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Morphological Changes in Cicatrical Stenosis of The Trachea. The Effect of Long-term Endoprosthesis on The Epithelium.

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ABSTRACT

Elimination of persistent and extensive defects of the anterior wall of the trachea is an urgent problem and continues to be the subject of research and discussion of thoracic surgeons, plastic surgeons and otolaryngologists. Despite the large number of studies devoted to this problem, to the present time, the morphogenesis of scar stenosis of the trachea has not been studied enough. The authors summarized the data available in the literature of morphological studies of tracheal stenosis and presented their own material on the structural changes of the tracheal wall during its stenosis and after dilation using a T-shaped endoprosthesis. Morphological studies performed by the authors have shown that in tracheal stenosis there is a reduction of the epithelial lining of the mucous membrane with a significant growth of coarse-fibered connective tissue. Primary in the development of tracheal stenosis is damage to the epithelial lining. Dilation with a T-shaped prosthesis for 5-6 months helps to restore the multilayer epithelium of the mucous membrane, longer stenting leads to the appearance of highly specialized ciliated and goblet-shaped cells.

At this time, there is a tendency to increase cases of long-term artificial ventilation of lungs, which is associated with the development of the level of resuscitation life support, in connection with which there is an increase in the number of patients with CST (cicatrical stenosis of the trachea), so the relevance of this topic is not in doubt [5, 6, 8]. On the third day of the artificial lung ventilation (ALV) in the cartilaginous semirings of the trachea, pathological changes characteristic of chondrolysis, sequestration, necrosis are observed, the consequence of these pathological processes is the loss of cartilage support function, which further leads to narrowing of the tracheal lumen [1, 2, 3]. The frequency of scarring of the trachea after resuscitation, accompanied by prolonged ventilation, and later tracheostomy, according to different authors, is from 1 to 25\% [10, 12]. Endoscopic examination remains the main in the detection of stenotic diseases of the respiratory tract.

In limited CST, the main method of treatment is circular resection of the trachea with the formation of an anastomosis to restore the integrity of the airway. If the patient has tracheomalacia, the volume of surgery expands. In some cases, resection should be abandoned in favor of staged reconstructive operations with the formation of a lumen of...
the airway on the T-shaped stent. Expressed respiratory disorders may require tracheostomy or endostenting. It is possible to implant autologous tissues, install biocompatible ceramic rings, etc. Hybrid and biodegradable stents have been developed, but the assessment of their clinical effectiveness is not sufficient, so they are not widely used [4]. Thus, the diagnosis of CST should be aimed at identifying not only the narrowing of the airway lumen, but also intramural changes in the tracheal wall, including tracheomalacia.

A quarter of all intubated patients in intensive care units are on ALV for more than 1 week, and 10% of them more than 2 weeks [9]. According to the literature [11, 13, 17], the frequency of tracheal stenosis after prolonged AVL is different and ranges from 0.1 to 20%. Prevention and treatment of postintubation tracheal stenosis is one of the actual issues of surgery. Despite the large number of studies devoted to this problem, to the present time, the morphogenesis of scar stenosis of the trachea remain poorly understood.

C. Zagalo et al. [21, 22] performed a number of morphological studies on scar stenosis of the trachea. In the study of resected tracheal rings in 20 patients with postintubation scar stenosis, factors of favorable and unfavorable prognosis of the disease depending on the morphological changes found were identified. On the basis of the studied materials, the authors concluded that the causes of narrowing of the tracheal lumen in the studied tissues were infiltrative inflammation and focal fibrosis of the mucosa. Ossification of cartilaginous half-rings, loss of mucosal epithelial villi are observed mainly in complete obliteration of the tracheal lumen and can be regarded as predictors of unfavorable prognosis in the formation of scar stenosis of the trachea.

M. Shetty et al. [19] in 2007 studied morphological changes in the larynx and trachea of 65 corpses. The selection criterion was a long-term ALV through the naso-or orotracheal tube. The aim was to study macro- and microscopic changes in the trachea after naso-or orotracheal intubation. In the morphological study of laryngeal-tracheal complexes, the most frequent postintubation injury was ulceration of the tracheal mucosa, which was recorded in 31% of observations. Hemorrhage into the submucosal membrane (21%) and acute erosion of the trachea (20%) were the second and third most common reasons. In 20% of cases, two or more variants of postintubation trauma were observed simultaneously. The study showed that one of the most important factors in the formation of postintubation complications is the duration of ALV. Thus, the earliest morphological changes in the form of erosions are observed in the first 24 hours, inflammatory changes, mucosal edema and submucosal hemorrhages can be detected as early as 27-31 hours after tracheal intubation, while after 240 hours ulcerative defects of the larynx and trachea prevail. In the cartilage tissue of the trachea, the development of destructive and dystrophic processes is associated not only with the duration of the ALV, but also with the severity of the general condition of the patient, functional disorders of the respiratory organs, cardiovascular and central nervous systems, as well as with early accession of nosocomial infection (tracheobronchitis, pneumonia, sepsis) [15, 20].

