Statistical Modelling of Human Blood Carbon Dioxide Partial Pressure

MASHHOUR BANI AMER

Department of Electrical Engineering, Al-Isra University, Amman, Jordan

ABSTRACT. This paper deals with statistical modelling of blood carbon dioxide partial pressure pCO₂. The measurements were carried out in the Arab Centre for Heart and Special Surgery in Amman. The statistical analysis of the obtained results showed that the pCO₂ for each kind of blood (arterial, venous and capillary) has a distribution approaching the normal one. Moreover, the practical results showed also that the blood pCO₂ can be expressed by a regression model L [pCO₂] $_i = a_i + b_i pH_i$. By making use of the model, the blood pCO₂ can be indirectly measured with accuracy that fulfils clinical requirements. Therefore, this will lead to less invasive methods and decrease the cost of projected analyser for blood gas analysis. The practical implementation of this model ensures its effectiveness as an indirect method for pCO₂ measurements.

1. Introduction

Evaluation of human blood carbon dioxide partial pressure is very important for diagnosis of cardiopulmonary diseases, particularly in assessment and management of the high risk patients^[1].

Blood pCO₂ can be measured invasively by electrochemical sensors^[2] or noninvasively by transcutaneous ones^[3]. Electrochemical sensors can be characterized by high accuracy and sensitivity^[4]. These sensors have many disadvantages. They are expensive and they must be calibrated frequently which requires the use of expensive calibration standards. Their life time is limited. Due to a deposit forming on the membrane, its frequent replacement is necessary. This increases the cost of analyses and requires additional work to control the useability of the sensor for further measurements. Moreover, these electrochemical sensors require blood sample collection of a value no less than 20 μ l (inva-

sive measurement). From the clinical point of view such volume is not small in the case of infants subjected to intensive therapy for whom pCO_2 measurements are made ten times a day.

In recent years, according to the quick development of the strict clinical requirements, methods to minimize the degree of analytical method invasiveness specially for infants in intensive care had to be found^[5]. Research methods for non-invasive continuous assessment of blood gas parameters in this field led to the development of transcutaneous measurement of blood pCO₂.

These transducers have been widely used in neonatal intensive care and are now a common sight in many hospital units. However, results with adults are not satisfactory because of the skin diffusion barrier "diffusion resistance" for carbon dioxide transport and change in peripheral blood perfusion. When the patient is in shock, or is hypothermic, the transducer will understudy^[6]. Moreover, they contain a heating element for arterialisation of the blood. Hence, leaving the sensor for relatively long time, on the skin surface, for continuous monitoring of pCO₂ may cause skin burns. On the other hand, an increase of body temperature may cause a shift of oxyhaemoglobin dissociation curve to the right. Clinically, this means an increased giving up of oxygen to the tissues with decrease of haemoglobin affinity to oxygen. This leads to negative effects for the patient's health^[7].

These failures pose the following questions:

1) Is it possible to measure the blood pCO_2 indirectly (that means without sensors for blood pCO_2)? How can it be done?

2) Will the precision of pCO_2 measured indirectly be consistent with clinical requirements?

3) What are the advantages of this method?

The answer to these questions is the subject of the present paper.

2. Experiments and Methods

Human blood can be divided into three types: arterial, venous and capillary. The measurements of arterial, capillary and venous blood pCO_2 were performed in the Arab Centre for Heart and Special Surgery by making use of two analysers: Instrumentation Laboratory (IL) type 1304^[8] and Corning (COR) type 168^[9], simultaneously.

Before performance of experiments a discussion with medical specialists about the physiologically significant parameters for pCO_2 modelling was provided. These parameters are discussed in the next sections. Then, for each collected blood sample (for each patient) the blood oxygen partial pressure (pO_2), hydrogen ion concentration (pH) and pCO_2 were measured directly and all possible indirect parameters (such as Biocarbonate (HCO₃) and Base Excess (BE)), calculated by the analysers used, were evaluated. The measurements of the above parameters were performed for two hundred different patients for each blood type. The blood samples were collected from patient's artery in case of arterial blood, vein in case of venous blood and patient's finger in case of capillary blood. Furthermore, at the same time with the above measured parameters, the Cardiac Output (CO) and Cardiac Index (CI) were controlled. Also, the patient's data such as sex, age, weight, height, temperature and clinical diagnostic were registered. Of course, the clinical diagnostic were supplied by the medical specialists.

