Modelling of Diffusing Capacity Measurement Results in Lung Microangiopathy Patients
A Novel Pulmonary Diagnostic Support

R. Kalicka¹; W. Słomiński¹; K. Kuziemska²
¹Department of Biomedical Engineering, Gdansk University of Technology, Gdansk, Poland;
²Department of Allergology, Medical University of Gdansk, Gdansk, Poland

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Summary
Background: Lung microangiopathy is a little known negative influence of diabetes mellitus on the functioning of the lungs. In current medical practice lung microangiopathy is diagnosed by comparing two measurements of lung diffusing capacity — once with the subject standing and once with the subject lying down. The necessity to take two measurements is inconvenient. Objectives: The aim of this study is to design a supportive method for diagnosing lung microangiopathy. This will be based on routinely performed pulmonary measurements as well as on investigation of process modelling and data processing. Methods: A model of the diffusion of oxygen from the alveoli to the blood has been described with a set of differential equations. The idea of the proposed model is based on the physiological analysis of the oxygen flow (caused by a concentration gradient) and on general knowledge regarding the kinetics of associating oxygen with haemoglobin. The model parameters are estimated using diffusing capacity and alveolar volume measurements — routinely performed in pulmonary tests. Results: The model parameter estimates proved good candidates for the binary classification of the presence or absence of microangiopathy. The proposed classification procedure, based on parameter values and established diagnostic thresholds, gives sensitivity Sens = 79.34% and specificity Spec = 87.08%. The results of classification with the use of diffusing capacity measurement are worse: Sens = 62.12% and Spec = 79.89%. Conclusions: The proposed classification procedure is based on the model parameters. These have proved to be sensitive indicators of lung microangiopathy. Close to 80% of microangiopathy cases have been classified as such. Less than 20% were false alarms. The oxygen pathway model allows for simulations. Blood saturation and oxygen partial pressure have been simulated for the organism’s various needs for oxygen, both for the normal and the impaired alveoli-capillary barrier.

1. Introduction

Lung microangiopathy is the little known negative influence of diabetes mellitus on the lungs. In such cases diffusing capacity reduction as well as lung flow and volume limitation are observed. Diabetes mellitus is a condition in which either the pancreas no longer produces enough insulin or the cells stop responding to the insulin that is produced. These abnormalities result in high glucose levels. Diabetes is a chronic illness that can lead to diabetic angiopathy, a disease of the blood vessels (arteries, veins and capillaries). There are two types of diabetic angiopathy: macraangiopathy (disease of the larger blood vessels) and microangiopathy (microvascular disease). The examples of angiopathy include: neuropathy (damage to nerves in the peripheral nervous system), nephropathy (damage to the kidneys) and retinopathy (damage to the retina).

Current knowledge regarding diabetic lung microangiopathy is limited. Histopathological examination of lung biopsy samples is not a conclusive test of the consequences of diabetes [1]. Animal experiments and post-mortem examinations have revealed the influence of diabetes on the lung capillaries and alveolar-capillary membranes [2–4]. Histopathological tests have revealed the thickening of the alveolar and venous capillary walls [5, 6].

Lung diffusing capacity measurements illustrate the state of alveolar-capillary barriers [7]. These are measurements of diffusion across the alveolar-capillary membrane. For diagnosing microangiopathy, the lung diffusing capacity is measured in two body positions: standing ($D_{L,standing}$) and lying on the back ($D_{L,lying}$) [8, 9]. On account of the human anatomic structure, diffusing capacity depends on the body position. For healthy subjects the diffusing capacity increases in the reclined position, $D_{L,lying} > D_{L,standing}$. The opposite is observed in the case of microangiopathic patients: the diffusing capacity decreases when the subject is lying $D_{L,lying} < D_{L,standing}$. This is the result of blood vessel damage and alveolar thickening caused by diabetes [10]. Only the fact that diffusing capacity increases or...
decreases in a given position is important as far as microangiopathy diagnosis is concerned.

