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IMPACT OF SYSTEMIC HYPOXEMIA ON CANCER AGGRESSIVENESS AND CIRCULATING VASCULAR ENDOTHELIAL GROWTH FACTORS A AND C IN GASTROESOPHAEAL CANCER PATIENTS WITH CHRONIC RESPIRATORY INSUFFICIENCY

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Aim: **Due to the common etiologic factor, a considerable number of esophagogastric cancer patients suffer from respiratory insufficiency in course of chronic obstructive pulmonary disease, primary to cancer. Systemic hypoxemia may account for poor oxygenation of tumor tissue-a main driving force of tumor neoangiogenesis. We hypothesized that in cancer patients with respiratory insufficiency, systemic hypoxemia may be related to enhanced aggressiveness of cancer on one side and to the elevation of angiogenic factors on the other.** ***Methods:*** **The levels of vascular endothelial growth factors A and C were determined with immunoenzymatic methods in patients diagnosed with esophagogastric cancer with or without co-existing respiratory insufficiency in course of chronic obstructive pulmonary disease and in healthy controls. Blood gasometry and hemoglobin levels of cancer patients were related to cancer histology and TNM status, and to circulating vascular endothelial growth factors A and C.** ***Results:*** **Patients with systemic hypoxemia had higher incidence rates of locally advanced tumors. Partial oxygen pressure and blood oxygen saturation were significantly lowered in patients with T4 cancers as compared to less advanced onces. Circulating vascular endothelial growth factor A, but not C, was more elevated in esophagogastric cancer patients with co-existing respiratory insufficiency, as compared to those without respiratory insufficiency. Vascular endothelial growth factor A was also strongly related to the extension of primary tumor.** ***Conclusion:*** **Our results show that systemic hypoxemia in esophagogastric cancer patients is associated with the extension of primary tumor and that this effect might be mediated by the up-regulation of circulating vascular endothelial growth factor A.**

Key Words: **hypoxemia, esophagogastric cancer, angiogenesis, VEGF-A, VEGF-C, COPD, respiratory insufficiency.**

Tumor hypoxia is considered an important therapeutic problem since hypoxic tumors are resistant to some forms of radiochemotherapy as well as photodynamic therapy. Therefore, studies on hypoxia in solid tumors have been included in the mainstream of cancer research. Current knowledge on the subject is pointing out at another alarming aspect of tumor hypoxia. Hypoxia has been found to induce genomic and proteomic changes in transformed cells, consequently contributing to the development of more aggressive tumor phenotypes [28].

The imbalance between oxygen delivery and consumption, present in majority of locally advanced solid tumors, is believed to result mainly from ischemic and diffusional hypoxia. However, a growing body of evidence has accumulated, suggesting that also a reduced oxygen transport capability of blood and decreased oxygen pressure may significantly contribute to the adverse effects of tumor hypoxia [5, 27–28].

Angiogenesis is one of the most important manifestations of the aggressiveness of hypoxic tumors, while hypoxia is considered a main driving force of neoangiogenesis [27, 28]. Still, the details of molecular basis of this relationship remain unknown and are intensively investigated [5]. Data on the impact of systemic hypoxemia on expression and secretion of factors involved in the induction and sustain of angiogenesis are scanty and so far confusing.

A considerable number of patients diagnosed with esophagogastric cancer suffer from chronic obstructive pulmonary disease (COPD) due to the common etiologic factor — smoking. Smoking is a recognized risk factor of esophageal cancers, which, in association with an alcohol abuse, accounts for more than 90% of esophageal squamous cell carcinoma cases in the developed world [3]. Similarly, up to 90% of COPD cases results from smoking. COPD is defined as a disease state with airflow limitation that is not fully reversible. Respiratory insufficiency, which may occur in COPD patients is mainly a result of ventilation/perfusion mismatching [17]. In addition to common etiologic factor, the involvement of vascular endothelial growth factor A (VEGF-A), a key regulator of angiogenesis, has been described in pathogenesis of both cancer [21] and COPD [8, 16].