The series of repeated measurements for particular patients were not made for two reasons. Firstly, the execution of measurements repeated for a particular patient requires the availability of the patient in the hospital for a long period of time which is not always possible. Moreover, even if the patient is available during that time, the carrying out of additional invasive measurements is not allowed in medical procedure if there is no clinical need. The more so because the pO_2 , pCO_2 , pH and CO measurements are invasive and each additional measurement means a risk of complications to which the patient may be exposed. Secondly, the patients investigated are described by similar clinical characteristics (homogeneous group). Thus, the deviation of the mathematical model describing a particular patient from the general model made for all patients tested is practically negligible.

3. Statistical Analysis of Results of Blood pCO₂ Measurements

The obtained results of pCO_2 measurements were analysed according to the following procedure:

3.1 Homogeneity Analysis of the Obtained pCO₂ Results

The obtained pCO₂ samples can be used to get results about the investigated population only if they are *medically* and *statistically homogeneous*. The medical homogeneity of pCO₂ sample was fulfilled by selecting patients who had similar clinical data^[10]. First the randomness of the obtained samples was tested using randomness test. The test results showed that all the obtained samples of the parameters measured were random. Then, statistical homogeneity was tested by making use of Dixon's test^[11]. The main purpose of statistical homogeneity of the sample was to eliminate the uncertain (outlier) results that were burdened with parasitic errors.

3.2 Sample Statistics

After the elimination of uncertain results of measurements, the sample statistics were estimated (Table 1). From these statistics the following results were concluded:

Measured parameter	pCO ₂ [mmHg]		
Sample statistics	а	v	с
Average	36.81	43.28	33.59
Median	37.12	43.27	33.60
Mode	35.85	42.60	33.00
Variance	13.43	29.34	19.16
Standard deviation	3.66	5.42	4.38
Coefficient of variation	9.94%	12.52%	13.03%
Interquartile range	4.58	7.42	5.50
Skewness	- 0.05	0.06	0.20
Kurtosis	0.11	- 0.40	0.26

TABLE 1. Summary statistics of the obtained results of pCO₂ measurements in case of (a) arterial (v) venous and (c) capillary blood.

1) The difference between average values of arterial blood carbon dioxide partial pressure pCO_2a and venous one pCO_2v was clinically and statistically significant. This confirmed that pCO_2a and pCO_2v have different clinical norms.

2) The coefficient of variation of venous blood pCO_2v was bigger than the coefficient of variation of arterial blood pCO_2a . This indicated that the biological deviation of venous blood pCO_2v was bigger than the corresponding one for pCO_2a . Clinically this meant that the range of pCO_2v normal values would be larger than the range for pCO_2a . Hence, the use of clinical standard for arterial blood pCO_2a for interpretation of venous blood pCO_2v would lead to interpretation errors and then to incorrect therapy of investigated patients. Moreover, it can be concluded that the difference between blood pCO_2v and pCO_2c was smaller than the one between the average values of pCO_2v and pCO_2c . Thus, the use of capillary blood pCO_2c as an indicator of arterial blood pCO_2a would be burdened by smaller error than the error that can appear if pCO_2c is used to indicate the venous blood pCO_2v . Therefore, the use of capillary blood instead of arterial or venous blood pCO_2v .

3) The skewness and kurtosis of investigated pCO_2a , pCO_2v and pCO_2c were small that allowed to hypothesize that the empirical distribution of pCO_2a , pCO_2v , and pCO_2c is approaching a normal distribution. The hypothesis was then verified using nonparametric tests.

3.3 Nonparametric Tests

These tests are used to test the conformity of the empirical distribution of the investigated blood pCO_2 with the theoretical one. Before performing these tests, the histograms for pCO_2a , pCO_2v and pCO_2c were determined (Figure 1).



Fig. 1. Histograms for a) arterial blood pCO_2a , b) venous blood pCO_2v and c) capillary blood pCO^2c .

