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CONTENS

СОДЕРЖАНИЕ

ХИРУРГИЯ

SURGERY

ХИРУРГИЯ

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Abzaliyev K.
https://orcid.org/0000-0003-2452-854X
Ghazwan Butrous
https://orcid.org/0000-0002-6640-6332
Abzaliyeva S.
https://orcid.org/0009-0004-9802-0129
Kurmanova A.
https://orcid.org/0000-0002-1859-3903
Bitemirova R.
https://orcid.org/0000-0002-5228-6018
Sundetova D.
https://orcid.org/0000-0003-2343-869X
Sagalbayeva U.
https://orcid.org/0000-0001-7903-9116
Bugibayeva A.
https://orcid.org/0000-0003-1417-2711
Baizhigitova N.
https://orcid.org/0000-0003-2452-854X
Kenzhebaeva A.
https://orcid.org/0009-0004-2678-1922
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MODERN BIOMARKERS - PREDICTORS OF EARLYCARDIOVASCULAR AGEING (LITERATURE REVIEW)

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Conflict of interest:
Authors declare that they have no conflicts of interest

Keywords:
biomarkers of ageing, predictors of cardiovascular ageing, theories of ageing, regulation of ageing, longevity

Annotation

An analysis of the current state of the problem of studying biomarkers of human cardiovascular ageing was carried out based on an analysis of international experience. Ageing is an inevitable, constantly progressive systemic process, which is a significant risk factor for the development of most common chronic human diseases, including cardiovascular diseases. Therefore, studying markers of early cardiovascular ageing is a logical goal for developing measures to prevent the development of cardiovascular disease and toimprove the quality of life and prolong active longevity. the intensive care unit. The application of a multidisciplinary approach to diagnose and treat a life-threatening complication as tracheal rupture in a short time allowed us to stabilize the patient's condition and avoid the development of further complications.

Жүрек-қантамырлардың ерте қартаюын болжаушы заманауи биомаркелер (әдебиет шолу)

Абдыкасымова М.[1], Абзалиев К.[1], Газван Бутрос[2], Абзалиева С.[3], Курманова А.[1], Битемирова Р.[1], Сундетова Д.[1], Сагалбаева У.[1], Бугибаева А.[1], Байжигитова Н.[4], Кенжебаева А.[1], Бауыржан М.[4]

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Түйінді сөздер:
қартаю биомаркерлері, жүрек-қантамырлары қартаюының болжаушылары, қартаю теориялары, қартаю дыреттеу, ұзақ өмір сүру.

Түіндеме

Халықаралық тәжірибеге сүйене отырып, адамның жүрек-қантамырлары қартаюының биомаркерлерін зерттеу дің қазіргі жағдайымен мәселелеріне талдау жасалды. Қартаю–бұладамның созылмалы ауруларының, соның ішінде жүрек-қантамырлары ауруларының дамуындамаңыздыққа уіпфактор болып табылатын, еріксіз, үнемі үдемелі жүретін жүйелі процесс. Жүрек-қантамырларының ерте қартаюының

маркерлерін зерттеу - жүрек-қантамырлары ауруларының дамуының алдыналу, өмір сүру сапасын жақсарту және белсенді ұзақ өмір сүруді ұзарту бойынша шараларды әзірлеу дің маңызды мақсаттарының бірі болыпта былады.

Современные биомаркеры – предикторы раннего сердечно-сосудистого старения (обзор литературы)

Абдыкасымова М.[1], Абзалиев К.[1], Газван Бутрос[2], Абзалиева С.[3], Курманова А.[1], Битемирова Р.[1], Сундетова Д.[1], Сагалбаева У.[1], Бугибаева А.[1], Байжигитова Н.[4], Кенжебаева А.[1], Бауржан М.[4]

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Аннотация

На основе международного опыта, был проведён анализ современного состояния и проблем изучения биомаркеров сердечно-сосудистого старения человека. Старение — неизбежный, постоянно прогрессирующий системный процесс, являющийся значимым фактором риска развития большинства распространённых хронических заболеваний человека, в том числе сердечно-сосудистых заболеваний. Изучение маркеров раннего сердечно-сосудистого старения является одним из значимых целей для разработки мер профилактики развития сердечно-сосудистых заболеваний, улучшения качества жизни и продления активного долголетия.

Ключевые слова:
биомаркеры старения, предикторы сердечно-сосудистого старения, теории старения, регуляция старения, долголетие

Introduction

According to World Health Organization (WHO) data from October 1, 2022, the number of people aged 60 years and older surpassed the number of children under 5 years of age in 2020. This trend highlights the urgent need to identify and determine the most significant biomarkers of ageing, which will hold immense value in assessing the health status of older and senescent individuals.Over the past few centuries, the global population has experienced a progressive shift towards ageing. In 2017, the number of individuals aged 60 years and older reached 962 million worldwide, more than doublingthe number from 1980. By 2050, the elderly population is projected to double again, reaching approximately 2 billion.[1]

Old age is recognized as the most significant risk factor for chronic age-related diseases. According to *Zhendong D. Zhang et al.*, over 90% of individuals over 65 years of age have at least one chronic disease, such as cardiovascular disease, cancer, dementia, diabetes, osteoarthritis, or osteoporosis, and more than 70% have at least two of these conditions. These data highlight the substantial socioeconomic burden that will be placed on healthcare systems. Therefore, studying the ageing process, maintaining health in older individuals, and developing methods for preventing and treating age-related diseases is crucial for extending the period of healthy ageing.[1]

Ageing is a systemic process that affects various levels of biological organization. It is characterized by gradually inhibiting fundamental bodily functions, including regenerative and reproductive capabilities, leading to decreased adaptability to environmental conditions.[2] This

decline in adaptability makes individuals less resilient to stress, diseases, and injuries, which ultimately makes death inevitable. Ageing is an inherently emerging, naturally developing, and destructive process that limits the body's adaptive capabilities, increases the likelihood of death, reduces life expectancy, and contributes to the development of age-related pathologies.

Currently, there are over 130 theories of ageing, among which the most studied are autointoxication, telomeric, free radical, genetic, and epigenetic theories.[3] Particular attention is focused on ageing and longevity's genetic and epigenetic mechanisms.[4]

In recent years, there has been a growing surge in scientific meetings, articles, and books dedicated to anti-ageing methods, reflecting the widespread interest in this topic among the general public. Consequently, the search for biomarkers of ageing continues unabated, as such biomarkers would offer several advantages:

1. Predicting Ageing Rate: Biomarkers would provide a precise indication of an individual's position within their lifespan, allowing for accurate predictions regarding their ageing trajectory.

2. Monitoring Ageing Processes: Biomarkers would enable monitoringof the underlying mechanisms driving the ageing process rather than simply assessing the effects of age-related diseases.

Ageing and risk of cardiovascular diseases

Ageing is a significant risk factor for most chronic diseases and functional impairments, and age-related diseases are the leading cause of death. Approximately 60% of all deaths are attributed to cardiovascular diseases, followed by oncological diseases, which account for 14% of all deaths.[2]

Over the last four decades, medicine has shifted from treating diseases as "patient care" to further identifying and preventing risk factors before they manifest as diseases, a concept referred to as "health care". For instance, high cholesterol and high blood pressure are not diseases themselves but increase the risk of heart attacks and strokes. Similarly, ageing is not a disease but a significant risk factor for various diseases, including heart attacks, strokes, certain cancers, macular degeneration, osteoarthritis, neurodegeneration, and many more. The risk of cardiovascular disease doubles every 10 years after age 40, even after adjusting for other risk factors - similar to adding a new significant risk factor (smoking, hypertension, etc.) every decade.[4] Decades of cardiovascular research have shown that treating risk factors, even in patients without symptoms, prevents harm. Identifying biomarkers of ageing and associated health consequences will allow early detection of individuals at high age-related risk throughout their lifespan and in different clinical settings.[5]

Even within the same age group, individuals exhibit varying disease risks and functional decline, highlighting the need for reliable biomarkers to track ageing processes and stages. The diversity of biological factors, lifestyles, and treatments further challenges biomarker identification. Therefore, no single biomarker can definitively assess healthy ageing.[6]

Cardiovascular diseases are the leading cause of death and disability worldwide (as per the WHO), including Kazakhstan. The ability to reach the current maximum lifespan (≥110 years) in low-mortality countries is attributed to protection from cardiovascular disease, as this system is particularly susceptible to oxidative stress and inflammation and plays a crucial role in maintaining oxygen and metabolite delivery to vital organs.[7] These findings emphasize the need for specific cardiac markers that predict premature ageing and prevent adverse outcomes during ageing.

Centenarians (≥90 years) extend the human lifespan by evading or surviving major illnesses. Identifying specific biomarkers associated with exceptional longevity may provide insights into combating ageing-related diseases.[8]

According study published in "Nature Communications" by Japanese researchers *Hirata A. et al., 2020,* examined the association of cardiovascular biomarkers and plasma albumin with exceptional survival to the highest ages.[7] They selected nine circulating biomarkers representing distinct cardioprotective and pathogenic pathways:

1. N-terminal pro-B-type natriuretic peptide (NT-proBNP)
2. Erythropoietin
3. Adiponectin
4. Extracellular superoxide dismutase (EC-SOD or SOD3)
5. Interleukin-6
6. Tumor necrosis factor-alpha (TNF-alpha)
7. Angiopoietin-like protein 2 (Angptl2)
8. Cystatin C
9. Cholinesterase

We comprehensively analyzed relevant scientific literature to understand better and assess healthy and pathological ageing indicators to identify risk markers for early involutional changes in the cardiovascular system and the development of age-associated cardiovascular diseases. We focused our literature search on peer-reviewed articles published in PubMed, Scopus, and Google Scholar, excluding non-peer-reviewed publications. We prioritized meta-analyses, systematic reviews, cohort studies, and cross-sectional studies, as these provide the most robust evidence. Our review summarizes current data on potential ageing biomarkers that are early predictors of cardiovascular ageing.[9,10] These include:

1. Biochemical markers: NT-proBNP
2. Oxidative stress
3. Cystatin C
4. Cholinesterase
5. Inflammatory and Immunological markers

B-type natriuretic peptide

A biologically active analogue of NT-proBNP, causes natriuresis and diuresis, dilation of arteries and antagonism of the renin-angiotensin-aldosterone system, thereby counteracting hemodynamic disturbances in heart failure. The underlying mechanisms responsible for the association between low circulating NT-proBNP levels and exceptional survival are currently unclear, but a potential explanation can be considered. In the present review, centenarians and (semi-)supercentenarians showed a low prevalence of clinical and subclinical cardiovascular disease detected by ECG and low cardiometabolic risk profiles, except for a relatively high prevalence of chronic kidney disease. However, median NT-proBNP levels increased consistently with age regardless of cardiovascular status, reaching 1530 pg/mL in individuals aged ≥110 years. In addition, 42.9% of centenarians had NT-proBNP levels ≥1800 pg/ml, which is the threshold value for diagnosing heart failure in people over 75 years of age.[11,12]

The study found that NT-proBNP, interleukin-6, cystatin C, and cholinesterase were significantly associated with increased survival to super centenary age, while adiponectin and erythropoietin were not significantly associated.[7,9,8,10]

Furthermore, combined data from three prospective cohort studies: the Tokyo Centenarian Study (TCS), the Japanese Semi-supercentenarian Study (JSS), and the Tokyo Oldest Study of General Health (TOOTH). Theanalytic cohort included a cohort of 1427 older adults of 36 centenarians (≥110 years), 572 semi-centenarians (105–109 years), 288 centenarians (100–104 years) and 531 very old people (85–99 years).[13] The concordance index (C-index) was calculated using Cox proportional hazards models to assess each biomarker's prognostic performance.