We designed our studies to test the hypothesis that respiratory insufficiency present in a number of patients with esophagogastric cancers due to the background chronic pulmonary diseases may be as-

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Abbreviations used: ADC – adenocarcinoma; COPD – chronic obstructive pulmonary disease; SCC – squamous cell carcinoma; VEGF-A – vascular endothelial growth factor A; VEGF-C – vascular endothelial growth factor C.

sociated with more aggressive tumors on one side and up-regulation of angiogenic factors on the other.

MATERIALS AND METHODS

Patients. A study group included 81 subjects: 34 patients diagnosed with esophagogastric cancer and 47 healthy individuals. Sera from blood donors (six females and 41 males; mean age 44.5 years) acknowledged healthy on the basis of routine laboratory tests served as controls and were obtained from Regional Center of Blood Donation and Therapeutics, Wroclaw, Poland. Cancer patients (seven females and 27 males; mean age 60 years) were treated in the Department of Gastrointestinal and General Surgery of our institution. All patients were informed about the study. The stady was approved with local ethic committec. They were staged clinically according to the guidelines of UICC TNM [20] system on the basis of upper digestive tract (udt) endoscopy with the biopsy and pathologic examination, contrast radiographic studies of the udt with barium or gastrografin, posteroanterior and lateral chest radiography, ultrasound examination of the abdominal cavity and cervical nodes, thorax and abdominal cavity CT, diagnostic laparotomy and thoracotomy. We examined 25 cases of squamous cell carcinomas (SCC) and nine cases of adenocarcinomas (ADC). Seven patients were presenting with disease stage II, 14 with stage III and 13 with stage IV. The recruited cancer patients had a long history of heavy smoking. The analysis of blood gases was performed as a part of the routine, pretreatment assessment of patients' general condition. Gasometric studies were conducted on patients at rest, breathing room air. Partial respiratory insufficiency (hypoxemia without hypercapnia) was recognized in 19 out of 34 cancer patients and was related to the co-existence of chronic pulmonary disorders (COPD). Mean pO_2 level in cancer patients was 61.4 mmHg, SaO_2 — 91.6%, pCO_2 — 37.4 mmHg. Presence of mild-grade anemia was recognized in 19 cancer patients. The following diagnostic criteria were applied: systemic hypoxemia — $pO_2 < 60$ mmHg or $SaO_2 < 90\%$; anemia — hemoglobin (Hb) < 13 g/dL or < 12 g/dL in male and female patients, respectively.

Analytical methods. VEGF-C and VEGF-A concentrations were assayed according to the manufacturer instructions by commercially available double antibody indirect enzyme-linked immunosorbent tests (DASI-ELISA) provided by IBL-Hamburg, Germany. Factors' levels were determined in sera obtained from blood by its clotting for 15 minutes at room temperature and subsequent centrifugation for 15 minutes at 3000 rpm. All measurements were duplicated.

Statistical analyses. Data distribution was analyzed with D'Agostino-Pearson test for normality. Levels of pO_2, SaO_2 and Hb were distributed normally but neither raw data nor log-transformed data on VEGF-A and VEGF-C levels had Gaussian distribution. Therefore, pO_2, SaO_2 and Hb levels are presented as mean values with standard error (SE), while VEGF-A and VEGF-C results are presented as median values with interquartile range (25–75%). The significance of differences between groups was examined with non-parametric Mann — Whitney *U* test (two-group comparisons) or Kruskal — Wallis ANOVA rank test (multigroup comparisons). Correlation analysis was conducted with Spearman or Pearson's test in respect to data type and distribution. Differences in incidence rates were analyzed with Fisher's exact test. Kendal *tau* (in 2 x 2 tables) or Spearman *rho* coefficients were calculated for evaluation of the strength of studied relation. All tests were two-sided and *p* values $\leqslant 0.05$ were considered significant. Statistical analysis was conducted with MedCalc® version 9.2.1.0 statistical software.