The plotted histograms present the graphical structure of the obtained results of pCO₂ measurements and give an approximate information about their empirical distribution. From Figure 1 it can be concluded that each kind of the investigated samples has an empirical distribution approaching the normal one. This hypothesis can be verified statistically using nonparametric tests such as: normality test, Kolmogrov test and chi-square one^[11]. The normality test is used only for verification of the hypothesis of the empirical distribution with the normal one. However, this gives only an approximate information. On the other hand, the use of Kolmogrov test requires a detailed determination of the hypothetical distribution function giving the value of its parameters (which is not fulfilled in case of the obtained blood pCO₂ samples). The chi-square test takes into consideration a substitution of the unknown parameters of the hypothetical distribution by their estimators from the sample tested. Hence, the chi-square test is used for verification of the conformity of the empirical distribution with the theoretical one (here it is a normal distribution). The application of this test showed that the carbon dioxide partial pressure pCO₂ had a distribution approaching the normal one irrespective of the blood type (Table 2). The chisquare test results presented in Table (2) showed that the calculated chi-square statistic χ^2 was less than the critical value χ^2_0 for each parameter irrespective of blood type. Hence it was not possible to reject the hypothesis that the data came from normal distribution. Therefore, each of the measured parameters had a distribution approaching the normal one.

Test results Parameter	Chi-square statistic (calculated) χ^2	Degree of freedom	Significance level α	Critical value χ_0^2
pO ₂ a	8.12	12	0.05	21.03
pCO ₂ a	4.71	13	0.05	22.37
рНа	2.16	6	0.05	12.60
pO ₂ v	10.25	9	0.05	16.92
pCO ₂ v	5.33	9	0.05	16.92
pHv	3.41	8	0.05	15.51
pO ₂ c	3.78	10	0.05	18.31
pCO ₂ c	2.54	7	0.05	14.07
рНс	3.17	10	0.05	18.31
Hb	12.27	7	0.05	14.07

TABLE 2. Results of chi-square test.

4. Modelling of blood pCO₂

Before the modelling of blood pCO₂ the following assumptions were made:

1) The use of pCO_2 sensor was abandoned so the fitted blood pCO_2 model must give an indirect method for measurement of blood pCO_2 .

2) The indirect method supplied must be universal for patients fulfilling the assumptions that the patients examined associated with the respiratory system, had a correct cardiac output and a correct peripheral blood flow.



FIG. 2. General structure of the built blood pCO_2 model.

Fortunately, the blood pCO_2 model input variables (Figure 2) are interdependent and these dependences can be expressed by the following general descriptions^[12]:

$$V_a = f_1 \left(V_d, P_d \right) \tag{1}$$

$$pH = f_2(HCO_3, pO_2, P_d)$$
⁽²⁾

$$pCO_2 = f_3 (V_a, CO, pH, Hb)$$
(3)

The symbols that appear in Figure 2 denote the following: pH - Hydrogen ion concentration; P_d – Patient's data (such as Age (A), Sex (S), Weight (W), Length (L) and Illness (I)); T – patient's temperature; CO – Cardiac output; V_d – Volume of dead space; V_a – Alveolar Ventilation; HCO_3^- – Actual Biocarbonate; pCO₂ – Carbon dioxide partial pressure; Hb – Hemoglobin and pO₂ –

Blood Oxygen partial pressure. Moreover, according to the previously stated assumptions, the investigated patients had correct Cardiac Output CO. Thus, the significance of this variable for blood pCO_2 model was very small and practically it can be eliminated from the built pCO_2 model. Furthermore, the investigated patients for whom the model was built, formed a homogeneous sample. This meant that the significance of patients clinical data was included by the homogeneity of the investigated patients sample.

From the above discussion and assumptions, it can be concluded that the most significance variables for blood pCO_2 are: pH, pO_2 , and Hb. Therefore, this greatly simplifies the blood pCO_2 built model.

5. The Fitting of Blood pCO₂ Model

From the previous discussion, it can be concluded that to build the pCO₂ model only three input variables are required (pO₂, pH and Hb). The correlation coefficients between these variables (in case of arterial blood as an example) are presented in Table 3. These results show that the strongest statistical dependence is existing between pCO₂ and pH. Moreover, the input independent variables are correlated with each other and these correlation coefficients are statistically significant. These correlation coefficients between Ln[pCO₂]_{*i*} and pHi are: -0.73 for arterial blood, -0.69 for venous blood and -0.57 for capillary blood. A graphical illustration of this correlation is shown in Figure 3.