N.V. Lafutkina [6] presented the results of intraoperative pathomorphological study of cartilage of the anterior wall of the trachea in 30 patients at different times of AVL. Morphological study of tracheal cartilage showed that by the 1st day of the ALV dystrophic changes with loss of cartilage cells are determined. On the 2nd day of the ALV, significant dystrophic changes were revealed in the cartilage of the trachea, the main substance was poorly stained, it was impregnated with plasma proteins, pyknosis of nuclei was noted in chondrocytes. By the 3rd day of the ALV, perichondrial detachment occurred. The surface of the cartilage, deprived of perichondrium, was usurated, covered
with fibrinous deposits, the cartilage cells were not detected. Therefore, the duration of intubation up to 3 days causes pathological changes not only in the mucous membrane of the larynx and trachea, but also destructive and dystrophic changes in the cartilages of the trachea. On the 4-7 day of the ALV, deeper dystrophic and destructive changes appear in the cartilages of the trachea - the perichondrium is usually absent, the surface of the cartilage is usurated, foci of chondronecrosis are observed. In some patients, against the background of pronounced dystrophic processes occurring in cartilage, the replacement of foci of chondronecrosis with granulation tissue was noted. Focal clusters of leukocytes and focal hemorrhages were found in the peritracheal connective tissue. In patients who are on an ALV for more than 7 days, along with cartilage degeneration and replacement with granulation tissue, the appearance of regeneration processes was revealed, which is expressed in focal proliferation of chondrocytes, thickening and fibrosis of the perichondrium, as well as in the appearance of sequestration of necrotized cartilage.

M.K. Nedzved et al. [7] examined resected stenotic tracheal fragments in 26 patients who underwent surgical treatment. Destructive-inflammatory processes in the studied preparations are observed in all layers of the tracheal wall, but are most pronounced in the submucosal layer, in which progressive circular fibrosis with hyalinization sites is detected. For the zone of maximum cicatrical narrowing of the trachea, thinning of the mucous membrane with the absence of epithelium or its metaplasia is characteristic. The defeat of cartilage in the zone of stenosis leads to its irreversible changes, replacement of cartilage with fibrous tissue with the development of foci of petrification and ossification.

A number of papers pay attention to the increased pressure in the cuff of the intubation tube as an etiological factor in the development of postintubation stenosis [12, 16, 17]. According to A. Stein et al. [20], half of intubated patients who died in the early postoperative period have tracheal lesions of varying degrees associated with intubation. R. Miller and G. Sethi [16] studied the causes of posttracheostomy stenosis of the trachea in an experiment on 23 dogs. The leading factor in the development of stenosis was the increased pressure of the intubation tube cuff on the tracheal wall. Also, the authors investigated the morphological preparations of the tracheal wall of patients who were on ALV and died from various causes. The most pronounced changes are observed in the place of standing of the inflated cuff of the tracheal tube. On average, after 36 hours after intubation, ulceration of the tracheal mucosa appears, and when the duration of prolonged ventilation is more than 14 days, pronounced destructive changes of the tracheal wall with the involvement of the cartilage framework were noted in the studied preparations. It is shown that as a result of prolonged increased pressure of the intubation tube cuff on the tracheal wall, the first will be to develop erosive changes in the tracheal mucosa, which gradually involve the underlying tracheal tissues and cartilaginous half-rings in the inflammatory process. Tracheitis and chondritis stimulate the proliferation of fibroblasts, which leads to sclerosis of the tracheal wall. The authors also noted the most pronounced destructive changes on the anterolateral surface of the trachea.

D.V. Trishkin [11] in the works devoted to the study of pathogenesis, diagnosis, treatment and prevention of postintubation changes of the trachea, identified and justified the concept of "postintubation tracheal disease", which is characterized by four main clinical and morphological variants: a) ulcerative tracheitis; b) granulation tracheal stenosis; c) inflammatory pseudotumor; d) cicatrical tracheal stenosis. In ulcerative tracheitis, an ulcerative defect is formed, the bottom of which is represented by necrotic masses and destructively altered leukocytes, the edge of the ulcer is granulation tissue with leukocyte infiltration and detritus on the surface, and if the defect exists for 3-5
weeks, 21.4% of patients have squamous metaplasia of the epithelium, destruction or focal ossification of cartilage structures. Histological examination of cicatrical stenosis of the trachea showed that the lumen is covered with epithelium with foci of squamous metaplasia; in the submucosal layer, excessive growth of connective tissue with lymphocytic infiltration around the glands; near destructively altered cartilaginous semicircles, massive growths of coarse-fibrous connective tissue. It should be noted that mainly occur marginal destruction of cartilage and its ligamentous apparatus. Cartilage tissue is involved in the destructive process, but complete lysis of the cartilage structure is not observed.