The finding suggested that adding each predictive biomarker (NT-proBNP, interleukin-6, cystatin C, and cholinesterase) to the baseline model significantly improved risk prediction with minimal optimism in the entire cohort. When stratified by age, the predictive power of the models decreased significantly, suggesting that age itself is the primary predictor.[11]

Thus, the base model weakly predicted mortality over age 105 (C-index 0.617 95% CI [0.577; 0.656], optimism-adjusted C-index = 0.588). However, NT-proBNP increase, and to a lesser extent, cholinesterase, significantly improved prognosis at older ages, NT-proBNP: C-index, 0.653 95% CI [0.615; 0.691], P = 0.001, C-index adjusted for optimism = 0.625; cholinesterase: C-index = 0.636 95% CI [0.596; 0.676], P = 0.019, Optimism-adjusted C-index = 0.609, respectively.[14]

Oxidative Stress

Oxidative stress is when the body produces excess free radicals, which can damage cells.[12] This process involves the pathogenesis of various diseases, including chronic heart failure (CHF).[15,16] Studies have shown that peo-

ple with CHF have lower levels of an enzyme that helps protect cells from free radicals.[17]

CHF is a significant health problem due to its high prevalence and mortality rates among working-age adults. Free radicals, produced in large quantities during oxidative stress in CHF patients, primarily damage the vascular endothelium and cardiomyocytes. They can also promote the activation of cytokines, which contributes to disease progression and often determines the prognosis in CHF patients.[15,16]

According study by Russian scientists *Polunina et al., 2018*, investigated 280 CHF patients and 60 healthy controls.[17] The patients were divided into groups depending on their left ventricular ejection fraction and the stage of their disease. The researchers found that the activity of superoxide dismutase (SOD), an antioxidant enzyme, was significantly lower in CHF patients compared to healthy individuals.[17] This suggests that oxidative stress plays a significant role in CHF pathogenesis.

Cystatin C

Accurate and early detection of nephropathy is crucial for timely intervention with nephroprotective and cardioprotective therapies, thereby reducing the risk of cardiovascular diseases and mortality.[6] Cystatin C, a novel biomarker, holds promise as a more sensitive indicator of reduced glomerular filtration rate (GFR) compared to traditional methods like serum creatinine.

Cholinesterase

As the prevalence of heart failure (HF) among older adults rises, it is increasingly important to consider not only the pathophysiology of HF but also the overall decline in health associated with ageing.[18,19] Nutritional status plays a crucial role in the prognosis of HF mortality, necessitating proper assessment and intervention.[8,10] In this regard, serum cholinesterase (ChE) levels have emerged as a potential new biomarker for nutritional status.ChE is a protein produced in the liver and is associated with prognosis in patients with HF.

Serum ChE levels as a potential biomarker for myocardial ischemia in stable coronary artery disease (CAD). A study involving 559 consecutive patients with suspected stable CAD and no prior cardiovascular history, investigated the relationship between myocardial ischemia and serum cholinesterase (ChE) levels.[20,21] The findings revealed that:

1. Myocardial ischemia incidence significantly increased as serum ChE levels increased ($p < 0.001$).

2. Higher ChE levels were associated with higher body mass index (BMI) ($p < 0.001$), dyslipidaemia ($p < 0.001$), including elevated low-density lipoprotein cholesterol (LDL-C) ($p <0.001$), triglycerides (TG) ($p < 0.001$), and serum albumin ($p < 0.001$), as well as younger age ($p < 0.001$).

3. At a ChE level of 286 IU/L, the specificity and sensitivity for myocardial ischemia were 0.599 and 0.658, respectively.

4. Elevated serum ChE levels (OR = 1.66, $p < 0.001$) were an independent risk factor for myocardial ischemia in patients with suspected stable CAD.

These findings suggest that serum ChE levels may be a valuable diagnostic biomarker for myocardial ischemia in patients with suspected stable CAD.[20,21]

Other Inflammatory and immunological biomarkers

In a prospective cohort study known as the Study of Ageing and Longevity in the Sirente Geographical Area, researchers investigated whether interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α) protein levels could predict all-cause mortality in older adults.[22] The study included 362 participants aged 80 years or older living in a mountain community in Italy. Participants were categorized based on the mean of three inflammatory markers: IL-6 (2.08 pg/mL), TNF-α (1.43 pg/mL), and CRP (3.08 mg/L). Additionally, a summary inflammation score was calculated. The primary outcome was the risk of death after four years of follow-up. During the four-year follow-up period, 150 deaths occurred.[23]

Unadjusted analyses revealed that elevated levels of each of the three markers were associated with increased mortality. After adjusting for potential risk factors, high levels of IL-6 hazard ratio (HR) = 2.18, 95% CI [1.29; 3.69] and CRP, HR = 2.58, 95% CI [1.52; 4.40] remained significantly associated with a higher risk of death. However, the association between TNF-α

protein levels and mortality was no longer significant, HR = 1.26, 95% CI [0.74; 2.15]. Thus, a composite summary score of inflammation demonstrated a strong association with mortality, with the highest risk estimated for those with all three inflammatory markers above the median. This study suggests that lower levels of inflammatory markers are linked to improved survival in older adults, independent of age and other clinical and functional variables.[22,23]

Older adults exhibit a higher level of lymphoproliferation, characterized by increased CD10+, CD25+ T-lymphocytes, and CD16+ natural killer (NK) cells compared to middle-aged individuals.[24] In the peripheral blood of elderly individuals, up to 95% of NK cells express high levels of CD16 but low levels of CD56. These NK cells exhibit high cytolytic activity but impaired secretion of TNF-α, IFN-γ, IL-5, IL-8, and colony-stimulating factors. Consequently, the reduced NK cell concentration in the peripheral blood of elderly individuals may diminish their ability to combat intracellular infections effectively.[25]

Recent studies have highlighted the role of immune inflammation in atherosclerosis development. Cytokines, critical mediators of immune inflammation, can be produced by altered endothelial cells and modulate vascular wall functions. TNF-α activates leukocytes involved in inflammatory reactions and induces the expression of adhesion molecules on endothelial cells, facilitating the adhesion of neutrophils, monocytes, and lymphocytes, leading to inflammatory infiltration of the vascular wall. IL-6, acting downstream of TNF-α, contributes to endothelial dysfunction and may trigger acute coronary events. Elevated IL-6 levels in arterial walls correlate with markers of endothelial dysfunction and signs of insulin resistance, which are associated with an increased risk of vascular damage and atherosclerosis progression.[26]

C-reactive protein (CRP) is another marker of cardiovascular risk. Inflammation, as reflected by increased CRP levels, contributes to the development of vascular atherosclerosis. Additionally, under experimental conditions, CRP has been shown to upregulate the expression of type II AG receptors on vascular smooth muscle cells.[7,16,20,24,25,] [8,17,22,25-27].

A study by *Niki Murtziet al.,* discovered that a genetic predisposition to downregulating IL-6 signaling, weighted by CRP levels, was associated with a lower risk of frailty.[27] IL-6, a pro-inflammatory cytokine implicated in various age-related ailments, including frailty, plays a significant role in this finding. Frailty is a syndrome characterized by physical weakness, fatigue, slowness, and unintentional weight loss, increasing the risk of hospitalization, institutionalization, and death. This finding supports a potential causal link between IL-6 signalingand frailty, suggesting that reducing IL-6 levels may lower frailty risk.[27]

Conclusion

A review of the available literature suggests that survival to the current highest age in low-mortality countries is supported by protection from cardiovascular disease, given the inherent susceptibility of this system to oxidative stress and inflammation and its central role in maintaining oxygen and metabolite delivery to major organ systems. These findings underscore the need to identify specific cardiac markers that can effectively predict premature ageing and prevent adverse outcomes during ageing.[27]

Median NT-proBNP levels increase consistently with age, regardless of cardiovascular status. Serum ChE levels may be a valuable diagnostic biomarker in patients with suspected stable CAD.

In the context of inflammatory markers, centenarians exhibited fewer signs of inflammation. Inflammatory peptides were either absent or present in lower abundance than in younger cohorts, while levels of anti-inflammatory cytokines such as IL-10 and transforming growth factor ß were elevated in centenarians.

Currently, the primary objectives in the review of ageing predictors are as follows:

1. To determine the characteristics of healthy and pathological (early) ageing, identifying risk factors (clinical, immunological, lifestyle-related, and functional state of the cardiovascular system, among others).

2. To assess the state of T-cell immunity in different types of ageing (healthy and previously pathological) and to investigate the population profile of lymphocytes, expression of activation markers, and functional state of immune cells (based on the expression of cytokines, primarily IL-6 and TNF, as the most significant markers of ageing) in different subtypes of ageing.

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THE STRATEGY OF MECHANICAL VENTILATION DURING CARDIOPULMONARY BYPASS AS A PREDICTIVE FACTOR FOR PULMONARY COMPLICATIONS IN THE INTENSIVE CARE UNIT

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The authors declare no conflict of interests

Key words:
Mechanical ventilation, Cardiopulmonary bypass, Atelectasis

Annotation

Background. Pulmonary complications are the second most common complication after cardiac surgery with cardiopulmonary bypass. Pulmonary atelectasis can occur from various intraoperative causes such as prolonged operation, time of anaesthesia more than 3-4 hours, use of a thoracic artery, use of cardiopulmonary bypass during surgery, lack of ventilation, haemotransfusion of 4 or more units of packed red blood cells in the perioperative period. Impact of mechanical venatilation during cardiopulmonary bypass still unknown.

Methods. Prospective, randomised study at one centre. Adult patients undergoing cardiac surgery with a pump by sternotomy for coronary artery disease were included.

Patients were randomised into two groups – one group receiving mechanical ventilation and one group receiving no ventilation during cardiopulmonary bypass. The main endpoint was PaO2/FiO2 as a marker for the quality of ventilation and perfusion measured. Secondary endpoints were postoperative pulmonary complications such as atelectasis and prolonged mechanical ventilation of more than 72 hours.

Results. 190 consecutive patients were included, 92 and 98 in each group. No significant difference was found in the PaO2/FiO2 ratio in the groups, p=0.591. A significant difference was found in the number of atelectasis during ultrasound investigation of the lungs in the non-ventilated group, p = 0.0001.

Conclusion. On-pump cardiac surgery without mechanical ventilation can lead to atelectasis of the lungs.

Қанның жасанды айналымы кезіндегі жүрек-өкпе ауа айналымының механикалық желдету жоспарының стратегиясы реанимация бөліміндегі өкпе асқынуларының болжамды факторы ретінде

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Түіндеме

Өзектідігі. Түйі нжасанды қан айналым кезіндегі қолданылатын кардиохирургиялық процедуралардан кейін өкпе асқынулары екінші орында тұр. Өкпе ателектазы операция себептерінен туындауы мүмкін, мысалы, ұзақ операция және анестезия

уақыты 3-4 сағаттан асатын жағдайда, кеуде артериясын қолдану, операция кезінде жасанды қан айналымын қолдану және механикалық желдетудің мүмкін еместігі, сондай-ақ периоперативті кезеңде 4 немесе одан да көп құты эритроциттерінен қан құюы. Жүрек-өкпе айналымы кезінде механикалық желдетудің әсері әлі белгісіз.

Әдістері. бір орталықта перспективалық рандомизацияланған сынақ. Зерттеуге жүректің ишемиялық ауруы үшін стернотомия арқылы сорғыны пайдаланып жүрекке операция жасаған ересек пациенттер енгізілді.

