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Lung function in chronic uremia

Czynność płuc w przewlekłej mocznicy

Chronic uremia is the final stage of uncontrolled renal insufficiency, which is characterized by a syndrome of clinical symptoms resulting from progressive destruction of all renal structures. Lung function damage and impaired regulation of breathing belong to uremia consequences.

Lung changes in the course of uremia attracted attention at the beginning of the 20th century. Radiologic picture of pulmonary oedema was then described in patients with chronic renal failure as parahilar thickening with the shape of butterfly wings which occupy two thirds of the central pulmonary region and disappear towards the periphery giving a zone of clearing up in chest X-rays (13).

In 1947 Doniach (7) performed histological examinations in 4 persons with uremia and changes in the lungs finding the presence of diffuse solid oedema caused by fibrinous and protein exudates in lung alveoli. He believed that it was associated with a stimulation of monocytes and formation of hyaline membranes covering alveolar ducts. He assumed that the exudate was caused by two factors: increased capillary pressure in the lungs which results from left ventricular cardiac insufficiency and a change in capillary permeability in the lungs caused by uremia. Doniach, like Barden et al. (4) in 1948, presumed that lung changes caused by uremia are not specific. Barden et al. were the first researchers who used the term "uremic pneumonia".

Alwall et al. (3) examined 16 patients with uremia caused by acute or chronic renal failure in whom changes found in chest X-rays were found called in literature "uremic

lung", "uremic oedema" or "uremic pneumonia". They observed gradual or complete regression of X-ray picture changes after dehydration of patients by means of 25-50% sodium sulphate.

A classic radiologic picture of uremic oedema is classified in the intraparenchymatous form of pulmonary oedema. A characteristic location of changes observed in chest X-rays depends on the anatomy and physiology of pulmonary circulation. Felix (8), basing on the length of vascular flow and proportion of the diameter of individual generation of vascular branches, distinguished three zones in the lungs: central, hilar and marginal. In the central zone, where the flow length is the shortest precapillary vessels immediately extend from a relatively big diameter of the vessels. Pressure decrease gradient connected with this affects the vessels of interalveolar septa. In the marginal zone of the lungs, however, there is a long way of flow – a gradual decrease of the diameter of subsequent vascular generation is preserved.

The reasons for pulmonary oedema in renal insufficiency have not been sufficiently clarified yet. Alwall et al. (3) believed that one of the main pathogenic factors of lung oedema is hyperhydration. Maria Werkenthin (19), a Polish researcher, thought that oedemic changes in the lungs in the course of uremia are connected with existing toxemia causing increased permeability of endothelia of pulmonary capillaries, while hyperhydration and circulatory failure can enhance these changes.

A new light on the etiopathogenesis of "a uremic lung" was shed by studies on an experimentally produced model of biochemic uremia in dogs in which hyperhydration, circulatory failure and arterial hypertension were excluded (1). Morphologic examinations showed that in the pathomechanism of pulmonary changes an important role is played by the cellular apparatus responsible for surfactant production. There was shown a considerable decrease in the number of granular cells in the lungs of dogs with experimental uremia in comparison with control group. Examinations using electron microscope showed emptying of lamellar structures of cellular organella producing and storing lung surfactant, which is closely connected with a light-microscope revealing a decrease in the number of gradual cells and subsequent deficiency of the superficial active factor.

A necessary condition for the development of pulmonary oedema is unstable balance between the number of filtered amount in excessive plasma from the capillaries and its absorption and transport by veins and lymphatic vessels. In renal failure this happens as a consequence of the increase of the general amount of circulation blood, reduced concentration of plasma proteins, increased permeability of capillaries resulting from hypoxia and the action of toxins. A considerable role is also played by decreased reflexive absorption of the lymph because of increased venous pressure and an increase of the general amount of extra cellular fluid. Depending on the velocity and intensity of filtrate fluid accumulation this is first intraparenchymatous lung oedema which can then develop into alveolar lung oedema. Lung oedema in renal insufficiency usually develops slowly and imperceptibly over weeks, this is most often intraparenchymatous oedema which can gradually subside due to pharmacological treatment and dialyses.

Morphological changes in the lungs in the course of uremia are considered chronic oedemic conditions. They have their own evolution. In the initial stage congestion and thickening of interalveolar septa are observed. Changes are caused by latent intraseptal oedema. Subsequently, in the alveolar lumen apparent oedema appears consisting of protein fluid and blood cells. Pulmonary macrophages phagociting intraalveolar content also appear. Gradually the septal epithelium gets exfoliated and atelectasis accompanying oedemic processes permanently increases. Contracting atelectatic peripheral alveolar sacks cause passing of liquid alveolar content towards respiratory brioncholes where it gets condensed forming hyaline membranes. This situation, after some time, gives rise to the organization of intraalveolar content, leading to pulmonary fibrosis.

All these morphological changes observed in the lungs are bound to affect lung function. Additional causes of lung function impairment in uremia can be weakening of respiratory muscles, uremic pleurisy, infections, fibrosis or calcifications in the lungs; besides, processes coursing subdiaphragmatically, such as ascites, can also weaken respiratory system functioning by decreasing diaphragm mobility.