RESULTS

Patients with systemic hypoxemia had higher incidence rates of locally advanced tumors. We evaluated whether and which (if any) of clinico-pathological factors were associated with the presence of systemic hypoxemia in a number of patients with esophagogastric cancers. The incidence rates of systemic hypoxemia in respect to tumor histology, disease TNM stage and co-existence of anemia, together with the strength of the association are presented in Table 1 (systemic hypoxemia in terms of pO_2) and Table 2 (systemic hypoxemia in terms of SaO_2).

Table 1. Evaluation of association between cancer-related variables and respiratory insufficiency determined in terms of decreased oxygen partial pressure (pO_2) in esophagogastric cancer

Parameter	Incidence of hypoxemia			Correlation analysis	
	Normoxemic	Hypoxemic	*p* value	Coefficient	*p* value
Histology:					
SCC	10	15	0.462	-0.138^K	0.237
ADC	5	4			
Disease stage:					
II–III	10	11	0.728	0.009^K	0.474
IV	5	8		(0.263^S)	(0.131)
Tumor extension:					
T2/T3	10	4	0.013*	0.460^K	<0.001*
T4	5	15		(0.466^S)	(0.007)*
Regional metastasis:					
N0	8	3	0.030*	0.398^K	0.001*
N1	7	16			
Distant metastasis:					
M0	11	13	1.000	0.054^K	0.679
M1	4	6			
Anemia presence:					
Non-anemic	8	7	0.488	0.165^K	0.179
Anemic	7	12			

SCC – squamous cell carcinoma; ADC – adenocarcinoma; ^{K}Kendall correlation coefficient; ^{S}Spearman correlation coefficient; *statistically significant at $p \leqslant 0.05$.

We found that regardless of the criteria of systemic hypoxemia, the strongest association was observed with the extension of primary tumor, followed by regional metastasis. Also mean levels of pO_2 and SaO_2 differed significantly in groups of cancer patients stratified according to the extension of primary tumor. The differences in pO_2 and SaO_2 levels in respect to other cancer-related features were found insignificant (Table 3).

Anemia did not account for the observed association between systemic hypoxemia and the extension of primary tumor. Anemia is one of the conditions, which may account for the occurrence of systemic hypoxemia. But we did not observe sig-

nificantly higher incidence rates of anemia in cancer patients with respiratory insufficiency (see Table 1 and Table 2). Moreover, mean pO_2 and SaO_2 levels did not differ in non-anemic *vs.* anemic cancer patients (Table 3). Yet, in order to fully exclude possible impact of anemia on hypoxemia relation to the extension of primary tumor, we determined whether a direct correlation between levels of pO_2 or SaO_2 and Hb concentration exists. We also examined whether anemia presence was related to the aggressive behavior of disease, analyzed in terms of local invasion (T), regional (N) or distant (M) metastasis. We found no direct correlation between Hb and pO_2 level (r = 0.074, p = 0.676), as well as Hb with SaO_2 level (r = 0.104, p = 0.557). Anemia was not related to clinical evaluation of cancer T stage (rho = 0.072, p = 0.679) and M stage (r = 0.054, p = 0.679), but was correlated with N stage (r = 0.525, $p < 0.0001$).

Table 2. Evaluation of association between cancer-related variables and respiratory insufficiency determined in terms of decreased oxygen saturation (SaO_2) in esophagogastric cancer.