2. Objectives

The aim of the study presented in this paper is to find a method to improve lung microangiopathy diagnostics. The research is based on diffusing capacity measurement $D_L$, obtained from routine pulmonary tests, and on oxygen diffusion modelling. The measured $D_L$ depends on the alveolar-capillary barrier condition.

A new model of oxygen diffusion has been designed and verified. The question is whether this model’s parameters provide new information concerning microangiopathy and whether these constitute a new, sensitive indicator of individual lung microangiopathy cases. Our research reveals that it is possible to distinguish between non-microangiopathic and microangiopathic subjects using this model’s parameter estimates.

Previously developed and published models of the transportation of oxygen from the alveoli into the blood have been designed to provide very detailed descriptions of the phenomenon (see Frank [11], Hsia [12], Federspiel [13], Wang and Popel [14], Roughton and Forster [15]). This emphasis on detail has increased model complexity and thus also the number of parameters, which in turn, on account of their number, has made it difficult to accurately identify all the model parameters, in accordance with the Akaike information criterion. By contrast, the aim of the research presented in this paper is to find a model of the functionality of the system (not a model of the system itself) and to estimate the model parameters using routine test results, $D_L$. The idea of the proposed model is based on the physiological analysis of oxygen flow, which is caused by a concentration gradient, and on general knowledge concerning the kinetics of oxygen association with haemoglobin.

3. Methods

The quality of gas exchange in the lungs depends on diffusing capacity $D_L$. During the measurement of $D_L$ [16] a person takes a full inhalation of air mixed with small amounts of carbon monoxide and helium. The mixture is held in the lung for a few seconds and then exhaled. The first part of the expired gas is discarded. The next portion, which represents gas from the alveoli, is collected. The $D_L$ is determined by analyzing the concentrations of carbon monoxide and helium in the samples of the inhaled gas and the exhaled gas. In the same test the alveolar volume $V_A$ is also determined using a single-breath helium dilution technique.

Figure 1 shows oxygen diffusion. Oxygen is supplied to the alveoli via pulmonary airways $(u(t))$. Oxygen transportation from the alveoli to erythrocytes, through the alveoli-capillary barrier, is presented as the flow $f_{21}[g \cdot s^{-1}]$.

The blood saturation $S \in (0,1)$, (also given as $Se(0,100\%)$) shows what part (percentage) of oxygen capacity (maximum amount of oxygen transported by the erythrocytes) is currently being transported by the blood. Poorly oxygenated blood enters the pulmonary artery and then, enriched in oxygen, flows out of the lung through the pulmonary vein. Lung arterial blood saturation $S_A$ differs from lung venous blood saturation $S_V$, $S_A > S_V$.

Flows $f_{21}[g \cdot s^{-1}]$ and $f_{21}[g \cdot s^{-1}]$ respectively represent the amount of oxygen in the blood flowing into the lung and the amount of oxygen flowing out of the lung.

The oxygen diffusion model is:

$$\begin{align*}
    m_1(t) &= -f_{21}(t) + u(t),
m_1(0) &= m_1(0) \\
    m_2(t) &= -f_{21}(t) + f_{20}(t) - f_{22}(t),
m_2(0) &= m_2(0)
\end{align*}$$

where the $m_1(t)[g]$ and $m_2(t)[g]$ are the $O_2$ masses in the alveoli and in the blood vessels respectively. The initial states $m_1(0)[g]$ and $m_2(0)[g]$ depend on oxygen partial pressure and region volume.

The oxygen partial pressure in the alveoli is $P_1(0) = 13.32 [kPa]$ and in the blood it is $P_2(0) = 13.63 [kPa]$, whereas the blood volume $V_2$ in lung capillary vessels is $10^{-4} [m^3]$ [1, 17, 20]. The alveoli volume $V_1 = V_3$ is measured during the diffusing capacity test. The relationship between the $O_2$ mass and the pressure is:

$$\begin{align*}
    P_1(t) &= \frac{RT}{M_{O_2}V_1} m_1(t) \quad \text{and} \\
    P_2(t) &= \frac{RT}{M_{O_2}V_2} m_2(t),
\end{align*}$$

$R[N m K^{-1} mol^{-1}]$ is gas constant, $T[K]$ is absolute temperature and $M_{O_2}[g mol^{-1}]$ is the molecular mass.