Muscle weakening is one of the commonest subjective feelings in patients with chronic uremia. In the group of ten patients chronically treated with haemodialyses Bark (5) found a decrease in maximal inspiratory pressure (MIP) to 58.2% and maximal expiratory pressure (MEP) to 50.8% of normal values. A highly significant correlation was found between these two parameters, which the authors explain as simultaneous damage of inspiratory and expiratory muscles.

Hormonal, metabolic disturbances, disturbances concerning hydro-electrolyte balance and acid-base balance occurring in uremia contribute to the development of muscular changes. They get intensified and deepened in the course of dialysis therapy.

Parathormone is regarded as a basic uremic toxin responsible for dysfunctions of many organs, among others skeletal muscles. It has been shown that this hormone aggravates the process of proteolysis in the muscles and disturbs the oxidation chain of free fatty acids thus handicapping bioenergetic processes in the muscle cell. A factor taking part in the development of myopathy in chronic uremia is chronic carnitin deficit both in blood serum and in muscular tissue. The clinical indicator of carnitin deficit is primarily weakening of skeletal muscles, conduction disorders in sensory and motor nerves, abnormal neuro-muscular transmission as well as symptoms of myocardial dysfunction (17).The involvement of uremic toxins and carnitin deficit in the development of uremic myopathy can be indirectly accounted for by correlations between the amplitude of functional potentials of skeletal muscles in global EMG examination as well as by the blood serum creatinine concentration and the amplitude of functional potentials of skeletal muscles in global EMG examination. Weakening of the force of skeletal muscles occurring in patients with chronic uremia treated with haemodialysis is caused by peripheral nerve damage, which is confirmed by results obtained due to global and elementary electromyography (17).

Lee et al. (12) found out that in uremia the presence of gas transport deficit through the alveolar-capillary was membrane manifested by a decrease in diffusion volume. Transfer factor in all patients examined by them was diminished. Since potentially accompanying lung diseases were excluded, this abnormality proves characteristic of renal failure. The cause of decreased component membrane diffusion volume can be ascribed to increased fluid permeability in oedema or/and to a chronic damage of alveolar-capillary membrane. Values of forced expiratory volume in one second (FEV_1) and of vital capacity (VC) in patients with uremia were also decreased compared with normal values. In patients with uremia many causes lead to the development of restrictive changes, among which there are included hyperhydration of the lungs, weakening of muscular strength, calcifications in pulmonary tissue, intravascular leucostasis (18). Narrowing of the respiratory tract was absent, which was estimated by the proportion of FEV_1 to vital capacity. Residual capacity, measured in 11 patients, was normal.

It is also emphasized that in the first period of oedemic changes in the lungs due to uremia and in other diseases causing a decrease in the amount of surfactant in the respiratory ducts there is observed an increase in closing volume i.e. this lung capacity at which respiratory ducts in segments most dependent on gravitation (lower respiratory tract) get closed and stop being ventilated. In chronic pulmonary oedema the walls of these small ducts thicken, which results in premature closure of respiratory ducts with subsequent increase in the closing volume. Examination of the closing volume is a sensitive test detecting early narrowing of respiratory ducts in patients who still have normal spirometric parameters. Stanescu et al. (15) explain increased closing volume in uremic patients as a result of fluid accumulation in affected lung areas, which was conducive to premature closure of respiratory ducts.

Considering the mechanisms leading to premature closure of respiratory ducts in resected lungs of dogs Hughes et al. (11) suggested that accumulated fluid between bronchial wall and confining bronchial membrane increases peribronchial pressure and presses on the bronchi causing closure of respiratory ducts at higher than usual lung capacity. Two other factors can also be responsible for an increase in the closing volume: loss of lung elasticity and of bronchial motor tension. Stanescu et al. (15), however, see no reasons for changes in bronchial motor tension taking into account stabilization of pulmonary function parameters. Permanently increased residual capacity after dialysis in a few patients suggests that chronic excess of fluid in the lungs modifies mechanic properties of the lower respiratory tract and causes a tendency for their premature closure, maybe due to a reaction with the surfactant. Closing volume higher than functional residual capacity (FRC) may impair ventilation of the base of the lung since closure of lower respiratory ducts may occur even during normal breathing. In none of the examined patients was closing volume higher than FRC though in some of them the difference was only 200-300 ml. After haemodialysis this difference increased but only insignificantly. Hence, it can be inferred that ventilation of the base of the lungs was not severely decreased (15).

Zidulka et al. (20) observed in 6 patients with advanced chronic uremia chronically haemodialysed the presence of restrictive pattern with normal maximal medial respiratory flows (MMFR) and deceased pulmonary volumes. Removal in the fluid resulted in an increase in residual capacity which was accompanied by an increase of vital capacity and MMFR. Before haemodialysis in most patients increased residual capacity was shown which decreased after haemodialysis. These results reflect premature, reversible bronchial closure and retention of the air at the base of the lungs, probably caused by oedema around lower respiratory ducts. Additionally, most patients were characterized by diminished ventilation and perfusion at the base of the lungs, which got improved after haemodialysis.

