DYNAMICS OF THE VENOUS BLOOD ACID-BASE BALANCE AND RELATIONSHIP BLOOD pH VS TUMOR IN LARYNGEAL CANCER PATIENTS

Abstract

The characteristic for most solid tumors cells is the intracellular alkalinization and acidification of the extracellular milieu and this pH gradient inversion (pHe < pH) is associated with tumor proliferation, invasion, metastasis, aggressiveness, and treatment resistance. However is there tumor pH changes affect on venous blood plasma pH?

Purpose of the study. The venous blood acid-base balance before and after the combined treatment, correlation of the venous blood pH indicators (pHb), relationship neoplasm and blood pH in patients with laryngeal cancer was study.

Material and methods. Studies were performed in patients with laryngeal cancer categories T2–3 N0 M0 before and after the combined treatment. The patients were divided into four groups: Group 1 – 25 patients before the start of treatment; Group 2 – 21 patients (from Group 1) after completion of the combined treatment; Group 3 – 14 patients from Group 2 with positive results of treatment and Group 4 – 7 patients from Group 2 with a negative result of treatment (recurrence and/or metastasis of the neoplasm). The control group consisted of 15 practically healthy people (Group C).

Examination of venous blood acid-base balance of patients, tumor pH and tumor cells pH and pHe was carried.

Results and discussion. The increase in pCO₂ and HCO₃⁻ concentration will result in decrease in the pH, but if these indicators have a clear correlation in the control group, then in patients...
groups there was a correlation for pHB & pCO₂ and pO₂ only. Besides, we marked increase in pCO₂, HCO₃⁻, K⁺, while pO₂ decreased in pHB after the combined treatment.

It is necessary to point out the differences between some benchmarks and indicators of acid-base balance in the plasma of venous blood in primary patients and patients with recurrent laryngeal cancer. So, if pHb, pO₂, and Cl⁻ patients have statistically significant differences from control data, then differences with control pCO₂ values are characteristic only for patients of Groups 1 and 3. On the contrary, differences in the HCO₃⁻ indices are characteristic only for patients of Group 4. There are statistically significant differences from the control indicators K⁺, Na⁺, Ca²⁺, Glu, Lac, mOsm in patients of the first group and Cl⁻ and Lac of patients in the third group. Among the indicators in the third and fourth groups of patients, statistically significant differences were noted in the values of pHb, HCO₃⁻ and Glu.

In patients of groups 1 and 4, the determination of pHt and the calculation of pHi, pHe revealed decrease in pHt and pHe with increasing pHi in patients with recurrence of the neoplasm.

The final stage of the study was to determine the relationship (and not correlation) of blood pH and laryngeal tumors and the relationship was noted in the «pHb-tumor» system in primary patients, but in patients in 3 and 4 Groups, that «pHb-tumor» system in primary patients, but in patients in 3 and 4 Groups, that «pHb-tumor» connection is rather contradictory.

Conclusion. Acid-base balance indicators obviously cannot be considered as unconditional markers of carcinogenesis, but their monitoring and, in particular, venous blood pH, of patients after special treatment, can help determine the risk group of patients who may develop of a malignant neoplasm recurrence.

Keywords: acid-base balance, laryngeal cancer, relapse, prognosis.
INTRODUCTION

Cells population growth is determined by the genetic program of metabolism, wherein cells, for the order to function optimally, must constantly maintain an intracellular pH within a narrow range (pHi = 7,1–7,2) through the activity of transporters located at the plasma membrane. These transporters can be modulated by endogenous or exogenous molecules and pHi changes have been implicated in both cell proliferation and cell death. Notably, if the intracellular alkalization is a common feature of proliferative processes, then the intracellular acidification has the cytotoxic effect through of apoptosis induction [1–3]. But for most cells of solid tumors characterized by the presence of intracellular alkalization of the cytoplasm (pHi > 7,2) and acidification of the extracellular milieu (pHe = 6,5–7,1) – a reverse pH gradient in cancer cells, unlike similar indicators of normal cells: pHi ≈ 7,2, pHe ≈ 7,4 [4–8]. The acidification environmental tumors occurs already on early in cancers (cancer in situ), during the avascular phase, and pH gradient inversion (pHe < pHi) is associated with tumor proliferation, invasion, metastasis, aggressiveness, and treatment resistance [8–10].