Correlation coefficients for arterial blood pCO ₂ model variables						
	pO ₂ a pCO ₂ a pHa Hb					
pO ₂ a	1.00	- 0.24	0.20	- 0.14		
pCO ₂ a	- 0.24	1.00	- 0.48	0.08		
рНа	0.20	- 0.48	1.00	- 0.01		
Hb	- 0.14	0.08	- 0.01	1.00		

TABLE 3. Correlation coefficients between arterial blood pCO_2 model variables	TABLE	3. Correlation	n coefficients between	n arterial blood pCC	, model variables.
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Each type of blood has its clinical standard and interpretation for blood gas parameters^[13]. Thus, three models would be required to be built and fitted:

- 1) Arterial blood pCO₂ model.
- 2) Venous blood pCO₂ model.
- 3) Capillary blood pCO₂ model.

These models would have the same structure but the difference would be that in each model the applied input and output variables must characterize the same



Fig. 3. Graphical illustration of Ln pCO_2 versus pH for a) arterial, b) venous and c) capillary blood.

type of blood. Therefore, the investigations of pH, pCO₂ and pO₂ must be done for each type of blood separately. The measurements of these parameters were performed for two hundreds different patients that covered the normal and pathological ranges of blood pCO₂. Then, by making use of the obtained results of measurements, the blood pCO₂ models for each type of blood were fitted by making use of regression methods^[14]. As a regression method the stepwise one was used. This method is one of the best regression methods that could be used for physiological mathematical models fitting. Its main advantage is that it allows apart from the testing of each individual input variables significance for it when they are all in the model. Thus, it allowed to discover and eliminate insignificant input variables for each pCO₂ model caused by the interdependence existing between them. That is why the pO₂ and Hb did not appear in the final fitted pCO₂ models.

The obtained general fitted blood pCO₂ model can be described by:

$$Ln \left[pCO_2(37^{\circ}C) \right]_i = a_i + b_i pH_i$$
(4)

where the subscript *i* refers to the investigated blood type, while the coefficients a_i and b_i are the estimated model parameters for the given blood type (see Table 4).

Estimated model	Blood type			
Parameters	а	v	с	
а	22.9628	26.6119	10.8740	
b	- 2.61710	- 3.1072	- 0.99363	

TABLE 4. Summary of estimated parameters for arterial "a", venous "v" and capillary "c" blood fitted Ln[pCO₂(37°C)] models.

Thus, to measure indirectly the blood pCO_2 , it was enough to know its pH. The blood pCO_2 models were fitted for the patient's temperature equal to 37°C. Thus, if it is not equal to 37°C, a correction for the estimated pCO_2 from this model had to be performed to actual patient's temperature "t" according to the following equation^[15]:

$$pCO_2(t) = pCO_2(37^{\circ}\text{C}) \times 10^{0.021(t-37)}$$
 (5)

where *t* is the actual patient's temperature.

Residual analysis of pCO_2 fitted models did not show any inconsistency with general assumptions about models residuals. To judge or measure the efficiency

and adequacy of the fitted pCO_{2i} models the coefficient of determination (R^2) was evaluated for each model. Moreover, the significance of each fitted model was tested using F-test. The obtained results are presented in Table 5. Statistical analysis of fitted pCO₂ models results shown in Table 5 confirm that these models are significant and adequate^[14]. Moreover, the precision of results of pCO₂ estimated from the fitted models fulfils the clinical requirements^[13]. This is because the combined standard uncertainty for the average value of model output pCO₂, determined using the "general law for error propagation"^[16], fulfils the clinical requirements. The permissible error for pCO_2 measurements is given by Tonk's criterion^[17]. According to this criterion the combined standard uncertainty of results of blood pCO₂ measurements must not exceed 1/4 the normal range 36-44 mmHg for pCO₂. Thus, in percentage, the permissible error for pCO_2 is 5%. The calculated combined uncertainty for indirect measured pCO_2 using the fitted model was 1.7%. This meant that the accuracy of the fitted pCO₂ models for measuring indirectly the blood pCO₂ fulfilled the clinical requirements.