Thus, endotracheal intubation is the leading risk factor for the development of acquired CST. The most significant for the development of inflammatory and degenerative changes of the trachea, according to most researchers, is the duration of ALV. Turning to the morphological changes occurring in the tracheal wall during the formation of postintubation stenosis, it is necessary to stay on several points. As confirmed by numerous studies, the most pronounced morphological changes in the formation of cicatrical stenosis of the trachea are found in the submucosal layer, where against the background of infiltrative changes there is a sharp thickening due to the growth of connective tissue with elements of hyalinization. The processes of fibrinous-purulent and productive inflammation, as well as maturation of granulation and fibrinous tissue do not occur simultaneously and have a mosaic character [6, 7, 8, 20, 22]. In the tracheal mucosa, the processes of erosive-ulcerative inflammation in various degrees occur - from superficial ulceration to the formation of deep defects involving all the underlying tissues [1, 7, 13, 17, 21]. Changes occurring in the cartilaginous framework of the trachea are characterized by the formation of destructive chondrite and the replacement of normal hyaline cartilage with connective tissue. The result is a violation of the processes of chondrocyte proliferation and cartilage regeneration, which leads to sequestration, and then to petrification and ossification [7]. It should be noted that the inflammatory process almost always involves not one, but at least two or three cartilaginous half-rings [15, 17, 19, 20, 21]. Changes in the membranous part of the trachea are similar to those occurring in the submucosal layer and the zone of the cartilaginous semirings. The adventitial membrane is compacted and thickened by the formation of fibrinous peritracheitis [7]. Accordingly, the morphological changes detected in cicatrical tracheal stenosis are characterized by the development of chronic pantraheitis with the replacement of normal structures of the tracheal wall with coarse-fibrous connective tissue.

Despite a large number of works devoted to the study of the morphology of postintubation tracheal stenosis, some aspects of the pathogenesis of this pathological process remain insufficiently studied. In the available literature there are no data reflecting the participation of factors of local immunity in the processes of alteration and regeneration of the tracheal wall. The role of the protective mechanisms of the tracheal mucosa in the formation of hypertrophic processes in its wall has not been sufficiently studied. The pathomorphological substrate of tracheomalacia formation has not been clarified. The mechanisms and factors contributing to the expansion of the stenosis zone after decanulation/extubation, when the action of the main etiological factor - the pressure of the tracheostomy tube cuff is already absent, have not been studied. In this regard, it is important to continue studies of morphological changes occurring in the trachea during the formation of postintubation stenosis, as their in-depth study not only contributes to a better understanding of pathological processes, but also provides an
opportunity to improve the methods of treatment and prevention of this pathological process.

The problem of adequate and complete repair of damaged organs and tissues to restore their specific functions is the most urgent for surgery. This issue is particularly acute in the treatment of patients with CST, since the healing process is complicated by the presence of saliva and sputum in the wound, i.e. it takes place in unfavorable conditions of primary infection [3].

In wound healing process there are three compulsory components: a damage – inflammation – recovery. These processes are typical for wounds of any genesis and are closely interrelated [18].

The peculiarity of inflammatory-reparative processes in the initial parts of the airways is due to the anatomical structure of these organs, and is also associated with complex structural interactions of various tissues of the anterior neck: skin, muscles, cartilage, mucous membrane [3, 14, 18]. These biological tissues differ not only in their morphological organization, but also in the reaction to damage and the ability to recover.

The trachea is a tubular formation, communicating in the upper parts with the larynx, and in the lower divided into two bronchi. The structure of the tracheal wall includes about twenty cartilages, which prevents its decline. The functional specificity of the trachea is determined by its mucous membrane. It is formed by a multi-row ciliated epithelium with goblet-shaped cells secreting mucus [14]. Resuscitation measures associated with intubation and tracheotomies inevitably lead to damage to the trachea, the development of cicatricial deformities and stenosis of its lumen.

One of the widely used methods of reconstructive intervention is the use of T-shaped prostheses. However, the structural changes of the trachea are not sufficiently studied, which makes it difficult to perform appropriate therapeutic and preventive measures to restore its patency.