Parameter	Incidence of hypoxemia			Correlation analysis	
	Normoxemic	Hypoxemic	*p* value	Coefficient	*p* value
Histology:					
SCC	18	7	1.000	0.052[K]	0.694
ADC	6	3			
Disease stage:					
II–III	16	5	0.450	0.156[K]	0.205
IV	8	5		(0.191[S])	(0.273)
Tumor extension:					
T2/T3	13	1	0.024*	0.409[K]	<0.001*
T4	11	9		(0.362[S])	0.037*
Regional metastasis:					
N0	10	1	0.113	0.308[K]	0.011*
N1	14	9			
Distant metastasis:					
M0	17	7	1.000	0.008[K]	0.972
M1	7	3			
Anemia presence:					
Non-anemic	10	5	0.717	–0.076[K]	0.504
Anemic	14	5			

SCC – squamous cell carcinoma; ADC – adenocarcinoma; [K]Kendall correlation coefficient; [S]Spearman correlation coefficient; *statistically significant at $p \leqslant 0.05$.

Table 3. Relation of mean levels of oxygen partial pressure (pO_2) and oxygen saturation (SaO_2) to cancer-related features in esophagogastric cancers

Parameters	pO_2 level mmHg	*p* value	SaO_2 level %	*p* value
Histology:				
SCC	60.6 ± 2.0	0.479	91.5 ± 0.6	0.952
ADC	63.6 ± 4.4		91.6 ± 1.7	
Disease stage:				
II/III	63.2 ± 2.3	0.204	92.2 ± 0.7	0.244
IV	58.4 ± 2.9		90.6 + 1.1	
Tumor extension:				
T2/T3	66.6 ± 2.6	0.015*	93.5 ± 0.6	0.011*
T4	57.7 ± 2.3		90.2 ± 0.9	
Regional metastasis:				
N0	64.5 ± 2.8	0.243	93.2 ± 1.0	0.071
N1	59.9 ± 2.4		90.8 ± 0.8	
Distant metastasis:				
M0	62.0 ± 2.1	0.592	91.6 ± 0.8	0.892
M1	59.8 ± 3.6		91.4 ± 1.2	
Anemia presence:				
Non-anemic	60.6 ± 2.5	0.713	91.5 ± 1.1	0.913
Anemic	62.0 ± 2.6		91.6 ± 0.8	

SCC – squamous cell carcinoma; ADC – adenocarcinoma; *statistically significant at $p \leqslant 0.05$.

VEGF-A, but not VEGF-C, was more elevated in esophagogastric cancer patients with systemic hypoxemia. We found that differences in circulating VEGF-A levels between healthy subjects and cancer patients with and without systemic hypoxemia, both when determined in terms of pO_2 ($p < 0.0001$) or SaO_2 ($p < 0.0001$), were significant. A strong tendency towards higher VEGF-A concentrations in hypoxemic *vs.* normoxemic cancer patients could be observed (Fig. 1). The strength of the relation between VEGF-A levels and the presence of hypoxemia was: rho = 0.335, p = 0.054, when pO_2 was applied as the criterion, and rho = 0.270, p = 0.121 in case of SaO_2. The tendency towards direct correlation between VEGF-A concentration and pO_2 or SaO_2 levels was rather weak: rho = –0.203, p = 0.243 and rho = –0.206, p = 0.237, respectively.