Currently, it is believed that pH inversion, like hypoxia, is a common symptom of cancer and on this peculiarity of tumors various strategies are being built to increase the effectiveness of their treatment [11–18], but individual tumors may be had both positive and negative (reverse) pH gradients [19]. But still, the relationship between extracellular and intracellular pH are dependent upon the pH range. Intracellular pH was relatively resistant to a change in extracellular pH over the pHe range of 6,8 to 7,8 (i.e., delta pHi congruent to delta pHe × 0,33) [20]. However is there tumor pH (pHi and/or pHe) changes affect on venous blood plasma pH?

\[
\text{pHi} = \text{pHconst} + [2 \times (\text{pHconst} – \text{pHt})] \times 0,33
\]

\[
\text{pHe} = \text{pHt} – (\text{pHi} – \text{pHconst})
\]

Comparisons of the studied parameters were carried out using the Wilcoxon Matched Pairs Test, Wald-Wolfowitz Runs Test and Spearman Rank Order Correlations, at the critical significance level of 0,05. The analyzed data are presented as «median and interquartile interval»: Me (RQ = UQ–LQ). The causal relationship between the indicators was evaluated using multiple logistic regression analysis. Statistical processing of the received data was made using computer programs of the STATISTICA package (StatSoft Statistica v.7.0).

RESULTS AND DISCUSSION

The data of pH venous blood plasma (pHb) of patients, before the beginning and after treatment in table 1 are present.

The change in plasma pH in patients after treatment (7,35 → 7,31; p = 0,071) is not statistically significant, but it is important from a clinical point of view. But it should be noted, that all changes pH occur through changes in three independent variables – carbon dioxide, relative electrolyte concentrations, and total weak acid concentrations and some of these characteristics change and have statistically significant differences in groups 1 and 2 (increase in pCO₂ 46,08 → 48,8; HCO₃⁻ 24,9 → 26,0 and K⁺ 3,95 → 4,5, while pO₂ decreased 37,98 → 23,63)[21].

However, the patients in Group 2 had both positive (14 patients, who third Group constituted)
and negative (7 patients) treatment results (Group 4). Moreover, when comparing the data of the first and third groups, statistically significant spills are noted in Ca\(^{2+}\) indicators only (1,14 \(\rightarrow\) 1,25), while comparing the data of the first and fourth groups, significant differences were observed in indicators of pH (7,35 \(\rightarrow\) 7,22) pO\(_2\) (37,98 \(\rightarrow\) 20,0), HCO\(_3\)\(^-\) (24,9 \(\rightarrow\) 22,2) and mOsm (284,1 \(\rightarrow\) 288,4).

It is known that increase in pCO\(_2\) and HCO\(_3\)\(^-\) concentration will result in decrease in the pH [21]:

\[
\text{pH} = \text{pK} \times \log \left[ \frac{\text{HCO}_3^-}{0,03 \times \text{pCO}_2} \right]
\]

But if these indicators have a clear correlation in the control group, then in 1, 2, 3 groups of patient there was a correlation for pHb & pCO\(_2\) and pHb & pO\(_2\) and no correlation for pHb & HCO\(_3\)\(^-\), and in the fourth group the insignificant correlation was noted for pHb & pCO\(_2\) and pHb & pO\(_2\) (table 2).