Пациенттер екі топқа бөлінді яғни рандомизацияланды бірінші топқа механикалық желдету қолданылды да, ал екінші топқа жасанды қан айналымы кезінде механикалық желдету берілмеді. Негізгі соңғы көрсеткіш желдету және перфузия сапасының көрсеткіші ретінде PaO2/FiO2 болды. Екінші соңғы көрсеткіште операциядан кейінгі өкпе асқынулары болды, мысалы, ателектаз және 72 сағаттан астам уақыт бойы механикалық желдету кезіндегі асқынулар.

Нәтижелері. қатарынан 190 пациентті, әр топта 92 және 98 науқас қатысты. Топтарда PaO2/FiO2 қатынасында айтарлықтай айырмашылық табылған жоқ p=0.591. Өкпенің ультрадыбыстық зерттеуінен кейін механикалық желдетусіз өткен топтағы p = 0.0001 көрсетіп ателектаздар саныайтарлықтай жоғары болды.

Қорытынды. жасанды қан айналым кезіндегі операция, өкпенің механикалық желдетуінсіз өткен жағдайда өкпе ателектазының жиілігі едәуір жоғары болады.

Түйінді сөздер:
механикалық желдету, жасанды қан айналымы, ателектаз

Стратегия механической вентиляции легких во время искусственного кровообращения как прогностический фактор легочных осложнений в отделении интенсивной терапии

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Аннотация

Введение. Легочные осложнения занимают второе место по распространенностипосле кардиохирургических операций с применением искусственного кровообращения. Ателектаз легочной ткани может возникнуть в результате различных причин, таких как длительная операция и анестезия, более 3-4 часов, выделение грудной артерии, искусственного кровообращенияи отсутствие искусственной вентиляции легких, а также массивные гемотрансфузии более 4 единиц эритроцитарной взвеси в периоперационном периоде. Влияние искусственной вентиляции легких во время искусственного кровообращения на осложнения послеоперационного периода до сих пор неясно.

Материалы и методы. Рандомизированное одноцентровое исследование. В исследование были включены взрослые пациенты, перенесшие открытую операцию на сердце с проведением искусственного кровообращения.

Пациенты были рандомизированы в две группы – одна группа с искусственной вентиляцией легких во время искусственного кровообращения, вторая без вентиляции во время искусственного кровообращения. Основной точкой измерения был индекс PaO2/FiO2 как показатель качества вентиляции и перфузии в легких. Вторичными показателями оценки были послеоперационные легочные осложнения, такие как ателектаз и длительная искусственная вентиляция легких более 72 часов.

Результаты. В исследование были включены 190 последовательных пациентов, 92 и 98 в каждой группе. Не было обнаружено существенной разницы в отношении PaO2/

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FiO2 индекса в группах, p=0.591. При ультразвуковом исследовании легких была выявлена достоверная разница в количестве ателектазов, большев группе без искусственной вентиляции легких, p = 0.0001.

Заключение. Операция на открытом сердце с применением искусственного кровообращения, без длительной вентиляции легких может привести к ателектазу легких.

Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) is highly associated with complications.[1] Acute lung injury is the second most common complication of CPB after the heart injury and ranges from mild pulmonary dysfunction to fatal acute lung injury.[2] Following cardiac surgery, more than 30% of patients are reported to have significant respiratory impairment for at least one week after surgery.[3]

CPB is a mandatory component of cardiac surgery and enables the maintenance of adequate body perfusion and oxygenation. Physiologically, the cardiopulmonary system should be partially bypassed during CPB and completely bypassed under aortic cross-clamping to create a bloodless and immobile surgical field.[4,5] On pump heart surgery, factors such as CPB, hypothermia, the surgical intervention, anaesthesia, medications, massive transfusions can cause diffuse lung injury.[6] During CPB, the lungs receive less blood from bronchial arterial flow, which leads to ischaemia.[7] The absence of pulsatile flow during CPB causes several changes in the lungs that lead to increased severity of inflammation.[8] There are several methods to prevent lung injury, improve gas exchange and reduce the increase in inflammatory responses during CPB, but the role of mechanical ventilation is still unclear.[9,10]

Atelectasis is a common pulmonary complication in patients undergoing cardiac surgery with cardiopulmonary bypass and an important cause of postoperative hypoxaemia.[11] Various reasons have been put forward to explain why patients undergoing on-pump cardiac surgery experience alveolar collapse. These include a relaxed diaphragm compressing the caudal parts of the lower lobes, surgical manipulations of pulmonary structures and depressurisation of the respiratory system during CPB to enable better visualisation of the surgical field. Although most of the mechanisms causing intraoperative lung collapse disappear when patients wake up and begin spontaneous breathing, postoperative atelectasis and hypoxemia may persist for several days.[6] Recent publications have shown that the best mechanical ventilation strategy during open-heart surgery with a pump is still unclear.[12] While some studies suggest a positive impact on oxygenation and systemic inflammatory response, the actual clinical effect of ventilation during cardiopulmonary bypass is controversial. Moreover, the results of these studies can't be consistently interpreted due to literature biases.[13]

Materials and methods

This is a prospective, randomised study conducted in patients undergoing elective on-pump CABG due to coronary arteries disease (CAD) from September till December 2023. Method of randomization:simple computer-generated random numbers (odd and even numbers).

Patients were recruited from a single regional healthcare centre in Kazakhstan. The study included all adult patients aged ⩾18 years that underwent cardiac surgery with CPB. Patients were randomised into two groups – one group receiving low tidal volume (LTV) mechanical ventilation and one group receiving no ventilation during CPB.

Mechanical ventilation strategy: Immediately after intubation, mechanical ventilation was started in volume-controlled ventilation mode with initial parameters VT 5-7 ml/kg, PEEP – 5-10 cmH2O. Immediately after initiation of CPB modes of mechanical ventilation in the LTV group – VT 3-5 ml/kg, PEEP – 5-8 mm H2O, frequency – 7-10 per minute. In the second Non-ventilated (NV) group, ventilation was stopped in standby mode. The original ventilation parameters were restored after weaning from CPB.

The main endpoint was PaO2/FiO2 as a marker for the quality of ventilation and perfusion measured in the ICU in the immediate postoperative period. Secondary endpoints were postoperative pulmonary complications such as pulmonaryatel-

ectasis and prolonged mechanical ventilation of more than 72 hours. Atelectasis was diagnosed using the US method (more than 3 B-lines in the lateral projection), and the shunt was measured in the arterial blood gases (ABG). Patients in both groups were comparable in terms of primary parameters.

ABG were measured several times just before intubation on spontaneous breathing with atmospheric O2, during CPB (they were not included because of extracorporeal oxygenation), immediately after admission to the ICU after surgery and 24, 48, 72 hours after surgery in the ICU.

Chest X - ray were conducted routinely (not more than 10 days before surgery). COPD, emphysema, fibrosis was combined in the meaning – pulmonary pathology.

Ethicalapproval.

This study was conducted in strict accordance with the principles outlined in the Helsinki Declaration. Before commencing the research, approval was obtained from the Local Bioethics Committee of the Corporate Fund "University Medical Center."

Statistical analysis

For continuous variables, the arithmetic mean, standard deviation (SD), median and range were calculated. For binary or categorical variables, absolute and relative frequencies (n, %) were calculated. To assess the differences between the groups, standard independent-samples t-tests were performed using pooled analyses for equal variances and Satterthwaite analyses for unequal variances. P values of <0.05 were taken to indicate significance. To determine whether the means of two datasets are different from each other the Z test was used. The Z score is used to assess the significance of an individual data point within a distribution, while the Odds Ratio and the Chi-Square test are used to analyse the association between variables in different contexts.

Results

A total of 190 patients were enrolled to the study, 92 of them were included in the LTV group and 98 patients in the NV group.

Table 1. Demographics and initial laboratory characteristics

	NV group, N=98	LTV group, N=92	Chi-squared	z-statistic	P value
Age, (years)	59±11.40	62±9.63	-	1.953	0.052*
Gender, n (%)					
Female	44 (44.9%)	52 (56.5%)	1.270	-	0.260
Male	54 (55.10%)	40 (43.48%)	1.228	-	0.268
BMI, m^2	27.4±3.56	29.7± 4.12	-	4.125	0.0001*
Comorbidity, n (%)					
Stroke	27 (27.55%)	22 (23.91%)	0.082	-	0.775
MI history	42 (42.86%)	34 (36.96%)	0.268	-	0.604
Diabetes	31 (31.63%)	32 (34.78%)	0.069	-	0.792
Surgery timings, median (range), minutes					
CBP time	88.5±38.2	92.0±27.56	-	0.38	0.56
Aortic cross clamp time	59.5±25.92	61.0±27.44	-	0.50	0.54
Baseline levels, median (range)					
PaO2/FiO2	422.6 ±164.6	409.53±170.12	-	0.538	0.591
F shunt	0.15±0.05	0.12 ±0.03	-	4.975	0.0001*
Haemoglobin	139.0±11.6	132.0±8.54	-	0.632	0.09
Haematocrit	42.0±6.71	39.0±5.12	-	0.174	0.32
Chest X Ray pathology	17 (17.36%)	14 (15.21%)	0.025	-	0.874

* z test statistical significance P≤0.05. LTV – Low tidal volume, NV – non ventilated, MBI – body mass index, CBP – cardiopulmonary bypass, MI history - myocardial infarction history

The demographic data is shown in Table 1. The characteristics were generally similar in both groups.

Before surgery, PaO2/FiO2 and F-shunt parameters were numerically in the normal range. Chest X-ray before surgery had revealed pulmonary pathologies due to chronic lung disease in 14 (15.21%) of patients. More than 1/3 of the patients had a history of comorbidity conditions such as type 2 diabetes, ischemic stroke and acute myocardial infarction.The postoperative ICU data with primary and secondary outcomes are shown in Table 2.

Table 2. Primary and secondary outcomes in the intensive care unit

	NV group (n= 98)	LTV group (n=92)	OR	z-statistic	P value
PEEP intraop. period (cmH2O)	0	7.38 ±2.12	-	-	-
PaO2/FiO2	312±155.4	328.64±170.6	-	0.704	0.482
PCO2	45.8±19.2	39.5±12.54	-	2.659	0.008*
F shunt	0.45±0.1	0.19±0.06	-	21.558	0.0001*
Pulmonary complications (%)					
Atelectasis signs (US)	30 (32.61%)	6 (6.52%)	6.32[a]	3.877	0.0001*
Recruitment manoeuvre	35 (38.04%)	11 (11.96%)	4.09[a]	3.667	0.0002*
Mechanical ventilation more than 72 hours	15 (15.3%)	12 (13.04%)	1.20	0.446	0.655

* z test statistical significance P⩽0.05
[a] OR - Odds ratio; OR>1 means that the event is directly related and has a chance of occurring in the first group
PEEP intraoperative period - Positive end-expiratory pressure intraoperative period, LTV – low tidal volume, NV – non-ventilated, US – ultrasound.

No significant difference was found between the groups for the primary endpoint PaO2/FiO2 ratio (p=0.482).

A significant difference was found for the F-shunt indicator 0.19±0.06 vs 0.45±0.1 with a p-value < 0.0001.