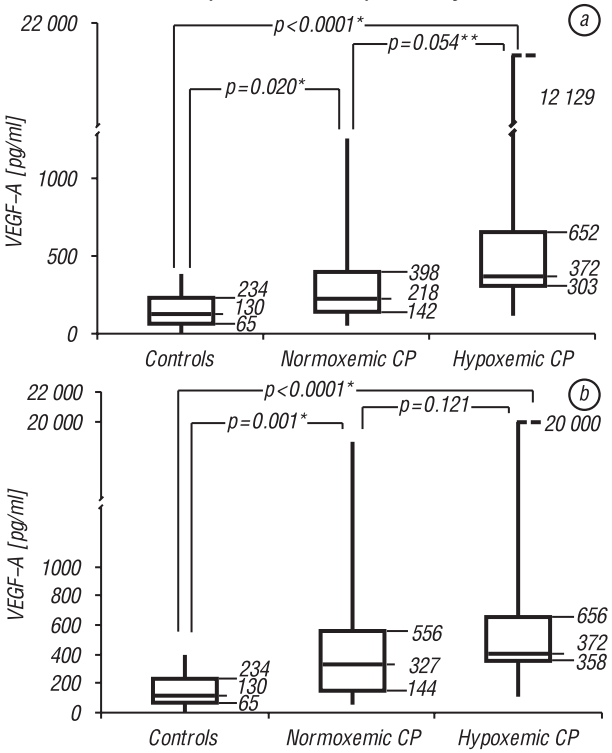

Fig. 1. Comparison of serum levels of vascular endothelial growth factor A (VEGF-A) in healthy individuals and cancer patients without and with systemic hypoxemia. *A.* respiratory insufficiency in terms of oxygen partial pressure. *B.* respiratory insufficiency in terms of oxygen saturation

Boxes represent interquartile range, bars inside boxes — medians, whiskers — 5 and 95 percentil; *statistically significant at $p \leqslant 0.05$; **statistically significant at $p \leqslant 0.1$; CP — cancer patients.

The differences between serum levels of VEGF-C between controls and cancer patients with and without systemic hypoxemia were found significant ($p < 0.0001$ for both pO_2 and SaO_2) as well. However, there was no difference in circulating VEGF-C between non-hypoxemic and hypoxemic cancer patients (Fig. 2). Accordingly, no tendency towards direct correlation between circulating VEGF-C and the presence of hypoxemia was found: rho = –0.118, p = 0.496 (for pO_2 as hypoxemia criterion) and rho = –0.018, p = 0.917 (for SaO_2 as hypoxemia criterion). Similarly, concentrations of circulating VEGF-C were not related to the

levels of pO_2 (rho = 0.066, p = 0.704) or SaO_2 (rho = 0.061, p = 0.724).

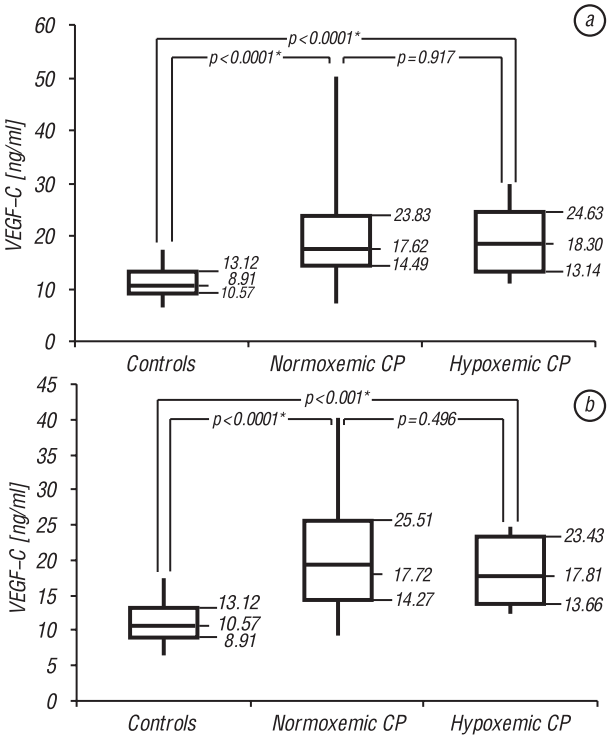

Fig. 2. Comparison of serum levels of vascular endothelial growth factor C (VEGF-C) in healthy individuals and cancer patients without and with systemic hypoxemia. *A.* respiratory insufficiency in terms of oxygen partial pressure. *B.* respiratory insufficiency in terms of oxygen saturation
Boxes represent interquartile range, bars inside boxes — medians, whiskers — 5 and 95 percentil; *statistically significant at $p \leqslant 0.05$; **statistically significant at $p \leqslant 0.1$; CP — cancer patients.