The mass diffusion, i.e. flow $f_{21}(t)$ via the membrane, has been presented using the diffusing capacity $D_L[mol s^{-1} kPa^{-1}]$.

The flow is caused by the concentration gradient $\Delta c = c_1 - c_2 > 0$, where

$$\begin{align*}
    c_1 &= \frac{m_1}{V_1} \quad \text{and} \quad c_2 = \frac{m_2}{V_2}.
\end{align*}$$

The signal $u(t)$ represents respiratory flow with the period $T_p$, the delay time $t_{d}[s]$ (the time the air passes through the airway to the alveoli) and the duty cycle $d$. For modelling, simulation and forced ventilation purposes, the respiratory input wave is presented as rectangular, a falling (triangular) or sinusoidal signal [18, 19]. The input amplitude $[g \cdot s^{-1}]$ depends on the organism’s metabolic rate $(MR)$, i.e. the organism’s need for oxygen. The period $T_p$ represents a single respiratory cycle.

The Metabolic Rate, $MR [g \cdot s^{-1}]$ depends on the organism’s state of activity and on the body weight. The metabolic equivalent of the task $(MET)$ is defined as oxygen consumption with the body at rest in $[g]$, during $1[s]$ per $1[kg]$ of body weight, thus $1[MET] = 1.02 \cdot 10^{-3} [g \cdot kg^{-1} \cdot s^{-1}]$.

While at rest the organism needs $1[MET]$ of oxygen per each kilo of the body weight, during an intense physical activity the need can increase even to $18[MET]$ [21].

In medical practice blood saturation $S$ gives the basic information concerning the quantity of oxygen transported from the lungs to all the other organs. The haemoglobin in erythrocytes is bound in reversible bonds with oxygen [22, 23]. One haemoglobin particle $[Hb]$ can bind a maximum of four particles of oxygen $[O_2]$. The final, fully saturated, form of haemo-

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globin $[HbO_3]$ is called oxyhaemoglobin. Haemoglobin may also be present in the blood in partially saturated states: $[HbO_2]$, $[HbO]$ and $[Hb]$. Let us assume that all the haemoglobin particles have the final form of saturation, $[HbO_8]$, i.e. the number of intermediary states is negligible. This assumption is based on the relationship between the transit time $T_{trans}$ and the oxidation time $t_{toxyd}$ of haemoglobin in lung vessels. Typical values are $T_{trans} = 0.75$ s and $t_{toxyd} = 0.25$ s and thus $T_{trans} > t_{toxyd}$. Hence all the haemoglobin particles stay long enough in the lung vessels to be fully oxygenated.

The kinetics of oxygen association with hemoglobin is described by Hill’s equation [24]:

$$S_V(t) = \frac{K \cdot P_2(t)^n}{1 + K_2(P_2(t))^n}, \quad (3)$$

where $P_2(t)$ is oxygen partial pressure in the blood, $n = 2.8$ is the Hill’s constant and $K = 1.2256 \cdot 10^{-10}[1/\text{Pa}]^n$ is the association constant.

The outflow $f_{02}$ depends on the blood velocity $\phi[m^3 \cdot s^{-1}]$, maximum erythrocyte oxygen capacity $\phi[mol \cdot m^{-3}]$ and venous blood saturation $S_V(t)$. The endogenous inflow $f_{20}$ depends on the outflow $f_{02}$ and the organism’s need for oxygen $MR$:

$$f_{20}(t) = f_{02}(t) - MR \quad (4)$$
$$f_{02}(t) = S_A(t) \cdot \phi \cdot \phi \cdot M_{O_2} \quad (5)$$

The elimination flow $f_{02}$, according to Hill’s equation, is as follows:

$$f_{02}(t) = \frac{c_{Hill}}{1 + c_{Hill} \cdot \phi \cdot \phi \cdot M_{O_2}} \cdot \frac{R \cdot T}{M_{O_2} \cdot V_3} \quad n \quad (6)$$

After applying (4), (5) and (6) to Equation 1 the oxygen diffusion model is as can be seen in Figure 2.