For arterial blood Ln pCO ₂ a fitted model							
Source of variation	Sum of squares	Degree of freedom	Mean square	F - ratio	F - table		
Model	1.39	1	1.390	695.00			
Error	0.32	190	0.002		3.89		
Total	1.71	191		4			
	Coefficient of determination $(R^2) = 0.81$						
For venous blood Ln pCO ₂ v fitted model							
Model	2.17	1	2.170				
Error	0.71	190	0.004	542.50	3.89		
Total	2.88	191					
Coefficient of determination $(R^2) = 0.75$							
	F	for capillary Ln p	CO ₂ c fitted mo	del			
Model	2.76	1	2.760				
Error	1.43	190	0.008	345.00	3.89		
Total	4.19	191		•			
Coefficient of determination $(R^2) = 0.66$							

TABLE 5. Analysis of variance for testing the significance of fitted models.

6. Practical Implementation of the Obtained pCO₂ Model

The human blood pCO₂ measurement can be carried out by an electronic instrument called blood gas analyser. The blood gas analyser can be used also to measure directly the blood oxygen partial pressure pO₂ and hydrogen ion concentration pH. Thus, the blood gas analyser consists of three electrochemical sensors; pO₂ sensor, pCO₂ sensor and pH sensor. Each of the sensors serves for measurement of one parameter. Of course, these sensors are very expensive. Moreover, each sensor requires special expensive standards for its frequent calibration. Thus, reducing the sensors from three into two sensors in blood gas analyser decreases the cost of blood gas analyser and increases its reliability. Furthermore, it leads to a reduction of the required volume of blood sample for blood (pH, pO₂, pCO₂) measurements from 40 μ l to 20 μ l. This will meet the strict clinical requirements for finding a new method for blood pCO₂ measurements that minimises the degree of analytical method invasiveness specially for infants in intensive care.

This research is done to eliminate the pCO_2 sensor and design a new blood gas analyser using only two sensors to measure three parameters, pCO_2 , pO_2 and pH. Of course, here the measurement of pCO_2 is done indirectly using the obtained fitted statistical model:

$$Ln [pCO_2(37^{\circ}C)]_i = a_i + b_i pH_i$$

This model represents mathematically the relationship between pCO_2 and pH. The coefficients a_i and b_i are estimated for capillary, venous and arterial blood. According to this model, if the blood pH is known which can be measured directly using a pH sensor then the blood pCO_2 can be measured indirectly with accuracy that fulfils the clinical requirements using the above model in a form of algorithm written in assembly language suitable for the used microprocessor. Of course, this algorithm must be stored in the analyser program memory. Thus, the fitted statistical model of pCO_2 forms an indirect method for pCO_2 measurements and allows to eliminate the pCO_2 sensor.

The obtained fitted pCO_2 model is experimentally tested. This is done by comparing the indirect measurements of blood pCO_2 determined using the fitted pCO_2 model with the measurements made with the standard IL 1304 blood gas analyser. In this analyser the pCO_2 is measured directly because it contains pCO_2 , pO_2 and pH sensors. This analyser can be interfaced with personal computer through the interface RS232. Thus, the measured pH, pCO_2 and pO_2 can be sent to PC to perform mathematical processing for the results of measurements. Moreover, a software is developed to determine indirectly the pCO_2 using the pCO_2 fitted models and then to perform a mathematical analysis of the obtained data. The measurements of directly measured pCO_2 using IL analyser are compared with the pCO_2 indirectly measured using the fitted model for five hundred different measurements that may cover the change range of pCO_2 . Of course, these measurements are made for new samples different from the blood samples for which the model is fitted. The obtained results show that the indirect pCO_2 measurements are highly correlated with the direct pCO_2 measurements and the correlation coefficients between them are 0.93 for arterial blood, 0.82 for venous blood and 0.71 for capillary blood. Thus it can be concluded that the obtained fitted pCO_2 model forms an accurate method for indirect measurements of pCO_2 and it may lead to produce an analyser with two sensors (pH and pO_2) for measurement of three parameters pH, pO_2 and pCO_2 instead of the design with three sensors.

From the experimental implementation of the models and the obtained correlation coefficients, it can be concluded also that the fitted pCO_2c model has the biggest error. This is because the randomness of the data obtained for arterial and venous blood is better than the randomness for capillary blood data. This effect is clearly observed in Figure 4. The data in Figure 4(c) is clustered in a small region while in Figure 4(a) and (b) the data are scattered over a wide region. Thus, to improve the accuracy of pCO_2c model, additional measurements of pCO_2c and pHc should be performed.