Circulating VEGF-A and VEGF-C levels are elevated in locally advanced tumors. We evaluated VEGF-A and VEGF-C relation with the extension of primary tumor. We found that serum VEGF-A level was significantly higher in T4 cancers as compared with less advanced ones (Fig. 3) and that circulating VEGF-A concentration also directly correlated with tumor extension: rho = 0.648, $p < 0.001$. Similarly, serum VEGF-C concentration was higher in locally more advanced tumors (see Fig. 3), but no direct correlation between parameters was found: rho = 0.227, p = 0.191.

Circulating VEGF-A exhibited tendency to be upregulated also in cancers metastasizing to regional lymph nodes. Median serum VEGF-A levels in N0 cancers was 327 pg/ml (97–356) *vs*. 372 pg/ml (198–652) in N1 cancers (p = 0.066). Median serum concentration of VEGF-C in N0 cancers was 15.96 ng/ml (13.79–18.17) *vs*. 20.05 ng/ml (13.83–25.72) in N1 cancers (p = 0.167).

The levels of circulating VEGF-A were correlated neither with Hb concentration (r = 0.052, p = 0.767) nor with anemia presence (r = 0.151, p = 0.385). In turn, serum VEGF-C levels tended to be related with anemia presence (r = 0.341, p = 0.050), but there was no direct correlation between VEGF-C and Hb (r = –0.164, p = 0.347).

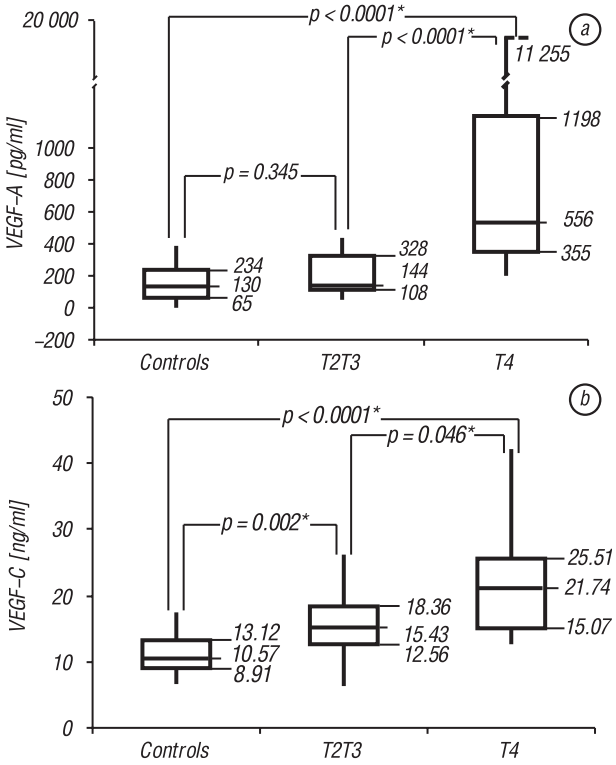

Fig. 3. Relation of serum levels of vascular endothelial growth factors with the extension of primary tumor (T). A. vascular endothelial growth factor A (VEGF-A). B. vascular endothelial growth factor C (VEGF-C)
Boxes represent interquartile range, bars inside boxes — medians, whiskers — 5 and 95 percentil; *statistically significant at $p \leqslant 0.05$; **statistically significant at $p \leqslant 0.1$.

DISCUSSION

We hypothesized that esophagogastric tumors from patients suffering from respiratory insufficiency in course of background chronic obstructive pulmonary disease may behave more aggressively than those from patients with cancer disease alone. The probability of enhanced aggressiveness in this subgroup of cancer patients together with possible involvement of angiogenesis mediators have not been addressed yet. Indeed, our results demonstrated that COPD-related hypoxemia in esophagogastric cancer patients was associated with higher incidence rates of locally advanced tumors and lymph node metastasis. The mean levels of pO_2 and SaO_2 were significantly lower in T4 cancer patients than in those with less advanced tumors as well. We also showed that a key regulator of angiogenesis, vascular endothelial growth factor A (VEGF-A), might be involved.