Mean paCO2 level in the immediate postoperative period was higher in the NV group although without significant statistical difference. In the non-ventilated group, there were more detected signs of pulmonary atelectasis during US30 (32.61%) vs.6 (6.52%), OR=6.32, 95%CI [2.49;16.07], z-statistic 3.877, P value <0.0001. The recruitment manoeuvre shortly after ICU admission was performed in 11 (11.96%) of patients in the LTV group and in35 (38.04%) of patients in the NV group, which was a significant difference between the groups, OR=4.09, 95%CI [1.92;8.68], z-statistic 3.667, P value 0.0002. In addition, the importance of the F-shunt was significantly higher in the NV group 0.45±0.1 vs 0.19±0.06 (p value <0.0001), substantiating the presence of venous blood shunt in the lung due to pulmonary atelectasis.

The need for prolonged mechanical ventilation for various reasons was approximately the same in both groups at 12 (13.04%) and 15 (15.3%) and was not significant, P value 0.655.

Discussion

The issue of mechanical ventilation has been a subject of debate for over three decades. The MECANO study by *Nguyen, Lee S., et al*, a single-center randomised clinical trial conducted on patients undergoing cardiac surgery, found no significant difference in the primary endpoint, which was a composite measure of postoperative mortality and pulmonary complications. In our study, the PaO2/FiO2 index also did not differ between groups.[14]

The same opinion was in the study conducted by *Zhang et al.*, 413 adult patients undergoing elective cardiac surgery with CPB were observed. The study examined non- ventilation or low tidal volume (VT) ventilation at 30% or 80% FiO2. The study concluded that the continuation of low VT ventilation did not offer any significant advantage over no ventilation during CPB, in relation to the incidence of PPCs during hospital stay after the surgery. However, due to the

limitations in the study's design, the authors were unable to draw a strong conclusion on the effects of the application of low VT ventilation at 30% on the severity of pulmonary complications.[15]

However, according to the recently conducted systematic review and meta-analysis, *Chi et al.*, 2017, continued ventilation during CPB showed a prominent increase of PaO2/FiO2 index in patients receiving ventilation support versus the patients whose ventilation support was turned off. This discrepancy could be explained from the standpoint of a reduced number of patients participating in the current research. Moreover there was some data in favour of mechanical ventilation during CPB.[16]

There is evidence from studies that the use of continuous mechanical ventilation during CPB can have significant clinical benefits. These benefits include improved oxygenation and reduced inflammation, which ultimately leads to less lung injury. A recent meta-analysis of 16 clinical trials also showed that mechanical ventilation during surgery resulted in a reduced shunt fraction and an increase in oxygenation immediately after weaning from CBP. The analysis also concluded that maintaining MV throughout the entire duration of extracorporeal circulation could reduce the CPB-related inflammatory response and tissue damage.[12]

In our study we have obtained data that the strategy of low tidal volume ventilation with a PEEP of more than 5 cm H20 during CPB may be beneficial to avoid the formation of atelectasis in the lung tissue. In addition, we were forced to apply strict ventilation parameters with high inspiratory pressure in the ICU due to pulmonary atelectasis in the postoperative period. In this study, we observed a correlation between preserved mechanical ventilation with PEEP and atelectasis formation in the postoperative period.

Limitations.

There are some limitations to this study. Small number of patients, a single-centre study, all of the perioperative management were carried out according to our hospital's clinical practice.

Conclusion

Maintaining a low tidal volume and PEEP during CPB may be beneficial for patients undergoing CABG cardiac surgery. In our opinion, it is a mandatory measure to maintain a PEEP of 5 to 10 during CPB in patients with excessive body weight.

What is already known on this topic: After cardiopulmonary bypass, patients are at risk of developing pulmonary complications such as pulmonary atelectasis and edema. Atelectasis, the collapse of alveoli, can occur due to the reabsorption of air from the alveoli during periods of reduced lung volume. Pulmonary edema may develop as a result of increased capillary permeability and fluid retention.

What this study adds: Determination of the effect of mechanical ventilation with positive PEEP to pulmonary atelectasisformation in the postoperative period still unknown and the benefit for cardiac surgery patients is to preserve mechanical ventilation during cardiopulmonary bypass.

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NONINVASIVE DIAGNOSIS OF HEART REJECTION AS A PREDICTOR OF LONG-TERM TRANSPLANT SURVIVAL

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Key words:
Chronic heart failure, Heart Transplantation, Endomyocardial Biopsy, donor-derived cell-free DNA.

Abstract

Background. Currently, in Kazakhstan, the issue of chronic heart failure is becoming increasingly relevant, with high mortality from the terminal stage of chronic heart failure, especially in patients with III-IV functional class. Heart transplantation represents the "gold" standard of surgical treatment for terminal chronic heart failure, but endomyocardial biopsy, used for monitoring the transplanted heart, is an invasive and inconvenient procedure.

Aim of this study is to generate data which can aid in more precise antibody-mediated rejection diagnosis, assisting in distinguishing between antibody-mediated rejectionand acute cellular rejection and helping us determine the appropriate treatment strategy

Materials and Methods. This article explores the potential of safe and accurate monitoring of acute transplant rejection using circulating donor-derived cell-free DNA(dd-cfDNA). The study included 40 patients who underwent heart transplantation.

Results. It was found that 60% of them had a repeat operation, while 40% had a primary one. Various cardiomyopathies, predominantly dilated and ischemic, were the cause of terminal chronic heart failure. The donor-derived cell-free DNA method demonstrates potential in differentiating T-cell-mediated and antibody-mediated rejection, with different patterns donor-derived cell-free DNA elevation. These differences have high clinical significance for diagnosis and treatment tactics.

Conclusion. Despite the prospects of using donor-derived cell-free DNA, further research is needed to establish threshold values and confirm its effectiveness in clinical practice.

Трансплантаттың ұзақ мерзімді өмір сүруінің предикторы ретінде жүректен бас тартудың инвазивті емес диагностикасы

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Мүдделер қақтығысы:
авторлар мүдделер қақтығысының жоқтығын мәдімдейді

Түіндеме

Өзектідігі: Бүгінгі таңда Қазақстанда созылмалы жүрек жеткіліксіздігі мәселесі барған сайын өзекті болып отыр. Созылмалы жүрек жеткіліксіздігі терминалдық сатысынан, әсіресе III-IV функционалдық класс пациенттерінде өлім-жітім жоғары.

Түйінді сөздер:
Созылмалы жүрек жеткіліксіздігі, Жүрек трансплантациясы, Эндомиокардиалдбиопсия, айналымдағы бос донорлық ДНК.

Жүрек трансплантациясы терминалды созылмалы жүрек жеткіліксіздігі үшін хирургиялық емдеудің «алтын» стандартын білдіреді, бірақ трансплантацияланған жүректі бақылау үшін қолданылатын эндомиокард биопсиясы инвазивті және ыңғайсыз процедура болып табылады.

Бұл зерттеудің мақсаты антидене арқылы қабылданбау диагностикасын дәлірек анықтауға көмектесетін, антиденелер арқылы қабылданбауды және жедел жасушалық қабылдамауды ажыратуға көмектесетін және тиісті емдеу стратегиясын анықтауға көмектесетін деректерді жасау болып табылады.

Материалдар мен әдістер: Бұл мақалада айналымдағы бос донорлық ДНҚ (dd-cfDNA) көмегімен жедел трансплантациядан бас тартуды қауіпсіз және дәл бақылау мүмкіндігі қарастырылады. Зерттеу нысандары жүрек трансплантациясынан өткен 40 пациент болды.

Нәтижелер. Олардың 60% - қайталама операция болғанын, ал 40% - бастапқы операция болғанын көрсетті. Созылмалы жүрек жеткіліксіздігі себебі әртүрлі, негізінен кеңею және ишемиялық кардиомиопатиялар болды. Айналымдағы бос донорлық DNA әдісі айналымдағы бос донорлық DNA жоғарылауының әртүрлі үлгілерімен Т-жасушалық және антидене арқылы бас тартуды саралау әлеуетін көрсетеді. Бұл айырмашылықтар диагностика мен емдеу тактикасында жоғары клиникалық маңыздылыққа ие.

Қорытынды. Дегенмен, айналымдағы бос донорлық DNA қолдану мүмкіндіктеріне қарамастан, шекті мәндерді белгілеу және оның клиникалық тәжірибеде тиімділігін растау үшін қосымша зерттеулер қажет.

Неинвазивная диагностика отторжения сердца, как предиктор долгосрочной выживаемости трансплантата

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Ключевые слова:
Хроническая сердечная недостаточность, Трансплантация сердца, Эндомиокардиальная биопсия,циркулирующие свободные ДНК донора.

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Аннотация

Фон. На сегодняшний день в Казахстане проблема хронической сердечной недостаточности становится все более актуальной, с высокой смертностью от терминальной стадии хронической сердечной недостаточности, особенно у пациентов III-IV функциональных классов. Трансплантация сердца представляет собой "золотой" стандарт хирургического лечения терминальной хронической сердечной недостаточности, но эндомиокардиальная биопсия, используемая для мониторинга трансплантированного сердца, является инвазивной и неудобной процедурой.

Целью этого исследования является получение данных, которые могут помочь в более точной диагностике антитело-опосредованного отторжения, помогая различать антитело-опосредованное отторжение и острое клеточное отторжение, а также помогая нам определить соответствующую стратегию лечения.

Материалы и методы. В данной статье исследуется потенциал безопасного и точного мониторинга острого отторжения трансплантата с использованием циркулирующей свободной ДНК донора (dd-cfDNA). Объектами исследования были 40 пациентов, перенесших трансплантацию сердца.

Результаты. Выявили, что у 60% из них операция была повторной, а у 40% - первичной. Причиной терминальной стадии хронической сердечной недостаточно-

сти были различные кардиомиопатии, преимущественно дилатационная и ишемическая. Метод определения циркулирующей свободной ДНК донора демонстрирует потенциал в дифференциации Т-клеточно-опосредованного и антитело-опосредованного отторжения, с различными паттернами повышения циркулирующихсвободных ДНК донора. Эти различия имеют высокую клиническую значимость для диагностики и тактики лечения.

Заключение. Несмотря на перспективы использования циркулирующих свободных ДНК донора, требуются дополнительные исследования для установления пороговых значений и подтверждения его эффективности в клинической практике.

Introduction

As of today, the problem of chronic heart failure is highly relevant in Kazakhstan, with annual mortality from the terminal stage of chronic heart failure significantly higher than in the general population, reaching 12% among patients with heart failure in functional classes III-IV, even under treatment in a specialized hospital. The primary method of treating the terminal stage of heart failure, when optimal medical therapy is ineffective, is surgical treatment - heart transplantation.[1,2]

According to the Republican Center for Coordination of Transplantation and High-Tech Medical Services of the Ministry of Health of Kazakhstan, more than 3 thousand Kazakhstanis are in need of organ transplantation, and 10 patients per 1 million population require heart transplantation. In recent years, not only has the number of transplantations worldwide increased significantly, but also the indicators of quality and duration of life for heart transplant recipients have improved.[1,3]

Heart transplantation is considered the "gold" standard for the surgical treatment of terminal heart failure. According to the International Society for Heart and Lung Transplantation (ISHLT) data from 2019, the overall median survival is 12.5 years, and the conditional survival is 14.8 years for those who survive the first year. Successful heart transplantation improves the quality of life and increases the survival of patients.[4,5]

One of the most serious complications, both in the early and late periods after transplantation, remains acute cellular and humoral antibody-mediated rejection (AMR). The probability of developing rejection of the heart transplant and coronary artery disease persists in patients after heart transplantation throughout their lives, necessitating continuous monitoring and correction of immunosuppressive therapy and early detection of signs of rejection.

Aim of this study is to generate data which can aid in more precise AMR diagnosis, assisting in distinguishing between AMR and acute cellular rejection (ACR) and helping us determine the appropriate treatment strategy.

