*. 2008 November: p. 1861-1868.
20. Machado C. Parietal cells and acid production. [Online].; 2015 [cited 2016 December 3. Available from: <https://www.youtube.com/watch?v=XLrqw6h2j3I>.
21. Brandis K. AnaesthesiaMCQ - 2.2.4 Other Buffers. [Online].; 2015 [cited 2017 February 27. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/ab2_2.php.
22. Wooten EW. Science review: Quantitative acid–base physiology using the Stewart model. *Critical Care*. 2005 July: p. 448-452.
23. The Medical Dictionary. Acidosis. [Online].; 2011 [cited 2016 October 29. Available from: <http://medical-dictionary.thefreedictionary.com/acidosis>.
24. SK E, N. S. Respiratory acidosis. *Respiratory Care*. 2001 April: p. 366-383.
25. Brandis K. anaesthesiaMCQ - 2.4 Renal Regulation of Acid-Base Balance (continued). [Online].; 2015 [cited 2017 February 24. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/ab2_4b.php.

26. Jr BN, JJ C, WB S. CARBON DIOXIDE TITRATION CURVE OF NORMAL MAN. EFFECT OF INCREASING DEGREES OF ACUTE HYPERCAPNIA ON ACID-BASE EQUILIBRIUM. *New England Journal of Medicine*. 1965 January: p. 6-12.
27. Bruno CM, Valenti M. Acid-Base Disorders in Patients with Chronic Obstructive Pulmonary Disease: A Pathophysiological Review [Online].; 2012.
28. Robert J. Fallat M, Jewitt B, Michael Bass M, Kamm B, Forbes H. Norris Jr M. Spirometry in Amyotrophic Lateral Sclerosis. *Arch Neurol*. 1979 February.
29. Brandis K. anaesthesiamcq. [Online].; 2015 [cited 2016 December 22. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/ab9_3.php.
30. Brandis K. anesthesiaMCQ - 5.5 Metabolic Acidosis - Compensation. [Online].; 2015 [cited 2017 February 25. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/ab5_5.php.
31. Albert M, Dell R, Winters R. *annals.org*. [Online].; 1976 [cited 2016 December 22. Available from: <http://annals.org/aim/article/681186/quantitative-displacement-acid-base-equilibrium-metabolic-acidosis>.
32. Ingelfinger JR. Physiological Approach to Assessment of Acid–Base Disturbances. *The new england journal of medicine*. 2014 October: p. 1434-1445.
33. The Medical Dictionary. Alkalosis. [Online].; 2012 [cited 2016 October 29. Available from: <http://medical-dictionary.thefreedictionary.com/alkalosis>.
34. Brandis K. anaesthesiaMCQ. [Online].; 2015 [cited 2017 January 06. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/ab6_2.php.
35. Seldin DW, Rector FCJ. The generation and maintenance of metabolic alkalosis. *Kidney International*. 1972: p. 306-321.
36. Emmett M, Szerlip H. UpToDate Pathogenesis of metabolic alkalosis. [Online].; 2016 [cited 2017 January 06. Available from: https://www.uptodate.com/contents/pathogenesis-of-metabolic-alkalosis?source=see_link.
37. Brandis K. anaesthesiamcq metabolic alkalosis - causes. [Online].; 2015 [cited 2017 January 06. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/ab7_2.php.