Our findings seem to be important from clinical point of view. Tumor hypoxia favors cancer aggressiveness, angiogenesis and metastasis, and consequently is associated with poorer prognosis regardless of treatment strategy [28]. Yet, the current methods of measuring the oxygenation status in tumor tissue are invasive and not applicable in clinical practice, while reliable surrogate markers are still being searched [22]. We showed that presence of systemic hypoxemia in cancer patients was associated with increased extension of primary tumors as well as with higher rates of regional metastasis. On

this basis, it can be suggested that co-existence of systemic hypoxemia may guide the selection of patients with more aggressive tumors, who probably would not benefit from oxygen-based treatment strategies and may help in directing their further management. It may also facilitate the selection of patients who are at higher risk of disease recurrence also when treated with surgery alone. This seems to be especially important in esophageal cancers characterized by reduced overall survival rates in comparison with other solid tumors and distinguished by high recurrence rates (up to 79% after curative resection) with lymph node metastasis being a common pattern [11, 26].

We also hypothesized that the presence of COPD-related respiratory insufficiency in cancer patients may be associated with more elevated secretion of pro-angiogenic factors as compared to cancer patients without hypoxemia. The rationale was that hypoxia alters gene expression in a way that enables the transformed cells to overcome oxygen deprivation mainly by hypoxia-induced transcription factor HIF-1α. In turn, HIF-1α activates a plethora of genes, *VEGF-A*, being one of the strategic targets [1]. Also *VEGF-C* has been reported to be up-regulated in response to hypoxia [18]. Accordingly, we found that serum levels of VEGF-A tended to be more elevated in cancer patients with respiratory insufficiency as compared to those with cancer disease alone. Moreover, similarly to systemic hypoxemia, circulating levels of VEGF-A were strongly related to the extension of primary tumor. Therefore, it is tempting to speculate that the impact of systemic hypoxemia on tumor local advancement is realized by oversecretion of VEGF-A.

The impact of systemic hypoxemia on up-regulation of angiogenesis mediators has been controversially discussed in the recent literature. The majority of limited studies concerned the conditions induced by exercise and/or high-altitude, or nocturnal episodes of hypoxemia in course of sleeping disorders. These reports were entirely focused on VEGF-A, but their results have been exceedingly confusing. While some authors reported the elevation of circulating VEGF-A in response to altitude-related hypoxemia [29] or the occurrence of acute mountain sickness [24], yet without correlation between VEGF-A concentration and pO_2 or SaO_2 levels, the others observed the adverse effect of VEGF-A down-regulation [4]. Similarly to the latter finding, the reduction of oxygen saturation in healthy men under experimental conditions caused the decrease in VEGF-A level, as reported by Oltmanns et al. [14].

Contrary to high altitude-related hypoxemia, night-time hypoxemia in course of obstructive sleep apnea seems to be associated with the up-regulation of circulating VEGF-A [6, 10, 19, 23] and to be significantly correlated with the degree of nocturnal desaturation [19, 23]. Yet, Valipour et al. [25] failed to confirm the relation of circulating VEGF-A to night-time hypoxemia in patients with sleep disorder.

Our results in part corroborate the findings of limited studies on changes in VEGF-A concentration related to systemic hypoxia in cancer. Matsuyama et al. [13] reported that serum levels of VEGF-A were higher in lung cancer patients with systemic hypoxemia as compared to patients with normoxemia. Moreover, the authors observed a direct negative correlation between VEGF-A concentration and the levels of oxygen partial pressure. In turn, Ono et al. [15] found that VEGF-A is more strongly expressed in colorectal cancer tissue from hypoxemic patients and that the level of VEGF-A expression adversely correlated with systemic pO_2. These authors reported systemic pO_2 to be an independent factor influencing VEGF-A content in colorectal cancer tissue.