For modelling and simulation purposes, we assume the input signal $u_1(t)$ at the mouth to have a rectangular form. The model parameters form the vector $p = [p_1, p_2]$. The measurements and constants form vectors $y = [y_1, y_2] = [D_l, V_4], V_1 = V_A$ and $b = [b_1, b_2, ..., b_{12}] = [T_p, t_p, d, V_2, \phi, \phi_i, m_t(0), m_i(0), MR, R, T, M_{O_2}].$ The model parameters have been estimated with the use of measurements $y = [y_1, y_2] = [D_l, V_4]$ and physiological constants $b[b_i] = [R, T, V_4, i = 1, 2, 3]$ according to Equation 7.

Measurements $y = [y_1, y_2] = [D_l, V_4], \Delta y_{1,2}$ were taken. On the basis of these measurements the model parameters $p = [p_1, p_2], \Delta p_{1,2}, i = 1, 2$ were calculated. The $\Delta p_{1,2}, i = 1, 2$ (which depends on the $\Delta y_{1,2}, j = 1, 2$) was computed using the error propagation formula:

$$\Delta p_i = \sqrt{\sum_{j=1}^{2} \left( \frac{\partial p_i}{\partial y_j} \right)^2 \Delta y_j}, \quad i = 1, 2 \quad (8)$$

$$\begin{cases}
\dot{m}_1(t) = -p_1 \cdot m_1(t) + p_2 \cdot m_2(t) + u_1(t), & m_1(0) \\
\dot{m}_2(t) = p_1 \cdot m_1(t) - p_2 \cdot m_2(t) - MR, & m_2(0)
\end{cases} \quad (7)$$

$$p_1 = \frac{D_l \cdot R \cdot T}{V_1}, \quad p_2 = \frac{D_l \cdot R \cdot T}{V_2}$$

$$u_i(t) = \frac{MR}{d} \cdot \sum_{i=1}^{n} [1((i \cdot T_p - t_0) - (i \cdot T_p - t_0) - T_p \cdot d)] \quad (9)$$
For \( \frac{\Delta y_1}{y_1} = \frac{\Delta y_2}{y_2} = 3\% \) (as declared by the manufacturers of measuring devices [25]) the relative uncertainties have been calculated as \( \frac{\Delta P_1}{P_1} = 3\% \) and \( \frac{\Delta P_2}{P_2} = 4.2\% \).

The model parameter estimates allow for the simulation of how oxygen diffusion functions. Blood saturation \( S_V(t) \) has clinical and physiological significance, which is why we have decided to present \( S_V(t) \) simulations as an example. Saturation \( S_V(t) \) depends on the metabolic rate \( MR \), which in turn, depends on the physical activity. To illustrate this, three metabolic rate values were taken into consideration: \( MR_{rest} = 1 \text{[MET]} \cdot W[kg] \) (rest, watching TV), \( MR_{meff} = 3.5 \text{[MET]} \cdot W[kg] \) (house work, light or moderate effort) and \( MR_{feff} = 18 \text{[MET]} \cdot W[kg] \) (forced effort, running at 7.5 [km \cdot h^{-1}], where \( W[kg] \) is the body weight [21, 26].