Material and methods

This is a cross-sectional analysis of a single-center, retrospectiveand prospective, observational clinical study-from 2023 to 2025. The study included 40 patients who had previously undergone orthotopic heart transplantation at the National Scientific Cardiac Surgery Center in the conditions of the Republic of Kazakhstan. The sample size was calculated from the 58 surviving patients after the orthotopic heart transplantation. Accordingly, a sample size of 40 adult patients (confidence level: 95%, margin of error: 5%) was determined. Clinical material samples (venous blood) were collected from participants aged 18 and older who had undergone heart transplantation. Patients who refused to undergo diagnostic procedures specified in the study protocol were excluded from the research. Participants provided questionnaire data, and informed consents for study participation were obtained. Inclusion criteria for study participants were adults after heart or kidney transplantation:

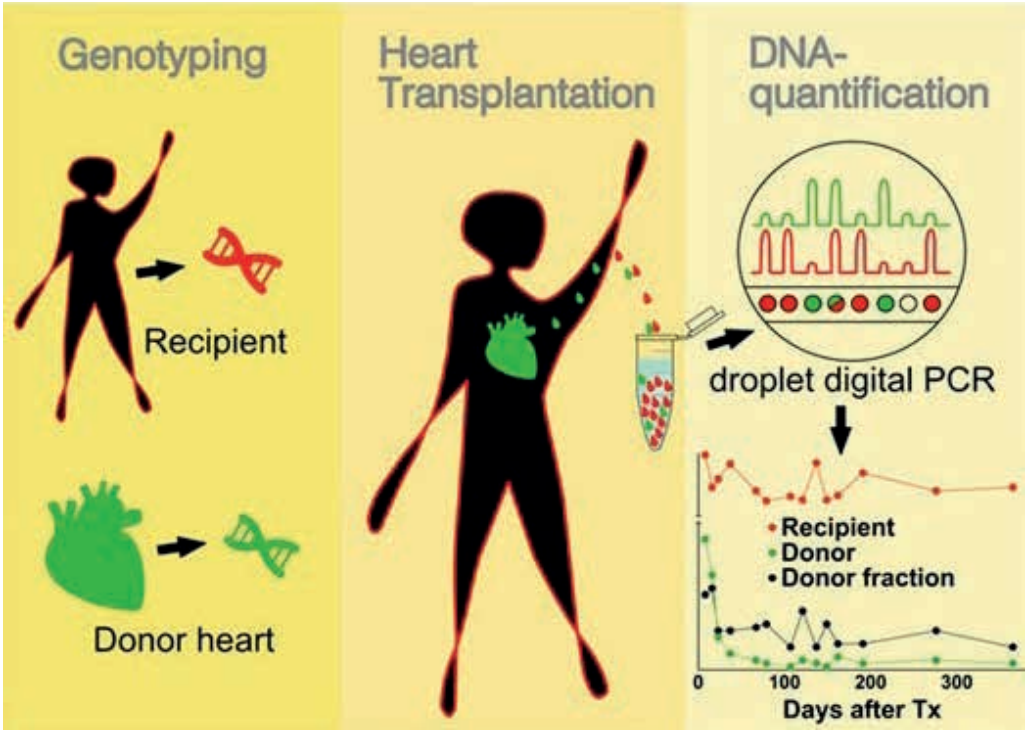
- Age over 18 years
- Both male and female gender
- Presence of transplanted heart, kidney, or liver
- Patients who signed informed consent to participate in the study.
- Exclusion criteria for study participants were:

- Refusal to undergo diagnostic procedures as specified in the study protocol
- Participation inanother study

Presence of anatomical or concomitant diseases, or other medical, social, or psychological conditions that, in the researcher's opinion, could limit the subject's ability to participate in the clinical study or meet the requirements of subsequent observation or affect the scientific validity of the results of the clinical study.

The assessment of the donor's donor-derived cell-free DNA (ddcfDNA) fraction relative to the total cell-free DNA in the recipients' blood is a non-invasive diagnostic method for acute rejection in patients after heart transplantation. Below are the interim results of the study, and all calculations were performed using Excel, presenting average statistical values.

Figure 1.
The principle of the diagnostic method.[6]



All patients are examined according to the schedule Table 1

Table 1.
Schedule of diagnostic procedures and studies

Criteria	0 day	6 month	12 month	24 month	30 month
Signing of informed consent	+				
Blood for sensitization	+			+	
CBC with differential	+	+	+		
Glycated hemoglobin, glucose	+	+	+		
AST, ALT	+	+	+		
Urea, Creatinine, Total Bilirubin, Direct Bilirubin, Total Protein, High-Sensitivity C-Reactive Protein (hs-CRP), Ferritin, Uric Acid, Total Cholesterol.	+	+	+		
Fibrinogen, D-dimer	+	+	+		
Expanded lipid profile (TC, LDL-C, HDL-C, TG, apoB)	+	+	+		
ApoA, Lipoprotein(a)	+				

Markers for hepatitis	+				
NTproBNP	+	+	+		
coronary angiography	+				
echocardiogram with myocardial deformation assessment	+	+	+		
24-hour Holter monitoring of ECG, blood pressure	+	+	+		
Duplex ultrasound of brachiocephalic vessels.	+	+	+		
12-lead electrocardiogram (ECG)	+	+	+		
ultrasound of the liver	+		+		
EMG	+		+		
bioinformatic analysis				+	+

Ethical approval

This study was conducted in strict accordance with the principles outlined in the Helsinki Declaration. Before commencing the research, approval was obtained from the Local Bioethics Committee of the Corporate Fund "University Medical Center."

Statistical analysis

Data were analyzed using IBM SPSS Statistics software (IBM SPSS Inc.). Numerical variables were expressed as mean ± SD and categorical variables as numbers and percentages. Nonparametric statistics were performed for dataset analysis. Between-group comparisons were assessed for numerical variables, and the Chi-square test was used for categorical variables. P value ⩽0.05 was considered statistically significant.

Results

A representative sample was collected based on the National Scientific Cardiac Surgery Center in Astana. The sample included 40 patients who had previously undergone orthotopic heart transplantation. The total sample size was 40 patients, of themsignificant more males 32 (80%) than 8 (20%) females, Chi-squared 10.32, 95%CI [21.6:78.2], p= 0.0013. The age range was 17 to 59 years. Of the patients, 24 (60%) had undergone previous surgeries, and 16 (40%) had heart transplantation as their primary surgical intervention, p= 0.221.

The terminal stage of heart failure was primarily caused by dilated cardiomyopathy in 19 cases (47.5%), ischemic cardiomyopathy in 7 cases (17.5%), hypertrophic cardiomyopathy in 4 cases (10%), non-compaction myocardium in 2 cases (5%), familial forms of cardiomyopathies in 4 cases (10%), and valvular cardiomyopathy in 4 cases (10%).

The echocardiography data were characterized by a pronounced decrease in left ventricular myocardial contractility - left ventricular ejection fraction (hereinafter - LVEF) of 17.6 ± 4.9% (8–27%), cardiomegaly (left ventricular end-systolic dimension 71.3 ± 9.8 mm (35–95 mm), left ventricular end-diastolic volume 273.25 ± 84.2 ml (52–524 ml), high pulmonary hypertension (mean pulmonary artery pressure 55.6 ± 13.27 mmHg (range 25–82 mmHg), laboratory data CRP 1.05 ± 0.95 mg/dl (normal 0.5 mg/dl), NT-ProBNP (B-type natriuretic peptide) 6000.8 ± 1699.2 pg/dl (normal range 125-700 pg/dl depending on age).

In the interim result of this clinical study, a positive cross-match reaction between the donor and the recipient was recorded in 5%. In 40 patients, the post-heart transplant survival duration at the time of the study ranged from 6 months to 11 years (average 6.9±4.07 years). All patients reported an improvement in their quality of life. Echocardiographic data showed a left ventricular ejection fraction (LVEF) of 56.6 ± 6.2% (range 49–61%), left ventricular end-systolic volume of 39.6 ± 17.9 ml (23–58.8 mm), left ventricular end-diastolic volume of 92 ± 53.3 ml (60–129 ml), and laboratory data CRP 0.63 ± 0.56 mg/dl (normal 0.5 mg/dl), NT-ProBNP (B-type natriuretic peptide) 1001.8 ± 866.25 pg/dl (normal range 125-700 pg/dl depending on

age).The average age of patients was 38.85±13.23 years, and dilated cardiomyopathy (47.5%) was the predominant cause of the terminal stage of heart failure in most cases.

Discussion

Endomyocardial biopsy (EMB) is the standard for monitoring and assessing a transplanted heart. Despite its increasing prevalence and widespread recognition, EMB is an invasive procedure prone to errors and may be associated with both procedural complications and long-term consequences.[7,8]

Furthermore, EMB, routinely used for monitoring during the first year after heart transplantation, is a costly medical procedure that is inconvenient for patients. Additionally, about 25% of biopsy samples are deemed unsuitable for use. In light of these limitations, extensive efforts have been made to develop non-invasive monitoring methods that could reduce the need for subsequent EMB. This emphasis is on monitoring the recipient's immune response to detect the onset of rejection. Currently, there is ongoing development of an analysis that directly assesses the health of the transplanted heart.[9,10]

Considerable efforts have been made to develop non-invasive diagnostic biomarkers that could replace or reduce the need for endomyocardial biopsy.

Episodes of acute rejection are most common in the first weeks after transplantation and can be categorized into T-cell-mediated and AMR. During acute cellular rejection, lymphocytes infiltrate and proliferate in the interstitial space. The adaptive immune system plays a central role in ACR. Direct allorecognition involves the interaction between the T-cell receptor (TCR) on recipient T cells and mismatched human leukocyte antigens (HLA) on donor antigen-presenting cells.[7,8,9,10] Indirect allorecognition also plays a role. The interaction of HLA/peptide-TCR and co-stimulatory signals promotes the proliferation and differentiation of T cells. CD8+ T cells release perforin and granzyme B, inducing apoptosis of target cells. Monocytes and myeloid dendritic cells (DCs) also infiltrate the graft and contribute to acute rejection.[8]

AMR can occur within the first year after transplantation. AMR is mediated by donor-specific antibodies targeting HLA or non-HLA antigens on the donor's endothelium. The antigen-antibody interaction leads to antibody-dependent cellular cytotoxicity and complement activation, causing lysis of target cells. Damage to endothelial cells results in platelet aggregation and recruitment of leukocytes through cytokines, chemokines, and chemo attractants, ultimately leading to acute rejection.[4]

Biomarkers are categorized into two groups: those reflecting allograft injury and those reflecting inflammatory and alloimmune processes underlying allograft rejection. Given the potential consequences of not diagnosing and treating acute rejection of a cardiac allograft, these biomarkers must be highly sensitive to rejection, even at the expense of low specificity.[3,11]

Non-invasive methods include AlloMap, detection of dd-cfDNA, microRNAs, extracellular vesicles, and donor-specific antibodies. Despite dozens of promising studies and potential biomarkers, only two have been approved by the Food and Drug Administration (FDA) and are used in everyday clinical practice: AlloMap and dd-cfDNA.[6,7,12,13]

Cell-free DNA of donor origin (dd-cf DNA) is present ubiquitously in biological fluids and various environments, including soil and water biotopes. Recently, studies have shown that certain types of extracellular DNA can play a significant role in living organisms and indicate pathological conditions. Cell-free DNA refers to all non-encapsulated DNA in the bloodstream and was first detected in the blood plasma of healthy individuals in 1948. Cell-free DNA consists of approximately 150 base pairs of double-stranded DNA released from nucleosomes during apoptosis and necrosis. cf-DNA molecules exist as monomers, dimers, and trimers. Most cf-DNA circulates as nucleosomes or chromatosomes, as free DNA is vulnerable to rapid degradation by nucleases. An important characteristic of cf-DNA is its half-life in the bloodstream (30 minutes to 2 hours), indicating continuous release from apoptotic or necrotic cells.[14,15,11]