We also evaluated whether VEGF-C, regarded as the most important mediator of lymphangiogenesis, yet with angiogenic potential as well, was affected by systemic hypoxemia. Especially that we observed a tendency towards higher incidence rates of cancers metastasizing to regional lymph nodes in cancer patients with respiratory insufficiency. The up-regulation of tissue expression [2, 12] and elevation of serum levels [9] of VEGF-C together with factor's relation to regional metastasis have previously been reported in esophageal cancer. Moreover, hypoxia through HIF-1α has recently been linked to lymphatic metastasis in this cancer type *via* VEGF-C up-regulation [7]. Yet, we failed to show VEGF-C overexpression in cancer patients with respiratory insufficiency. The elevation of factor's level in cancers metastasizing to regional lymph nodes was not significant in this group of patients. It can be a result of relatively small number of observations. However, it can not be excluded that the relation of systemic hypoxemia to lymph node metastasis observed here may be mediated by other lymphangiogenic factors.

Anemia may account for the presence of systemic hypoxemia on one side and up-regulation of angiogenic factors on the other [28]. Our results showed, however, that at least in population studied here, the anemia presence did not mediate the observed relationships between hypoxemia, cancer clinicopathological variables and angiogenesis mediators. Lack of correlation between VEGF-A and Hb reported in this paper is in agreement with our previous findings (manuscript submitted) - we have observed a rise in VEGF-A level only when Hb level dropped below 11 g/dL, while anemia in currently studied patients was of a mild grade.

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ВЛИЯНИЕ СИСТЕМНОЙ ГИПОКСЕМИИ НА АГРЕССИВНОСТЬ ЗАБОЛЕВАНИЯ И СОДЕРЖАНИЕ ЦИРКУЛИРУЮЩИХ ФАКТОРОВ РОСТА ЭНДОТЕЛИЯ СОСУДОВ А И С У БОЛЬНЫХ ГАСТРОЭЗОФАГАЛЬНЫМ РАКОМ С ХРОНИЧЕСКОЙ РЕСПИРАТОРНОЙ НЕДОСТАТОЧНОСТЬЮ

Цель: **в связи с общим этиологическим фактором заболевания, значительное количество больных гастроэзофагальным раком страдает от респираторной недостаточности в процессе хронического обструктивного легочного заболевания, которое предшествует раку. Системная гипоксемия может влиять на пониженную оксигенацию опухолевой ткани — основной источник опухолевого неоангиогенеза. Авторы предположили, что у больных онкологического профиля с респираторной недостаточностью системная гипоксемия может быть связана с повышенной агрессивностью опухолевого процесса, с одной стороны, и повышенным уровнем ангиогенных факторов — с другой.** ***Методы:*** **содержание факторов роста эндотелия сосудов A и C (VEGF) определяли иммуноферментными методами у пациентов с гастроэзофагальным раком на фоне респираторной недостаточности в процессе хронического обструктивного заболевания легких или в отсутствие такового, а также у здоровых доноров. Анализировали данные газометрии и содержания гемоглобина в зависимости от гистологии новообразования, статуса TNM и уровня VEGF A и C.** ***Результаты:*** **у больных с системной гипоксемией частота появления новообразований была выше. Парциальное давление кислорода и насыщение крови кислородом значительно снижено у пациентов с категорией T4. Повышение содержания циркулирующего VEGF A, но не C, более выражено у больных с респираторной недостаточностью, чем без нее. Содержание VEGF коррелировало с объемом первичной опухоли.** ***Выводы:*** **наши результаты показывают, что системная гипоксемия у пациентов с гастроэзофагальным раком связана с увеличением объема первичной опухоли, и такой эффект может быть опосредован повышением содержания циркулирующего VEGF A.**

Ключевые слова: **гипоксемия, гастроэзофагальный рак, ангиогенез, VEGF-A, VEGF-C, COPD, респираторная недостаточность.**