The measurements \( V_A^{angiop} = 5.71 \cdot 10^{-3} \text{[m}^3 \text{]}, V_A^{no \, angiop} = 5.42 \cdot 10^{-3} \text{[m}^3 \text{]}, D_L^{angiop} = 1.54 \cdot 10^{-7} \text{[mols}^{-1} \text{Pa}], D_L^{no \, angiop} = 1.59 \cdot 10^{-7} \text{[mols}^{-1} \text{Pa]} \) were taken and used for simulations together with the constants: \( M = 32 \text{[gmol}^{-1} \text{]} \) (the molecular mass), \( V_2 = 0.10 \cdot 10^{-3} \text{[m}^3 \text{]} \) (blood volume in lung capillary vessels), \( \varphi = 9.24 \cdot 10^{-3} \text{[molm}^{-3} \text{]} \) (maximum erythrocyte oxygen capacity), \( \phi = 8.33 \cdot 10^{-3} \text{[m}^3 \text{s}^{-1} \text{]} \) (blood velocity), \( T = 293.15 \text{[K]} \) (absolute temperature), \( R = 8.314 \text{[N} \cdot \text{m} \cdot \text{mol}^{-1} \text{K}^{-1}] \) (gas constant), \( T_p = 4 \text{[s]} \) (period \( u(t) \)), \( t_0 = 0.5 \text{[s]} \) (time delay \( u(t) \)), \( d = 0.25 \text{[s]} \) (duty cycle \( u(t) \)) and the initial values \( m_1(0) = 0.967 \text{[g]} \) (oxygen mass in alveoli) and \( m_2(0) = 0.016 \text{[g]} \) (oxygen mass in blood). A Simulink scheme for modelling and simulation of oxygen diffusion (Eq. 7) is presented in Fig. 3.

The results of simulations are shown in Fig. 4. For a healthy patient (top), moderate effort causes a very small, almost unnoticeable, lowering of blood saturation compared to when that person is at rest. Forced effort causes a further lowering of the saturation, which nevertheless still remains at a safe level of above 96%. Until oxygen saturation falls below, no deficiency of oxygen in the tissues is observed.

The bottom graph shows the simulations for patients suffering from microangiopathy. The state of blood saturation with the patient at rest is already very low, less than 95%. Any further increase of the metabolic rate causes a serious, even life threatening, decrease in saturation, far below the normal to range. The stronger the physical effort, the more drastic the oxygen saturation reduction in microangiopathic patients.

4. Results

Measurements were made on two groups of diabetic patients: ones with diagnosed microangiopathy (\( M^{angiop} = 44 \text{ patients} \))
Currently available and applied methodology of diagnosing lung microangiopathy is based on the comparison of the diffusing capacity $DL_{\text{standing}}$ measured in standing and $DL_{\text{lying}}$ in lying body positions. Lung microangiopathy is diagnosed when $DL_{\text{standing}} > DL_{\text{lying}}$. This examination also gives the alveoli volume $VA$. The patients classified as suffering from microangiopathy had breathing impairment symptoms caused only by diabetes. They were all non-smokers and had not been diagnosed with any other acute or chronic respiratory disease.

A new methodology of differentiating non-microangiopathic and microangiopathic patients, based on the model parameters $p_1, p_2$ and the measurements $DL, VA$ was examined. First a statistical comparison of modelling results was made by means of hypothesis testing. The null hypothesis $H_0$: $\mu_{\text{angiop}} = \mu_{\text{no angiop}}$ assumes that the mean values in both groups of patients are the same. This hypothesis was verified using the test-T. Calculated $ex \ post$ significance level $p$ was compared with $ex \ ante$ significance level $\alpha$. If a test of statistical significance gives $ex \ post$ significance level $p$, which is lower than the $\alpha$, the null hypothesis is rejected. Otherwise we fail to reject the hypothesis.

Measurements were taken from the 62 patients: 44 with microangiopathy and 18 without microangiopathy. The mean $DL$ and $VA$ are presented in Table 1. For $DL_{\text{lying}} \ ex \ post$ significance level $p < 0.05$ was obtained therefore the null hypothesis