The above-stated determined the objectives of this section of the study: to study the structural changes of the tracheal wall during its stenosis and after dilation using a T-shaped endoprosthesis.

**Materials and methods:**

The Department of surgery of lungs and mediastinum SI "RSSPMCS named after akad. V. Vakhidov" has experience in treating 212 patients with CST from 2008 to 2019. Only in 42 cases it was possible to perform radical surgery-circular resection of the trachea. Some patients were cured by endobronchial interventions. 120 patients underwent multi-stage reconstructive interventions on the trachea, as they had severe comorbidities, neurological deficits, and other aggravating factors, which did not allow them to be cured simultaneously.

In 28 cases, morphological studies of the wall of the altered trachea were performed. Tracheal tissue samples for light microscopy were obtained during surgery, as well as mucosal samples during biopsies at various times after T-stenting. The tissue was fixed in 10-12% formalin solution on phosphate buffer by Lily. Paraffin sections stained with hematoxylin-eosin. Stereomorphometric study was performed by G.G. Avtandilov. Microphotos were obtained on the microscope "Axioscope" (Zeizz) with a digital camera "Sony".

Cicatricial stenosis of the trachea causes significant changes in its walls. The epithelial lining of the mucous membrane is practically not determined (Fig. 1-2). The main structural component of the tracheal wall is coarse connective tissue.
Fig. 1-2. Connective tissue fibers, the lysis of the epithelium in the CST. H-E. 10x10.

Closer to the lumen, dense deposits of dark brown color, representing a carbon pigment, are determined (Fig. 2). The basis of coarse-fibrous connective tissue consists of hyalinized collagen fibers and a small number of small fibroblasts with medium-sized nuclei (Fig. 3-4).

Fig. 3-4. Connective fibers in CST, the remnants of the epithelium in cicatricial stenosis of the trachea. H-E. 10x40.

Among the hyalinized fibers are emptied vessels (Fig. 5). There are small clusters of inflammatory infiltrate cells (Fig. 6).

Fig. 5-6. Connective tissue fibers, inflammatory infiltrates in CST. H-E. 10x40

In some areas, the remains of epithelial cells of the multi-row epithelium, including goblet-shaped cells, are determined. In the zones with the remains of cells of the multi-
row epithelium in the own connective tissue layer of the tracheal mucosa, numerous emptied vessels and inter-fiber slits are determined (Fig. 7-8).

Fig. 7-8. Connective tissue fibers, the lack of epithelium in the CST. H-E. 10x40

Morphological studies of tracheal mucosal biopsies after dilation on a T-shaped endoprosthesis have shown that this procedure leads to the restoration of multi-row epithelium of the mucous membrane. After 5 months, the multi-row epithelial lining with the accumulation of surface prismatic cells is determined. At the same time, moderate perinuclear edema and mitosis in the basal parts of the multi-row epithelium are observed in prismatic cells. In its own connective tissue layer of the mucosa revealed quite large vacuoles. However, during this period, there is no appearance of prismatic cells with characteristic cilia, as well as goblet-shaped cells (Fig. 9-10).

Fig. 9-10. Multi-row epithelial lining with a concentration in the surface of prismatic cells. 5 months of T-shaped stenting. H-E. 10x10

10 months after stenting, there is a clearly formed multi-row epithelial lining, but without the presence of ciliated and goblet-shaped cells. At the same time, there are quite a lot of blood vessels in the own connective tissue layer of the mucous membrane, in the basal parts of the multi-row epithelium there are mitosis figures (Fig. 11-12).
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**Fig. 11-12. Multi-row epithelium, moderate perinuclear edema and mitosis in the basal parts. 10 months of T-shaped stenting. H-E. 10x40**

In more distant terms of stenting (15 months) there is a marked tendency of appearance of ciliated and goblet-shaped cells in the surface layers of multi-row epithelium. In its own connective tissue layer are quite numerous vessels, there are small clusters in the perivascular zones of inflammatory infiltrates (Fig. 13-14).

**Fig. 13-14. Multi-row epithelial lining with a concentration of prismatic cells in the surface. 15 months of T-shaped stenting. H-E. 10x40**

**Conclusion:**

Performed studies have shown that tracheal stenting with traditional therapy leads to a decrease in edema and inflammation of the tracheal walls. Morphological studies have shown that in tracheal stenosis there is a reduction of the epithelial lining of the mucous membrane with a significant growth of coarse connective tissue in the tracheal wall. Primary in the development of tracheal stenosis is damage to the epithelial lining.

Dilatation with a T-shaped prosthesis within 5-6 months helps to restore the multilayer epithelium of the mucous membrane, longer dilatation leads to the appearance of highly specialized ciliated and goblet-shaped cells.

**References:**