There are various types of cf-DNA, with the most important being cell-free mitochondrial DNA, tumor DNA, and fe-

tal DNA, all possessing similar properties. Concentrations of cfDNA vary under both normal physiological conditions (7-18 ng/ml in healthy individuals) and diagnosed diseases (800 ng/ml in patients with esophageal cancer). The initial discovery of cell-free DNA in 1948 *by Mandel P. and Metais P.* led to numerous studies assessing the role of cfDNA in various diseases. Initially used to study oncological markers in cancer patients, the most successful application of cf-DNA as a clinical biomarker is non-invasive prenatal testing (NIPT) for detecting fetal pathologies, showing higher accuracy compared to biochemical screening. Recently, interest in cell-free DNA has increased in the field of transplantation. Determining the quantity of donor-derived cell-free DNA in a patient's blood plasma can aid in early detection of organ rejection after transplantation.[6,7,12,13]

Non-cellular DNA serves as a marker for transplant viability. During graft rejection, caused by the breakdown of its cells, dd-cfDNA is released into the bloodstream, leading to increased levels in the recipient's body. Early elevation of dd-cfDNA levels is observed in patients during acute graft dysfunction, suggesting potential use of quantitative dd-cf DNA levels as an alternative rejection marker. Some studies report temporary elevation of dd-cfDNA levels in the early post-transplant period; however, in stable patients receiving immunosuppressive therapy, this indicator decreases to baseline levels around 7-10 days post-transplantation. Overall, research indicates that donor non-cellular DNA levels demonstrate high accuracy and can predict acute rejection of the transplanted organ, with consistent predictive ability across all organ types. Highest cf-DNA levels are observed during acute antibody-mediated graft rejection. Several studies have compared dd-cf DNA with other markers of graft injury.[10,14] Methods for quantifying recipient dd-cfDNA in plasma include real-time PCR, droplet digital PCR (ddPCR), and massively parallel sequencing, also known as next-generation sequencing (NGS). ddPCR and NGS require donor genotyping, evaluating the presence of a single nucleotide polymorphism where the recipient is homozygous for a specific allele and the donor is not.[11]

As a non-invasive quantitative marker of allograft injury, dd-cfDNA promises to become a safe, accurate, and feasible method for monitoring acute rejection in heart transplant recipients. Although further research is necessary to confirm specific threshold values for routine clinical use, dd-cfDNA currently demonstrates the greatest potential as a monitoring tool, screening patients who would benefit most from preemptive biopsy. Advancements in rejection monitoring using dd-cfDNA further our efforts towards developing precise medicine methods for heart recipients. Patterns of dd-cfDNA elevation also vary between AMR and ACR, which can facilitate diagnosis and have different fragment lengths of cfDNA with shorter fragments. These unique data can aid in more precise AMR diagnosis, assisting in distinguishing between AMR and ACR and helping us determine the appropriate treatment strategy.[10,11]

The diagnosis of acute and chronic rejection of cardiac allograft remains a complex task, as rejection often occurs asymptomatically, impacting short-term and long-term transplant outcomes. Significant progress has been made in molecular diagnostics for non-invasive monitoring of acute rejection after heart transplantation over the last decade. Alternative non-invasive biomarkers may replace or reduce the need for endomyocardial biopsy. The effectiveness of this rejection diagnosis method has been actively studied over the last 10 years.

Cell-free DNA is widely used as a prognostic and predictive biomarker, entering the bloodstream due to cell death and being present in much higher concentrations in diseased individuals compared to healthy ones. Each fragment of cfDNA carries molecular characteristics of the cell it originated from, such as DNA methylation status.[16] Donor-derived cfDNA detected in transplant recipients' blood has been proposed as a potential biomarker for organ rejection or cell transplant damage.[17]

The first method of detecting cfDNA involved genetic differences, such as donor-recipient sex mismatch, where the Y-chromosome was detected in a female recipient.[18] cfDNA data were evaluated

based on HLA donor-recipient mismatch in the HLA-DRB1 locus using optimized droplet digital PCR. Another method of cfDNA detection involves a quantitative approach using PCR and genomic sequencing.[19,20]

According to *De Vlaminck et al.,* by comparing endomyocardial biopsy results and cfDNA fraction, the latter was significantly elevated by 5 months post-transplantation, whereas biopsy results were negative. Their results indicate that determining the amount of cfDNA may replace endomyocardial biopsy and that these measurements can be used for other aspects of patient management, such as rejection event prediction and immunosuppressant dosage management. As explained by Zangwill, a higher overall level of cfDNA in the early stages post-transplant predicted death.[21]

This method will allow differentiation between acute cellular and antibody-mediated rejection, which have different therapeutic approaches, and has high clinical significance. At the same time, this method requires further study: first, new clinical trials are needed to obtain compelling evidence for this method; second, to determine its clinical effectiveness compared to invasive approaches (transplant biopsy); third, by studying the sensitivity and specificity of the method, to determine threshold values at which clinicians could diagnose acute rejection. Moreover, current approaches to ddCF-DNA determination have several limitations, including the labor intensity and high cost of these methods.

Limitation

During the course of this study, several limitations were encountered. Firstly, patient refusal posed a challenge as some individuals declined to participate, potentially introducing selection bias and impacting the generalizability of the findings. Secondly, the scope of the research was confined to primary investigation regarding cell-free DNA as a biomarker for detecting acute rejection in heart transplant recipients. Further exploration involving larger cohorts and diverse clinical settings is imperative to validate and extend the results. Lastly, the external validity of the findings may be constrained by the specific population and context in which the research was conducted, limiting their applicability to broader patient populations and clinical settings.

Conclusion

The study highlights the potential of cell-free DNA as a non-invasive biomarker for detecting acute rejection in heart transplant recipients. The findings underscore the importance of early rejection detection and differentiation between acute cellular and antibody-mediated rejection for tailored therapeutic interventions. However, further research is needed to address methodological limitations, validate the clinical utility of cfDNA testing, and establish threshold values for accurate rejection diagnosis. Despite these challenges, cfDNA testing holds promise for revolutionizing rejection monitoring post-heart transplantation, potentially enhancing patient outcomes and quality of life.

What is already known on this topic: Values of non-invasive diagnostic biomarkers of organ transplant rejection. AlloMap method and determination of donor-derived cell-free DNA. The quantitative marker of allograft damage donor-derived cell-free DNA is a safe, accurate method for monitoring acute rejection in heart transplant recipients.

What this study adds: For the first time in Kazakhstan, donor-derived cell-free DNA was assessed as an early predictor of heart transplant rejection.

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EXPERIENCE OF RESORPTION OF LUMBAR SPINE HERNIAS

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Key words:
resorption, hernia, intervertebral discs, physiotherapy.

Annotation

Background. In most cases, the reduction in pain and clinical manifestations is associated with a decrease in the size of the hernia or its resorption, which is the natural process of reduction or complete disappearance of the hernia without the need for surgical intervention. Currently, there are several intensive physical therapy methods that influence the process of hernia resorption, making conservative treatment preferable.

Materials and methods. At the «Expert Neuro» clinic, as part of a prospective observational study from 2023 to 2024, 30 patients with a confirmed diagnosis of "herniated intervertebral discs of the lumbar spine" were analyzed based on the results of magnetic resonance imaging. The main group of patients received conservative treatment using modern high-intensity physiotherapy methods, the control group received classical methods of conservative treatment.

Results. According to magnetic resonance of the spine, 3 patients developed resorption of a herniated intervertebral disc. In all patients, radiculopathy symptoms improved after 1 month and lower back pain symptoms improved after 2 to 3 months.

Conclusion. According to our clinical experience and relevant literature, sequestered disc herniations have a high rate of resorption. Pathophysiological processes of inflammation and regeneration are the main mechanisms of this phenomenon. Conservative management of such patients in the absence of definitive surgical indications should not be underestimated.

Бел омыртқасының омыртқа-аралық диск грыжасын резорбциялау тәжірибесі

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Мүдделер қақтығысы:
авторлар мүдделер қақтығысының жоқтығын мәдімдейді

Түйінді сөздер:
резорбция, грыжа, омыртқааралық дискілер, физиотерапия.

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Түйіндеме

Өзектідігі. Бел омыртқасының дискілерінің грыжалары (жарық) төменгі арқадағы ауырсынудың ең көп таралған себептерінің бірі болып табылады, көп жағдайда ауырсыну мен клиникалық көріністердің төмендеуі грыжаның кішіреюі мен резорбциясымен байланысты.

Грыжа резорбциясы-бұл хирургиялық емсіз грыжа мөлшерінің өздігімен мөлшерінің азаюы немесе толығымен жоюлу процесі.Бүгінгі күні грыжа резорбциясының патофизиологиялық процесіне әсер ететін бірқатар қарқынды физиотерапиялық әдістер бар, бұл консервативті емдеуді қолайлы етеді.

Материалдар мен тәсілдер. "Expert Neuro" клиникасының базасында перспективалық бақылау зерттеуінің аясында 2023-2024 жылдар аралығында магнитті-резонанстық томография нәтижелері бойынша "бел омыртқасының омыртқа-аралық диск грыжасы" диагнозы расталған 30 науқасқа талдау жасалды. Науқастардың негізгі тобы заманауи жоғары қарқынды физиотерапиялық әдістерді қолдана отырып, консервативті ем алды, ал бақылау тобы консервативті емдеудің классикалық әдістерін алды.

Нәтиже. Омыртқаның магнитті-резонанстық томография мәліметтері бойынша 3 науқаста грыжа дискінің резорбциясы дамыды. Барлық науқастарда радикулопатия белгілері 1 айдан кейін, ал төменгі арқадағы ауырсыну белгілері 2-3 айдан кейін төмендеді.

Қорытынды. біздің клиникалық тәжірибемізге және тиісті әдебиеттерге сәйкес секвестрленген диск грыжалары жоғары резорбцияға ие. Қабыну мен регенерацияның патофизиологиялық процестері бұл құбылыстың негізгі механизмдері болып табылады. Нақты хирургиялық көрсеткіштер болмаған жағдайда, мұндай науқастарды консервативті әдістерімен емдеу жолдарын қарастырған жөн.

Опыт резорбции грыж поясничного отдела позвоночника

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Ключевые слова:
резорбция, грыжа, межпозвонковые диски, физиолечение.

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Аннотация

Введение. Грыжи поясничных дисков представляют собой одну из наиболее частых причин болей в пояснице, в большинстве случаев уменьшение боли и клинических проявлений связаны с уменьшением грыжи или ее резорбцией. Резорбция грыжи — это процесс естественного уменьшения размеров или полного исчезновения грыжи без хирургического вмешательства. Сегодня существуют ряд интенсивных физиотерапевтических методов влияющих на патофизиологический процесс резорбции грыжи, что делает консервативное лечение предпочтительным.

Материалы и методы. На базе клиники «ExpertNeuro» в рамках проспективного обсервационного исследования с 2023 по 2024 годы было проанализировано 30 больных с подтвержденными дигнозом «грыжа межпозвонковых дисков поясничного отдела позвоночника» по результатам магнитно-резонансной томографии. Основная группа пациентов получали консервативное лечение с применением современных высокоинтенсивных физиотерапевтических методов, контрольная группа получала классические методы консервативного лечения.