<table>
<thead>
<tr>
<th></th>
<th>Microangiopathic</th>
<th>Non-microangiopathic</th>
<th>Statistical significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$DL$</td>
<td>$1.64 \cdot 10^{-7}$</td>
<td>$0.14 \cdot 10^{-7}$</td>
<td>$1.48 \cdot 10^{-7}$</td>
</tr>
<tr>
<td>$VA$</td>
<td>$5.95 \cdot 10^{-3}$</td>
<td>$0.21 \cdot 10^{-3}$</td>
<td>$5.65 \cdot 10^{-3}$</td>
</tr>
<tr>
<td><strong>Lying on back</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$DL$</td>
<td>$1.35 \cdot 10^{-7}$</td>
<td>$0.06 \cdot 10^{-7}$</td>
<td>$1.63 \cdot 10^{-7}$</td>
</tr>
<tr>
<td>$VA$</td>
<td>$6.04 \cdot 10^{-3}$</td>
<td>$0.27 \cdot 10^{-3}$</td>
<td>$5.90 \cdot 10^{-3}$</td>
</tr>
</tbody>
</table>
The mean values and standard deviations calculated according to

\[ H_0 : \bar{D}_{L, \text{standing}} = \bar{D}_{L, \text{lying no angiop}} \] was rejected and the conclusion is: \( \bar{D}_{L, \text{standing}} \neq \bar{D}_{L, \text{lying no angiop}} \). This suggests the possibility of diagnosing microangiopathy on the basis of \( D_{L, \text{standing}} \) only instead of \( D_{L, \text{lying}} \) and \( D_{L, \text{lying no angiop}} \), as it is currently applied.

The lack of statistical significance for \( D_{L, \text{standing}} \) means that it is not useful as an individual value for microangiopathy diagnosis.

Next, the \( p_1, p_2 \) parameters and the \( P_1, P_2, S_V \) signals were examined for each of the 62 subjects. The 62 \( p_1, p_2 \) estimates were calculated according to a normality hypothesis concerning these estimates at the significance level of \( p < 0.01 \). The mean values and standard deviations calculated for \( p_1 \) and \( p_2 \) are shown in Table 2. After that, the null hypothesis \( H_0 : \bar{D}_{L, \text{lying no angiop}} = \bar{D}_{L, \text{lying angiop}} \) was tested.

For \( p_1 \) and \( p_2 \), in the lying body position the ex post significance level \( p < \alpha, \alpha = 0.01 \) and so the \( H_0 \) was rejected. The parameters enabled a distinction to be made between patients with and without microangiopathy.

<table>
<thead>
<tr>
<th>Algorithm and the optimization criterion</th>
<th>The whole group of 62 subjects</th>
<th>The subgroup: 13 women, over 50 years old and under 1.75 m tall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algorithm 1: ( p_1, p_2 )</td>
<td>50.21</td>
<td>62.50</td>
</tr>
<tr>
<td>Algorithm 2: ( p_1, p_2 )</td>
<td>54.54</td>
<td>75.64</td>
</tr>
<tr>
<td>Algorithm 3: ( p_1, p_2 )</td>
<td>75.77</td>
<td>79.34</td>
</tr>
<tr>
<td>( D_1 )</td>
<td>33.36</td>
<td>62.12</td>
</tr>
</tbody>
</table>

### 5. Discussion

The above statistical analyses show that the model parameters \( p_1, p_2 \) contain information concerning lung microangiopathy.

In a standing position (\( p \geq 0.05 \)) the parameters were not statistically significant, and therefore not useful for microangiopathy diagnosis.

Similar calculations were made for \( P_1, P_2 \) and \( S_V \). The steady state mean values of the signals were calculated for both groups: \( M_{\text{angiop}} = 44 \) and \( M_{\text{no angiop}} = 18 \). In every case the ex post significance level was \( p > \alpha, \alpha = 0.05 \), and therefore we failed to reject the \( H_0 \) hypothesis – i.e. \( P_1, P_2 \) and \( S_V \) cannot be used for microangiopathy diagnosis.

In medical practice two measurements, \( D_{L, \text{standing}} \) and \( D_{L, \text{lying}} \), have so far been required for microangiopathic diagnosis. The presently obtained results, given in Table 1 and Table 2, indicate the possibility of using a diagnostic test based on a single measurement \( D_{L, \text{lying}} \), combined with the use of modelling results \( p_1 \) and \( p_2 \).