Fig. 4. Graphic presentation of fitted pCO₂ models for arterial blood a), venous blood b) and capillary blood c).

7. Conclusions

Modeling of human blood carbon dioxide partial pressure is very important and may lead to development of less invasive methods for pCO_2 measurements. The fitted pCO_2 model can be used as an indirect method for carbon dioxide partial pressure measurements. This new method has the following advantages in comparison with the traditional ones (the methods that depend on the application of pCO_2 sensor for pCO_2 measurements):

1) It reveals numerically the dependence between blood gas parameters.

2) Fulfils the clinical requirements.

3) More economical because neither pCO_2 sensor nor calibration standards is required.

4) Less invasive method than traditional ones. This is because the required blood sample for blood gas measurements is less than that one in case of traditional methods.

5) It simplifies the design, operation, calibration process and maintenance of blood gas analyser.

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*ا*لمستخلص . إن معرفة ثاني أكسيد الكربون pCO₂ في دم الإنسان مهم جداً من الناحية الطبية خاصة في غرف العمليات الجراحية والعناية الحثيثة لتشخيص الأمراض التنفسية من أجل تحديد العلاج اللازم .

إن أجهزة قياس الغازات في الدم المتوفرة حاليًا في الأسواق التجارية تقيس إلى جانب الضغط الجزئي لثاني أكسيد الكربون pCO₂ الضغط الجزئي للأكسجين pO₂ ، وتركيز أيونات الهيدروجين (درجة الحموضة) pH . إن هذه الأجهزة تحتوى على ثلاث مجسات إلكتر وكيمائية لقياس العناصر الثلاثة السابقة . وتحتاج هذه المجسات إلى معايرة مستمرة والتي تتطلب محاليل معايرة غالية الثمن مما يترتب عليه ارتفاع سعر أجهزة الغازات . كما تحتاج أيضًا إلى صيانة دورية بسبب تكون ترسبات على الغشاء النفاذ (الذي يعتبر أحد الأجزاء الرئيسية للمجسات الإلكتر وكيمائية) للغاز مما يتطلب تغييراً دوريًا لهذا الغشاء وهذا يسبب عملاً إضافيًا للشخص الطبي المستخدم لهذا الجهاز للتأكد من صلاحيته للقياس . إضافة إلى ما تم ذكره فإن هذه الأجهزة تحتاج إلى عينة دم لا تقل عن ٢٠ ميكروليتر . إن هذا الحجم اللازم (٢٠ ميكروليتر) من وجهة نظر الطب الحديث ليس قليلا وخاصة عند الأطفال في غرفة العناية الحثيثة والمصابين بأمراض الجهاز التنفسي الذين يتم قياس الغازات لهم في الدم حوالي عشر مرات يوميًا . ولهذا فإن أجهزة قياس الغازات المصنعة حاليًا لا تتوافق مع المتطلبات الطبية من حيث حجم العينة المأخوذة من الإنسان ولا من حيث تكلفة هذه الأجهزة .

للتقليل من حجم العينة المأخوذة من الإنسان لقياس الغازات في الدم

بما يتناسب مع متطلبات الطب المعاصر فقد تم التوصل إلى طريقة جديدة لقياس ضغط ثاني أكسيد الكربون كنتيجة للتمثيل الإحصائي للضغط الجزئي لثاني أكسيد الكربون في دم الإنسان ، حيث تم عمل قياس للغازات لحوالي (٢٠٠) مريض ذوي أعمار وأطوال وأوزان وأمراض مختلفة في المشفى العربي للقلب والجراحة الخاصة في عمان ، ثم إيجاد النموذج الرياضي ل PCO2 والذي يمثل طريقة جديدة لقياس PCO2 . وأما الميزة الأخرى لهذه الطريقة فهي أنها أقل تكلفة من الطرق المعتادة لقياس PCO2 لأنها لا تحتاج إلى وجود مجس كما هو الحال في الأجهزة المصنعة حاليا بل تستخدم مجسا H لمعرفة 200 مما يؤدي إلى توفير مجس في أجهزة الغازات فيما إذا استغلت هذه الطريقة .