**Table 1**

| Test     | Group 1 (n = 25) | Group 2 (n = 21) | Group 3 (n = 14) | Group 4 (n = 7) | p-level          |
|----------|------------------|------------------|------------------|-----------------|------------------|
| pHb      | 7,35             | 7,31             | 7,32             | 7,29            | 0,071            |
|          | (7,42 – 7,31 = 0,11) | (7,34 – 7,31 = 0,03) | (7,38 – 7,31 = 0,07) | (7,31 – 7,26 = 0,05) | 0,509            |
| pCO\(_2\) mm/Hg | 46,08         | 48,8             | 48,8             | 56,1            | 0,027            |
|          | (47,1 – 42,2 = 4,9) | (53,8 – 48,7 = 5,7) | (49,2 – 47,9 = 1,3) | (62,9 – 48,7 = 14,2) | 0,018            |
| pO\(_2\) mm/Hg | 37,98         | 23,63            | 29,0             | 19,0            | 0,002            |
|          | (49,95 – 35,0 = 14,95) | (29,4 – 19,0 = 10,4) | (32,0 – 19,0 = 13,0) | (20,0 – 14,1 = 5,9) | 0,096            |
| HCO\(_3\) mmol/l | 24,9          | 26,0             | 25,02            | 25,8            | 0,017            |
|          | (25,19 – 24,65 = 0,54) | (28,7 – 25,1 = 3,6) | (26,0 – 24,8 = 1,2) | (29,0 – 20,7 = 8,3) | 0,799            |
| K\(^+\) mmol/l | 3,95          | 4,5              | 4,35             | 4,9             | 0,009            |
|          | (4,13 – 3,9 = 0,23) | (5,1 – 4,1 = 1,0) | (5,0 – 4,0 = 1,0) | (5,2 – 4,5 = 0,7) | 0,010            |
| Na\(^+\) mmol/l | 140,0         | 140,0            | 139,5            | 139,4           | 0,972            |
|          | (140,4 – 139,5 = 0,86) | (142,0 – 139,0 = 3,0) | (142,0 – 139,0 = 3,0) | (144,0 – 139,0 = 5,0) | 0,949            |
| Ca\(^{2+}\) mmol/l | 1,14         | 1,19             | 1,25             | 1,22            | 0,106            |
|          | (1,2 – 1,07 = 0,13) | (1,26 – 1,17 = 0,09) | (1,27 – 1,18 = 0,09) | (1,27 – 1,0 = 0,27) | 0,041            |
| Cl\(^-\) mmol/l | 107,0         | 108,0            | 110,0 – 108,0 = 3,0 | 111,0 – 108,0 = 3,0 | 0,866            |
|          | (109,0 – 107,0 = 2,0) | (109,0 – 107,7 = 1,3) | (109,0 – 104,0 = 5,0) | (111,0 – 108,0 = 3,0) | 0,753            |
| Glu mmol/l | 5,5             | 5,5              | 5,5              | 5,5             | 0,788            |
|          | (5,7 – 4,9 = 0,8) | (5,9 – 5,2 = 0,7) | (5,9 – 4,7 = 1,2) | (5,9 – 5,2 = 0,7) | 0,754            |
| Lac mmol/l | 1,65            | 1,8              | 1,75             | 2,0             | 0,112            |
|          | (1,81 – 1,5 = 0,31) | (2,2 – 1,6 = 0,6) | (2,2 – 1,5 = 0,7) | (2,3 – 1,5 = 0,8) | 0,379            |
| mOsm mmol/l | 284,1          | 285,6            | 284,05           | 288,0           | 0,395            |
|          | (284,5 – 283,8 = 0,7) | (289,1 – 283,0 = 6,1) | (289,1 – 282,0 = 7,1) | (291,5 – 284,5 = 7,0) | 0,638            |

Note: *p-level for G1 Vs G2 groups; *p-level for G1 Vs G3 groups; *p-level for G1 Vs G4 groups

**Table 2**

| Spearman Rank Order Correlations | Groups | GC | Group 1 (n = 25) | Group 2 (n = 21) | Group 3 (n = 14) | Group 4 (n = 7) |
|---------------------------------|--------|----|-----------------|-----------------|-----------------|-----------------|
|                                 |        | R  | p       | R  | p       | R  | p       | R  | p       |
| pHb & pCO\(_2\)                | 0,53   | 0,042 | -0,75 | 0,0001 | -0,61 | 0,003 | -0,74 | 0,002 | -0,39 | 0,378 |
| pHb & HCO\(_3\)                | 0,56   | 0,029 | -0,14 | 0,499  | 0,34  | 0,003 | -0,07 | 0,819 | -0,18 | 0,699 |
| pHb & pO\(_2\)                 | 0,72   | 0,0003 | 0,65  | 0,001  | -0,61 | 0,003 | 0,91  | 0,000 | 0,38  | 0,398 |
Changes in blood pH induce powerful regulatory effects at the level of the cell, organ, and organism, but how tumor pH (pH of cytoplasm + interstitial fluid) does it affect on blood pH and whether and to what extent it is possible to consider its dynamics as a predictor of the course of the disease or as performance evaluation of cancer patients treatment. However, we should highlight a few problems, associated with both the tumor and its microenvironment [7, 19–27].

Firstly, the resting pHi of a cell can be defined as the steady-state point at which net metabolic acid production is balanced by net membrane H+/H+-equivalent transport. But these fluxes to show considerable regional variation in solid tumors, resulting in the potential for large pH gradients alongside pHe non-uniformity.