### Statistical significance level \( p \)

| \( p_1 \) | \( 6.6176 \cdot 10^{-2} \) | 0.4720 \( \cdot 10^{-2} \) | 6.1900 \( \cdot 10^{-2} \) | 0.2792 \( \cdot 10^{-2} \) | \( p \geq 0.05 \) |
| \( p_2 \) | 3.9330 | 0.3447 | 3.5301 | 0.2730 | \( p \geq 0.05 \) |

### 5. Discussion

The above statistical analyses show that the model parameters \( p_1, p_2 \) contain information concerning lung microangiopathy.

The question remains as to whether or not such parameters can be used for binary classification. Binary classification is the classifying of the members of mixed group \( M_{\text{angiop}} + M_{\text{no angiop}} \) into two subgroups, \( M_{\text{angiop}} \) and \( M_{\text{no angiop}} \), on the basis of whether or not they have microangiopathy.

Four binary classification algorithms were tested. To select the best of these in each case the statistical measures, sensitivity and specificity [28], were considered. The sensitivity Sens is the ability of a test to detect the disease status when it is truly present. Specificity Spec is the ability to confirm the absence of the disease in patients who do not have the disease.

The theoretically optimal prediction is: Sens = 100% (all the sick patients were identified as sick) and Spec = 100% (none of the healthy patients was identified as sick).

For binary classification the discrimination levels (boundaries, diagnostic thresholds) \( H_{\alpha} \), \( H_{\beta} \), and \( H_{\epsilon} \) have been calculated, respectively for \( D_{L} \), \( p_1 \), and \( p_2 \). The discrimination levels classify the test result as positive or as negative. The range of each parameter value was divided into subintervals with a 1% width. The Sens and the Spec were calculated in every subinterval, according to Equations 9 and 10. The parameter value where Sens + Spec = max was chosen as the parameter’s diag-

\[
\text{Sens} = \frac{\text{True positive}}{\text{True positive} + \text{False Negative}} \quad (9)
\]

\[
\text{Spec} = \frac{\text{True Negative}}{\text{True Negative} + \text{False Positive}} \quad (10)
\]
nostic threshold. This procedure was applied to define $H_{p_1}, H_{p_2}$, and $H_{D_L}$.

The binary classification was performed for the 62 subjects. The results were compared with already known medical diagnoses of 44 microangiopathic patients and 18 patients with no microangiopathy. Then the sensitivity and the specificity were calculated (Table 3). The larger the Sens and the Spec, the better.

The classification algorithms with the use of $p_1, p_2, H_p$ and $H_{D_L}$ are:

- **Algorithm 1**:  
  Step 1: from $M = M_{\text{angio}} + M_{\text{no angio}}$ select $M_1, p_1 < H_p$, classified as microangiopathic cases, and classify the rest, i.e. $M - M_1$, as non-microangiopathic cases.
  Step 2: from $M_1$, select $M_2, p_2 < H_p$, classified as microangiopathic cases, and classify the rest, i.e. $M - M_2$, as non-microangiopathic cases.

- **Algorithm 2**:  
  Step 1: from $M = M_{\text{angio}} + M_{\text{no angio}}$ select $M_1, p_1 < H_p$, classified as microangiopathic cases, and classify the rest, i.e. $M - M_1$, as non-microangiopathic cases.
  Step 2: from the rest, $M - M_1$, select $M_2, p_2 < H_p$, also classified as microangiopathic cases; thus we obtain the total of microangiopathic cases $M_1 + M_2$ and classify the rest, i.e. $M - M_1 - M_2$, as non-microangiopathic cases.

- **Algorithm 3**:  
  Step 1: from $M = M_{\text{angio}} + M_{\text{no angio}}$ select $M_1, p_2 < H_p$, classified as microangiopathic cases, and classify the rest, i.e. $M - M_1$, as non-microangiopathic cases.
  Step 2: from the rest, $M - M_1$, select $M_2, p_2 < H_p$, also classified as microangiopathic cases; thus we obtain the total of microangiopathic cases $M_1 + M_2$ and classify the rest, i.e. $M - M_1 - M_2$, as non-microangiopathic cases.