Myers et al. (14) examined ventilation and analysed gases in arterial blood in 29 patients with chronic uremia undergoing haemodialysis. 23 of 29 examined patients showed nearly normal lung function and water accumulation in the body in the interdialysis period did not considerably affect ventilation impairment. These patients, however, suffered from uremic pneumonia and pleurisy as well as had extensive serous adhesions as a remainder of this process.

Most of these patients had normal pulmonary capacities (vital capacity - VC, functional residual volume - FRC, total lung capacity - TLC) with a small increase in residual volume (RV) and thoracic gas volume (TGV) indicating slight pulmonary distension. This picture was found at normal resistance and specific conductivity of respiratory ducts (Raw and SGaw) and which pointed to the lack of narrowing at the level of big respiratory ducts. Decreased TGV after dehydrating dialysis suggests narrowing of lower respiratory ducts caused by peribronchiolic accumulation of this fluid. Stanescu et al. (15) examining 12 patients with a long uremic history and chronic hyperhydration (in some episodes of pulmonary oedema occurred) before and after haemodialysis did not find any changes suggesting obturative restrictive confinement of ventilation. Lower than expected values of peak expiratory flow (PEF) and its subsequent decrease after dialysis is ascribed by the authors to weakening of muscular strength and of general physical fitness. The fact that this decrease in peak expiratory flow is not connected with the obstructive syndrome is indicated by normal FEV_1, SGaw, maximal expiratory flow rate (MEFR). The only found abnormalities were the increase in closing volume and capacity, which got decreased after haemodialysis. MEFR, a sensitive indicator of early narrowing of respiratory ducts, especially MEF_{25} was within normal limits. Difficulty in air flow in distal respiratory passages is one of the commonest consequences of uremia after clinical and radiological exclusion of pathology in the cardio-pulmonary system.

Frank-Piskorska et al. (10) among 11 patients with chronic uremia treated by repeated dialyses did not find restrictive impairment of ventilating reserves. Before dialysis they observed discreet ventilation disorders of the obturative type (evidencing themselves by increased total resistance of respiratory ducts (Rt) and restriction of flow (MEF_{50}), decreasing due to the procedure and normal oxygen pressure in arterial blood, which after the procedure decreased on the average by 8 mmHg.

Observations describing the development of asthmatic attacks in the course of haemodialysis considered a possibility of reversible bronchial obturation in dialysed patients with uremia (2). Davenport et al. (6) found a significant decrease in peak expiratory flow (PEF) in most patients during haemodialysis, the decrease at being more marked when cuprophane membrane was used. Yet, excessive reactivity of the bronchi during haemodialysis was not confirmed in more recent studies in which only patients with chronic uremia clinically stable, without circulatory failure were observed (9,16).

Oedema of the bronchial wall in uremia may also lead to excessive bronchial reactivity. Ferrer et al. (9) examined 9 men and 3 women with renal insufficiency, with normal chest X-ray, without accompanying diseases. They performed plethysmographic measurements of lung function determining Raw, TGV, VC and carrying out provocation tests with the use of metacholine in inhalation. Results obtained by Ferrer et al. point to significant improvement in VC and flows in haemodialysis. These authors also found FEV_1 increase after haemodialysis which correlated with the decrease in body weight indicating that the cause of functional lung impairment in patients with chronic uremia is intraparenchymatous lung oedema. A slight, but statistically significant increase in TGV observed by the authors can also be interpreted as a reflection of decreased elastic leap of the lungs caused by diminished amount of extracellular water. Ferrer et al., however, did not find bronchial hyperactivity in patients with uremia.

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STRESZCZENIE

Uszkodzenie czynności płuc i regulacji oddychania należy do części następstw mocznicy. Przewodnienie, przewlekły śródmiąższowy obrzęk płuc występujący w mocznicy, zaburzenia czynności surfaktanta, uszkodzenie błony pęcherzykowo-włośniczkowej, osłabienie mięśni oddechowych, mocznicowe zapalenie opłucnej, infekcje, włóknienie lub zwapnienia w płucach, wewnątrznaczyniowa leukostaza, nadto procesy toczące się podprzeponowo (np. wodobrzusze) wpływają na zmiany czynności płuc. Najbardziej powszechnymi zmianami czynności płuc w mocznicy jest obniżenie pojemności dyfuzyjnej dla tlenku węgla, wzrost objętości zalegającej, torakalnej objętości gazu, zmniejszenie natężonej pojemności wydechowej pierwszosekundowej, pojemności życiowej, zazwyczaj niewielki wzrost oporu dróg oddechowych, upośledzenie przepływu powietrza w drogach oddechowych, szczególnie końcowowydechowego. Najczęściej spotykanym obrazem zmian czynnościowych płuc w mocznicy jest wzorzec restrykcyjny, szczególnie widoczny w przypadkach zmian opłucnowych oraz mocznicowego zapalenia osierdzia, a także współistnienie niewydolności krążenia. W przebiegu mocznicy nie obserwuje się natomiast nadmiernej reaktywności oskrzeli na nieswoiste bodźce prowokacyjne.