Результаты. По данным магнитно-резонансной позвоночника у 3 пациентов развилась резорбция грыжи межпозвонкового диска. У всех пациентов симптомы радикулопатии уменьшились через 1 месяц, а симптомы боли в пояснице — через 2-3 месяца.

Заключение. Согласно нашему клиническому опыту и соответствующей литературе, секвестрированные грыжи дисков имеют высокую степень резорбции. Патофизиологические процессы воспаления и регенерации являются основными механизмами этого явления. Не следует недооценивать консервативные методы лечения таких пациентов при отсутствии окончательных хирургических показаний.

Introduction

According to foreign authors, the prevalence of general pain ranges from 30 to 78.6%. The definition of the International Association for the Study of Pain (IASP), «pain is an unpleasant sensory and emotional experience associated with existing or possible tissue damage or described in terms of such damage».[1,2,3,4] Lower back pain is the most common health problem among the population aged 30 to 65 years.[5,6-8]

Herniated lumbar discs are one of the most common causes of lower back pain, in most cases, pain reduction and clinical manifestations are associated with a decrease in herniation or its resorption.[1,2,5,8]

Thanks to the improvement in the quality of neuroimaging research methods, especially MRI, it has been demonstrated that with conservative treatment of this category of patients, as symptoms alleviate, a decrease in the size of the hernial protrusion is sometimes observed. This phenomenon has been called "resorption of intervertebral disc herniation." According to a meta-analysis, the frequency of this phenomenon is 62.5–82.9%.[8,9,6]

The purpose of the study is to demonstrate the results in the use of high-intensity physiotherapeutic methods of influencing the process of resorption of herniated intervertebral discs of the lumbar spine.

Materials and methods

The cross sectional analysis of the observation study was conducted on the basis of the Expert Neuro clinic, 30 patients with confirmed diagnoses of «herniated discs» were analyzed and examined as part of a dissertation study from 2023 to 2024 according to the results of magnetic resonance imaging (MRI).

The sample size of 30 patients was calculated based on the number of patients among the adult population who came to our center over the past year with a diagnosis of lumbar intervertebral disc herniation. Accordingly, a sample size of adult patients was calculated (confidence level: 95%, margin of error: 5%). Patients were recruited from clinics in urban areas of Almaty with the support of local medical staff.

The control (I) group received 1-2 courses of treatment with classical methods of conservative treatment: nonsteroidal anti-inflammatory therapy (NSAIDs), B vitamins, electropharesis, low-intensity magnetic therapy, acupuncture No. 10 doses 1 time per day.

The main (II) group of patients received 1-2 courses of treatment using: HIL therapy (high-intensity laser treatment), SIS therapy (High-intensity magnetotherapy), acupuncture No. 10 doses 1 time per day. Groups were formed by continuous sampling method.

The clinical and neurological status of patients, the assessment of the severity of pain syndrome using a visual analog scale (VAS), as well as the results of MRI (or CT) before the start of treatment and after 3 months were taken into account.

Inclusion criteria: patients aged 30 to 65 years, the presence of a clinical diagnosis of «herniated intervertebral discs in the lumbar spine» in accordance with ICD-10, confirmed by MRI (or CT) results, the duration of pain up to 6 weeks, the intensity of pain in the leg is at least 6 points on the visual analog scale, VAS.

Exclusion criteria: epilepsy, serious mental disorders, significant cognitive impairment, severe, uncontrolled somatic diseases, pregnancy or lactation, absolute indications for surgery; a history of herniated discs, participation in other clinical studies.

Ethical approval. This study was conducted in strict accordance with the principles outlined in the Helsinki Declarationof the World Medical Association «Ethical Principles of medical research with human participation». Before commencing the research, approval was obtained from the Local Bioethics Committee of the Syzganov National Scientific centre of surgery (as amended in October 2013).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics software version 17.0 (IBM SPSS, USA). Numerical variables were expressed as mean±SD and categorical variables as numbers and percentages. Nonparametric statistics were performed for dataset analysis. Between-group comparisons were assessed for numerical variablesand the Chi-square test was used for categorical variables. P⩽0.05 was considered statistically significant.

Results

Participants in both groups underwent CT scanning of the lumbar spine. Spinal CT was performed in 1 (3.3%) patient in each of the groups. In the remaining 28 (93.4%) patients with lumbalgia, MRI of the lumbar spine was most widely used.

Table 1.
Patients' characteristics in groups

	I group	II group	Chi-squared	P value
Patients	15(50.0%)	15 (50.0%)		
Male	8 (26.67%)	9 (30.0%)	0.021	0.883
Female	7 (23.33%)	6 (20.0%)	0.019	0.890
Statistically not significant difference P⩾0.05 Statistically significant difference P⩽0.05				

Before starting treatment, the characteristics of patients in group I were as follows: all 15 (100%) patients had lumbalgia, lumbar muscle defiance was detected in 4 (26.7%) patients, 5 (33.3%) patients had sharp pain when bending, and 9 (60.0%) patients were found to have soreness of spinous processes and paravertebral points. In 1 (6.7%) patient, lumbosacral syndrome was observed, with radiating pain in the lower limb, decreased or revived tendon reflexes, as well as with sensitive disorders.

In group II, before the start of treatment, the characteristics of patients looked somewhat different: all 15 (100%) patients had pain in the lumbar spine, tenderness of spinous processes and paravertebral points. Lumbar muscle defiance was detected in 11 (73.3%) patients, in 8 (53.3%) patients, lumbosacral syndrome, radiating pain to the lower limb with a decrease or revival of tendon reflexes, as well as with sensitive disorders was detected. Sharp pain when bending only in 3 (20.0%) patients. Therefore, statistical difference was insignificant in both groups.

As a result of treatment of patients in both groups, regression of neurological symptoms was observed, but it was more pronounced in group II.

Table 2.
Regression of clinical and neurological symptoms in group I

№	Symptoms and syndromes	Before treatment	After treatment			
			1 month	P value	3 months	P value
1	Sharp pain when bending over	15(50.0%)	10 (33.33%)	0.419	7 (23.33%)	0.248
2	Lower back muscle defense	4(13.33%)	2 (6.67%)	0.823	2 (6.67%)	0.823
3	Pain in the lumbar spine	5 (16.67%)	3 (10.0%)	0.807	2 (6.67%)	0.748
4	Pain in the spinous processes and paravertebral points	9 (30.0%)	4 (13.33%)	0.537	3 (10.0%)	0.507
5	Lumbosacral syndrome	1(3.33%)	-	-	-	-
6	Radiation of pain to the lower limb	1 (3.33%)	-	-	-	-
7	Decreased or increased tendon reflexes	1 (3.33%)	-	-	-	-
8	Sensory disorders	1(3.33%)	1 (3.33%)	1.000	-	-
Statistically not significant difference P≥0.05 Statistically significant difference P≤0.05						

Table 3.
Regression of clinical and neurological symptoms in group II

№	Symptoms and syndromes	Before treatment	After treatment			
			1 month	P value	3 months	P value
1	Sharp pain when bending over	3(10.0%)	1 (3.33%)	0.856	-	-
2	Lower back muscle defense	11 (36.67%)	7 (23.33%)	0.564	1 (3.33%)	0.519
3	Pain in the lumbar spine	15 (50.0%)	10 (33.33%)	0.419	1 (3.33%)	0.381
4	Pain in the spinous processes and paravertebral points	15 (50.0%)	10 (33.33%)	0.419	1 (3.33%)	0.381
5	Lumbosacral syndrome	8 (26.67%)	4 (13.33%)	0.616	-	-
6	Radiation of pain to the lower limb	8 (26.67%)	4 (13.33%)	0.616	-	-
7	Decreased or increased tendon reflexes	8 (26.67%)	4 (13.33%)	0.616	-	-
8	Sensory disorders	8 (26.67%)	4 (13.33%)	0.616	-	-
Statistically not significant difference P≥0.05 Statistically significant difference P≤0.05						

We conditionally divided the visual analogue scale (VAS) as follows: • 0 no pain; • 1-2 mild pain; • 3-6 average pain; • 7-10 severe pain

Table 4.
Results of the VAS questionnaire before treatment

VAS	0 no pain	1-2 mild pain	3-6 average pain	7-10 severe pain
I – group N 17	-	5	10	-
II – group N 13	-	-	12	3

Table 5.
Results of the VAS questionnaire after treatment after 3 months

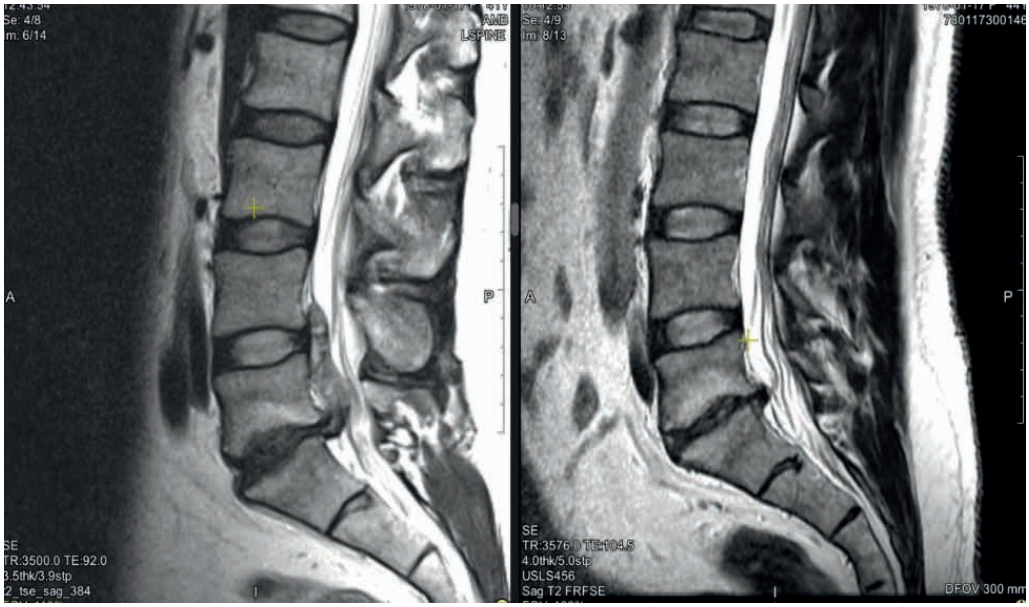
VAS	0 no pain	1-2 mild pain	3-6 average pain	7-10 severe pain
I – group N 15	1	13	1	-
II – group N 15	3	12	-	-

Table 6.
Results of control MRI and CT images of the lumbar spine

№	Before treatment	After 1 month	After 3 months	Before treatment
I – group N 15	Intervertebral disc herniation 15 (100%)	Transient reduction of hernia 5 (33.3%)	Persistent hernia reduction 6 (40%)	Resorption - no
II – group N 15	Intervertebral disc herniation 12 (80%) Sequestrated hernia 3 (20%)	Transient reduction of hernia 1 (6.6%)	Persistent hernia reduction 12 (80%)	Resorption - 3 (20%)

Based on the presented data, it can be concluded that the treatment of herniated discs can cause a temporary increase and change in the structure of the hernia, possibly due to an inflammatory reaction and infiltration of herniated tissue by immune cells. These changes can affect clinical manifestations and neurological symptoms. It is important to note that such changes should not be considered solely as a negative trend, since in most cases they will be followed by a decrease in the size of the hernia and an improvement in clinical manifestations. Figure - 1,2,3 shows MRI images of 3 patients before and after inclusion in the study, observed from 1 to 3 months, with spontaneous resorption of a herniated intervertebral disc.