Second, tumor histology and tumor volume is the most important factors determining the range of pHe's. A combination of poor vasculature perfusion, regional hypoxia and increased flux of carbons through fermentative glycolysis leads to extracellular acidosis in solid tumors, with extracellular pH values as low as 6,5, but overall, actual pH in squamous cell carcinomas is 7,20 ± 0,07 (pHt in range 6,2–7,6) with the pHi and pHe values lying mostly in the range 7,1–7,65 and 6,2–6,9 respectively [28–32].

Thirdly, tissue pH is difficult to investigate by measuring pH in cells suspensions or monolayers prepared from cultured cells. Besides no equations which would allow accurate calculation of indicators pHi or pHe based on the pHt indicator. Rather, these calculations will confirm the trend – pHi and pHe will change in opposite directions (extracellular acidification and intracellular alkalinization).

In patients of groups 1 and 4, the determination of pHt and the calculation of pHi, pHe revealed decrease in pHt and pHe with increasing pH in patients with recurrence and/or metastasis of the neoplasm (table 3). Obviously this can be explained by surviving in treatment tumor cells begin to actively proliferate and the acidic environment of the microenvironment contributes to tumor progression, stimulating invasion and metastasis, acidosis can be toxic to normal cells and mediate degradation and remodeling of the extracellular matrix, can enhance angiogenesis due to release of vascular endothelial growth factor, but themselves abnormal cells become less vulnerable [31, 33–37].

| Test | Group (Me; RQ = UQ–LQ) | p-level |
|------|------------------------|---------|
|      | Group 1 (n = 25)       |         |
| pHt  | 7,05                   |         |
|      | 7,09–7,02 = 0,07       |         |
|      | 6,98                   |         |
|      | 7,035–6,915 = 0,12     | 0,002   |
|      | Group 4 (n =7)         |         |
| pHHe | 6,87                   |         |
|      | 6,852–6,712 = 0,14     |         |
|      | 6,75                   |         |
|      | 6,742–6,502 = 0,24     | 0,002   |
| pHi  | 7,51                   |         |
|      | 7,636–7,596 = 0,04     |         |
|      | 7,741–7,621 = 0,12     | 0,057   |

It is necessary to point out the differences between some benchmarks and indicators of acid-base balance in the plasma of venous blood in primary patients and patients with recurrent laryngeal cancer. So, if pHb, pO2, and Cl- patients have statistically significant differences from control data, then differences with control pCO2 values are characteristic only for patients of Groups 1 and 3. On the contrary, differences in the HCO3- indices are characteristic only for patients of Group 4. There are statistically significant differences from the control indicators K+, Na+, Ca++, Glu, Lac, mOsm in patients of the first group and Cl- and Lac of patients in the third group. Among the indicators in the third and fourth groups of patients, statistically significant differences were noted in the values of pHb, HCO3- and Glu (table 4).

Thus, the presented data indicate the presence of significant discrepancies in the control values of a number of indicators of acid-base balance and indicators of acid-base balance of patients who successfully completed treatment, from the corresponding indicators of primary patients and patients with recurrent neoplasm.

However, how pHb is coupled to cancer cell growth? The final stage of the research was the determination of the relationship (not correlation) of blood pH and laryngeal tumors and it is necessary to recall that the odds ratio (OR) from 0 to 1 indicates a low probability of the event being investigated, the OR of 1 means that the likelihood of an event is the same in both groups. The greater the odds ratio unit, the more likely it is to expect an even to develop (table 5). The analysis is carried out in groups G1 & GC, G4 & GC and G3 & G4.

From the data presented in the table indicate the presence of a causal relationship in the pHb–tumor system in primary patients, but in patients in 3 and 4 Groups, the pHb – tumor connection is rather contradictory. Obviously, this can be explained both by the presence of a progressive neoplasm and by the aggressive nature of the treatment methods carried.
Table 4

The acid-base balance indicators in the venous blood plasma in the control group and in the first, third and fourth group patients