38. Paulaa JMPd, Hídalgo SF, Gallardo LB, Toranzo EM. The Importance of Identifying the Association Between Metabolic Alkalosis and Respiratory Acidosis. Arch Bronconeumol. 2012 February; 48(2).
39. Jazeela Fayyaz D, Guy W Soo Hoo M. Medscape - Hypoventilation Syndromes. [Online].; 2016 [cited 2017 February 25. Available from: <http://emedicine.medscape.com/article/304381-overview#a4>.
40. Stewart PH. Independent and dependent variables of acid-base control. Respiration Physiology. 1978 April: p. 9-26.
41. Sterns RH. UpToDate - Stewart approach. [Online].; 2016 [cited 2017 January 22. Available from: https://www.uptodate.com/contents/strong-ions-and-the-analysis-of-acid-base-disturbances-stewart-approach?source=search_result&search=stewart&selectedTitle=1~19.
42. Sterns RH. UpToDate - Effective strong ion difference formula. [Online].; 2016 [cited 2017 January 22. Available from: https://www.uptodate.com/contents/image?imageKey=NEPH%2F59352&topicKey=NEPH%2F2311&rank=1~19&source=see_link&search=stewart.
43. Dubin AM, Meneses MMP, Masevicius FDM, Moseinco MCM, Kutscherauer DOM, Ventrice EM, et al. Comparison of three different methods of evaluation of metabolic acid-base disorders. Critical Care Medicine. 2007 May: p. 1264-1270.
44. Kellum JA. Clinical review: Reunification of acid–base physiology. Critical Care. 2005 August: p. 500-507.
45. Angus S. Acid Base Online Tutorial - Stepwise approach to interpreting the arterial blood gas. [Online].; 2006 [cited 2017 February 24. Available from: http://fitsweb.uchc.edu/student/selectives/TimurGraham/Stepwise_approach.html.
46. Oracle.com - The History of Java Technology. [Online]. [cited 2017 February 12. Available from: <http://www.oracle.com/technetwork/java/javase/overview/javahistory-index-198355.html>.
47. Gosling J, McGilton H. Oracle java language introduction. [Online].; 1996 [cited 2017 January 06. Available from: <http://www.oracle.com/technetwork/java/intro-141325.html>.

48. Wilczynski C. Medscape - Anion Gap. [Online].; 2014 [cited 2017 January 15]. Available from: <http://emedicine.medscape.com/article/2087291-overview>.
49. Fernando J. Life In The Fast Lane - Acid Base Interpretation. [Online].; 2012 [cited 2017 January 16]. Available from: <http://lifeinthefastlane.com/cc/acid-base-interpretation/>.
50. Angus S. Acid Base Online Tutorial - Compensatory response. [Online].; 2015 [cited 2017 January 16]. Available from: http://fitsweb.uhc.edu/student/selectives/TimurGraham/Compensatory_responses_summary.html.
51. Brandis K. Anesthesia MCQ - Acid Base Physiology Case 1. [Online].; 2015 [cited 2017 January 21]. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/AB9_6Case1.php.
52. Brandis K. AnaesthesiaMCQ - Acid Base Physiology Case 18 A lady with respiratory failure and failure to improve. [Online].; 2015 [cited 2017 January 20]. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/AB9_6Case18.php.
53. Nagami GT. Hyperchloremia – Why and how. Nefrología. 2016 July-August: p. 347-353.
54. Berend K, de Vries APJ, Rijk O.B. G. Physiological Approach to Assessment of Acid–Base Disturbances. The New England Journal of Medicine. 2014 October;(371): p. 1434-1445.
55. McAuley D. GlobalRPh. [Online].; 2016 [cited 2017 January 21]. Available from: http://www.globalrph.com/abg_analysis.htm.
56. Kraut JA, Madias NE. Clinical Journal of the American Society of Nephrology. [Online].; 2006 [cited 2017 January 21]. Available from: <http://cjasn.asnjournals.org/content/2/1/162.full.pdf+html>.
57. Java - About Java. [Online]. [cited 2017 January 21]. Available from: <https://www.java.com/de/about/>.
58. Kaliciński W. Android Developers Blog - Understanding APK packaging in Android Studio 2.2. [Online].; 2016 [cited 2017 January 22]. Available from: <https://android-developers.googleblog.com/2016/11/understanding-apk-packaging-in-android-studio-2-2.html>.

59. Brandis K. Anesthesia MCQ - Acid Base Physiology Case 3. [Online].; 2015 [cited 2017 January 21. Available from: http://www.anaesthesiamcq.com/AcidBaseBook/AB9_6Case1.php.