Next the quality of the algorithms was assessed. We considered Sens and Spec (Table 3) results that were larger than 75% to be satisfactory. Therefore we looked for an algorithm which satisfied this requirement. Diagnostic thresholds, calculated for the 62 subjects, were: $H_p = 5.80 \times 10^{-3}$, $H_p = 3.50$ and $H_{D_L} = 1.57 \times 10^{-2}$. The best statistical measures were: Sens = 75.77% (algorithm 3) and Spec = 87.08% (algorithm 1), both were larger than 75%. The results for $D_L$, Sens = 33.36% and Spec = 61.11%, were less than 75% and left much to be desired.

The thresholds established as common for the whole group did not take into consideration such important factors as age, height and gender. This may be the reason for the not fully satisfactory results. Therefore we selected a subgroup of 13 women, over 50 years old and less than 1.75 m tall. Then the new diagnostic thresholds $H_p = 5.42 \times 10^{-3}$, $H_p = 3.06$, $H_{D_L} = 1.30 \times 10^{-2}$ and the new Sens and Spec were calculated.

As expected, both the new Sens and Spec were noticeably larger. Algorithm 1 had good specificity (Spec = 87.08%), while at the same time less than good sensitivity (Sens = 62.50%). Algorithms 2 and 3 gave very satisfactory results — both the sensitivity and the specificity were above 75%.

The $D_L$ parameter proved not to be a competitive candidate for binary classification in comparison with parameters $p_1$ and $p_2$. The only acceptable result, Spec = 79.89%, was still worse than any result obtained for $p_1$ and $p_2$. Therefore we recommend the diagnostic procedure shown in Figure 5.

The measured $D_L$ and $V_A$ and the physiological constants $R$, $T$, and $V$ were used to calculate the $p_1$ and $p_2$ for every tested patient. Then algorithm 3 (with the most conclusive Sens) and the algorithm 1 (with the most conclusive Spec) were applied with $H_p$ and $H_{D_L}$ diagnostic thresholds to obtain binary classification results.

These results, intended as an aid for medical staff, have two forms:

A. High probability of lung microangiopathy.
B. High probability of no lung microangiopathy.

The final decision is made by the doctor conducting the diagnosis, who can take into account this classification result along with other diagnostic data.

**6. Conclusions**

In clinical practice, lung microangiopathy is diagnosed by comparing two diffusing capacity measurements, taken with the patient standing up and lying down. The aim was to find an auxiliary method for diagnosing lung microangiopathy with the use of routine clinical tests and modelling results. Here a new model of oxygen diffusion from the alveoli to the blood has been presented. The model parameters have been calculated using routine medical test results and the physiological constants.

The single measurement of diffusing capacity $D_L$ and the model parameter estimates $p_1$ and $p_2$ turned out to be useful for binary classification in lung microangiopathy diagnosis. The diagnostic thresholds $H_p, H_{D_L}$ were calculated and the binary classification was performed. Four classification algorithms were tested, based on statistically significant model parameters $p_1, p_2$ and $D_L$. None of the tested algorithms proved equally efficient in terms of both the sensitivity and specificity required for classification. Therefore we propose to use algorithm 3 to obtain the most conclusive Sens and algorithm 1 to obtain the most conclusive Spec. Both these algorithms are based on the comparison of model parameters $p_1, p_2$ with the diagnostic thresholds $H_p, H_{D_L}$. The choice of thresh-
olds with regard to age, height and gender is essential in obtaining reliable classification results. The classification results obtained with the diagnostic thresholds calculated for a broad range of anthropometric data are far less satisfactory than those obtained with the diagnostic thresholds calculated for a limited anthropometric data range.

This procedure produces one of two possible results: 1) high probability of lung microangiopathy or 2) high probability of no lung microangiopathy. This can serve as useful confirmation in a doctor’s diagnosis.

The model allows for the simulation of oxygen diffusion. Thanks to this simulation can predict how the organism will react to alveoli-capillary barrier deterioration.

References