| Test | Group C (n = 15) | Group 1 (n = 25) | Group 3 (n = 14) | Group 4 (n = 7) | p-level |
|------|------------------|------------------|------------------|-----------------|---------|
| pH   | 7,39 (7,41–7,36 = 0,05) | 7,35 (7,42–7,31 = 0,11) | 7,32 (7,38–7,31 = 0,07) | 7,22 (7,31–7,11 = 0,2) | 0,002 × 0,038 + 0,001 ° 0,003 |
| pCO₂ | 46,7 (48,2 – 45,8 = 2,4) | 46,08 (49,2 – 47,9 = 1,3) | 48,8 (58,8 – 48,3 = 10,5) | 48,8 (58,8 – 48,3 = 10,5) | 0,000 × 0,038 + 0,299 ° 0,673 |
| pO₂  | 44,2 (45,5 – 42,5 = 3,0) | 37,98 (32,0 – 19,0 = 13,0) | 29,0 (22,5 – 19,0 = 3,5) | 20,0 (22,5 – 19,0 = 3,5) | 0,000 × 0,0007 + 0,353 |
| HCO₃⁻| 24,1 (25,0 – 24,1 = 0,9) | 24,9 (26,0 – 24,8 = 1,2) | 25,02 (23,8 – 20,7 = 3,1) | 22,2 (23,8 – 20,7 = 3,1) | 0,266 × 0,040 + 0,052 |
| K⁺   | 4,7 (5,0 – 4,4 = 0,6) | 3,95 (5,0 – 4,0 = 1,0) | 4,35 (5,2 – 4,5 = 0,7) | 4,9 (5,2 – 4,5 = 0,7) | °0,005 °0,982 °0,151 |
| Na⁺  | 142,0 (144,0 – 140,0 = 4,0) | 140,0 (142,0 – 139,0 = 3,0) | 139,5 (144,0 – 139,0 = 5,0) | 139,2 (144,0 – 139,0 = 5,0) | 0,032 × 0,347 + 0,628 ° 0,933 |
| Ca²⁺ | 1,28 (1,31 – 1,24 = 0,07) | 1,14 (1,27–1,18 = 0,09) | 1,25 (1,31–1,02 = 0,29) | 1,25 (1,31–1,02 = 0,29) | 0,032 × 0,187 + 0,628 ° 0,151 |
| Cl⁻  | 105,0 (107,0 – 102,0 = 5,0) | 107,0 (109,0 – 107,0 = 2,0) | 109,0 (111,0 – 108,0 = 3,0) | 109,0 (111,0 – 108,0 = 3,0) | 0,013 × 0,038 + 0,040 ° 0,353 |
| Glu  | 4,7 (5,1 – 4,4 = 0,7) | 5,5 (5,9 – 4,7 = 1,2) | 5,15 (5,9 – 5,2 = 0,7) | 5,9 (5,9 – 5,2 = 0,7) | °0,072 °0,574 °0,040 °0,544 |
| Lac  | 2,1 (2,4 – 1,9 = 0,5) | 1,65 (2,2 – 1,5 = 0,7) | 1,75 (3,2 – 1,5 = 1,7) | 2,0 (3,2 – 1,5 = 1,7) | °0,032 °0,319 °0,933 |
| mOsm | 288,0 (291,1 – 286,0 = 5,1) | 284,1 (284,5 – 283,8 = 0,7) | 284,05 (289,1 – 282,0 = 7,1) | 288,4 (290,0 – 284,5 = 5,5) | °0,000 °0,187 °0,077 °0,673 |

Note: *p-level for GC vs G1 groups; †p-level for GC Vs G3 groups; ’p-level for GC Vs G4 groups; p-level for G3 Vs G4 groups.

Table 5

Relationship of the progressive tumors and venous blood plasma pH, pCO₂, pO₂ and HCO₃⁻

| Test | G1 & GC | G4 & GC | G3 & G4
|------|---------|---------|---------|
| pH   | pCO₂   | pO₂   | HCO₃⁻  | pH   | pCO₂   | pO₂   | HCO₃⁻  | pH   | pCO₂   | pO₂   | HCO₃⁻  |
| Estimate | 11,91 | 0,026 | 0,025 | 0,909 | 0,94 | 0,67 | 2,96 | 1,03 | 6,5E+01 | 6E+01 | 0,17 | 1,5E+0 |
| OR (unit ch) | 141312 | 1,026 | 1,026 | 0,402 | 0,39 | 0,51 | 19,5 | 2,8 | 1,18 | 4,4E+0 |
| OR (range) | 12,95 | 1,619 | 4,109 | 0,013 | 0,65 | 0,01 | 366 | 1,18 | 4,5E+01 | 5E+10 | 218 | 4,5E+0,5 |
CONCLUSION

Acid-base balance indicators obviously cannot be considered unconditional markers of carcinogenesis, but their monitoring and, in particular, venous blood pH, of patients after special treatment, can help determine the risk group of patients who may develop of a malignant neoplasm recurrence.

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