Figure 1.
A 39-year-old man, followed for 3 months, herniated L5-S1, there is a partial restoration of the MR signal and the height of the disc on thebackground of a decrease in herniation.



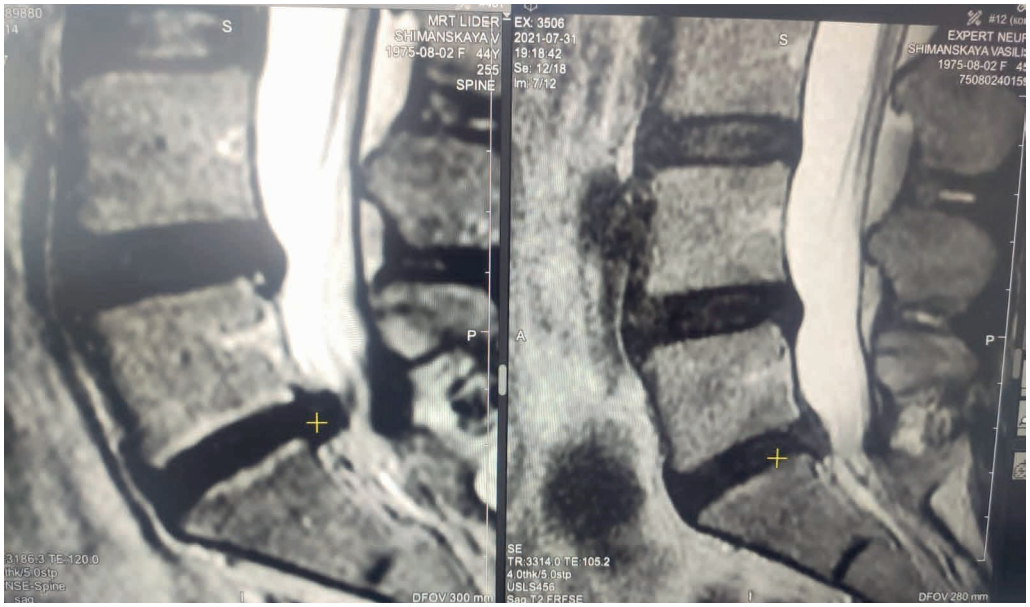


Figure 2.
A 31-year-old man, followed for 3 months, herniated L5-S1, there is a partial restoration of the MR signal and the height of the disc on the background of a decrease in herniation.

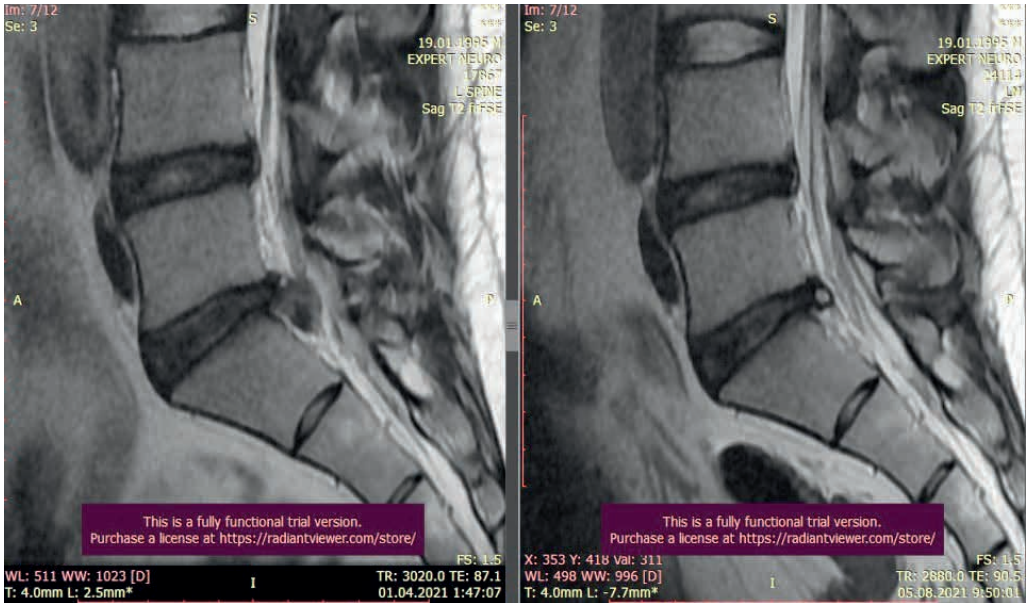


Figure 3.
A 45-year-old man, followed for 3 months, herniated L5-S1, there is a partial restoration of the MR signal and the height of the disc on the background of a decrease in herniation.

Discussion

The phenomenon of lumbar disc herniation resorption following nonsurgical interventions has been extensively documented since its initial observation in 1984. These reports describe lumbar disc herniations diminishing or disappearing gradually over time. The non-surgical treatment cited in these reports encompass a range of approaches, including rest, lumbar support, pain relievers, oral steroids, non-steroidal anti-inflammatory drugs, epidural steroid injections, caudal epidural injections of local anesthetic, manipulation, heat therapy, ultrasound, electrotherapy, traction, exercises, Traditional Chinese Medicine, and integrative Korean medicine. However, the specific treatments crucial for facilitating resorption and the timing of the resorption process remain uncertain. [7,10,11]

The North American Spine Society has suggested that the possibility of resorption should be considered when treating lumbar disc herniation. Although it is known that sequestered and large lumbar disc herniations have a greater likelihood of resorption, it is still impossible to accurately predict resorption in individual cases. Even the possibility of resorption cannot be predicted for individual cases. [5,6,10]

The frequency of resorption varies in different reports due to the varying

durations of observation. *Lee et al.*, documented the highest resorption rate at 96%, with an average observation period of 341.38 ± 306.83 days. Conversely, two studies showed no resorption over shorter observation periods (45 days and 20 days), suggesting that resorption typically does not occur too quickly following nonsurgical interventions.[12,13,14,15]

Physical therapy can play an important role in helping the resorption of lumbar disc herniation. Although it is not possible to directly stimulate resorption using physiotherapy, the use of high-intensity physical influences in our case made it possible to do this.

Limitation.

The limitations were mainly associated with cases of breakdown of diagnostic equipment, lead to minor changes in control testing schedule. Also, all diagnostic studies were carried out only by the same doctor and equipment.

Conclusion

To date, there are many ways to treat herniated discs, but the levels of evidence of various methods create many questions, with the improvement of medical technology, planned therapeutic and diagnostic tactics lose their relevance in the 5-year period. Prognostic criteria have not yet been identified for the phenomenon of hernia resorption, which is important for choosing treatment tactics for patients with this pathology. In addition, the stages of resorption are not entirely obvious. Further research in this area is needed to identify imaging markers and more accurately allocate patients at the outpatient stage to choose conservative or surgical treatment.

What is already known on this topic: A factor in the spontaneous resorption of a disc herniation is neovascularization. Physiotherapy can achieve a similar effect.

What this study adds: High-intensity physiotherapeutic methods at the stage of sequestration of a herniated disc are a promising treatment model for accelerating the resorption of the hernia. Control point of the study reducing the intake of anti-inflammatory drugs.

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COMBINED TREATMENT OF DIGEORGE SYNDROME

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The authors declare no conflict of interests

Keywords:
DiGeorge syndrome, thymic hypo/aplasia, tetralogy of Fallot, thymus transplantation.

Annotation

Background. DiGeorge syndrome is a rare congenital disease associated with a deletion of chromosome 22q11.2, which is characterized by the occurrence of various anomalies, such as hypo/aplasia of the thymus and parathyroid glands, which leads to T-cell immunodeficiency and hypoparathyroidism; this syndrome is also characterized by congenital heart disease (tetralogy of Fallot), anomalies in the development of craniofacial structures are observed, in the form of non-fusion of the hard palate and upper lip (cleft palate and cleft lip).

Results. This article will examine a clinical case of DiGeorge syndrome in a child, with the classic triad characteristic of this condition (immunodeficiency, hypoparathyroidism and congenital heart disease). The patient underwent the first stage of correction of a combined heart defect against the background of constant (monthly) immunocorrection. Due to the COVID-19 pandemic, our patient was unable to receive scheduled hospitalization for blood replacement and immunocorrective therapy in a timely manner. The key to increasing the survival rate of patients with DiGeorge syndrome is prenatal screening, timely correction of the anomaly and immunoreplacement therapy, which are actively used in foreign countries. Also, incomplete treatment of DiGeorge syndrome can subsequently lead to various other manifestations, such as autoimmune diseases, infectious diseases, etc.

Conclusion. The prognosis of DiGeorge syndrome is that this disease has various clinical manifestations, is combined with other variants of the anomaly that are incompatible with life and lead to delayed psychomotor development and have an unfavorable prognosis.

Ди Джорджи синдромын біріктірілген емдеу

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Мүдделер қақтығысы:
авторлар мүдделер қақтығысының жоқтығын мәдімдейді

Түйінді сөздер:
Ди Джорджи синдромы, тимус гипо/аплазиясы, Фалло тетралогиясы, тимус трансплантациясы.

Түйіндеме

Өзектідігі. Ди Джорджи синдромы – 22q11.2 хромосомасының жойылуымен байланысты сиректуа біткен ауру, ол тимус және қалқаншамаңы бездерінің гипо/аплазиясы сияқты әртүр-

лі ауытқулардың пайда болуымен сипатталады, бұл Т-жасушалық иммунтапшылығына және гипопаратиреозға әкеледі; Бұл синдром сонымен қатар туабіткен жүрек ақауымен (Фалло тетралогиясы) сипатталады, ал бас-жаққұрылымдарының даму аномалиялары қаттытаңдай мен жоғарғы еріннің біріктірілмеуі түрінде байқалады (жарықтаңдай және ерін жырығы).

Нәтижелер. Мақалада осы жағдайға тән классикалық триада (иммунитет тапшылығы, гипопаратиреоз және туа біткен жүрек ақауы) бар баладағы Ди Джорджи синдромының клиникалық жағдайы қарастырылады. Науқасқа тұрақты (ай сайынғы) иммунокоррекция фонында қатар жүретін жүрек ауруын түзетудің бірінші кезеңі өтті. COVID-19 пандемиясына байланысты біздің пациент қан алмастыру және иммунокоррекциялық терапия үшін жоспарлы госпитализацияны уақтылы ала алмады. Ди Джорджи синдромы бар науқастар дың өмірсүру деңгейі нарттырудың кілті - пренаталды скрининг, аномалияны дер кезінде түзету және шетелдерде белсенді түрде қолданылатын иммунорыналмастыру терапиясы. Сондай-ақ, Ди Джорджи синдромын толықем демеу кейіннен аутоиммундық аурулар, жұқпалы аурулар және т.б. сияқты басқа да көріністерге әкелуі мүмкін.

Қорытынды. Ди Джорджи синдромының болжамы – бұл аурудың әртүрлі клиникалық көріністері бар, аномалияның өмірге сәйкес келмейтін басқа нұсқаларымен біріктіріліп, психомоторлы дамудың кешігуіне әкелетін және нашар болжамға әкеледі.

Комбинированное лечение синдрома Ди Джожди

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Ключевые слова:
синдром Ди Джорджи, гипо/аплазия тимуса, тетрада Фалло, трансплантация тимуса, COVID-19.

Аннотация

Синдром Ди Джорджи — редкое врожденное заболевание, связанное с делецией хромосомы 22q11.2, которое характеризуется возникновением различных аномалий, таких как гипо/аплазия тимуса и паращитовидных желез, что приводит к Т-клеточному иммунодефициту и гипопаратиреозу; данный синдром ассоциирован с врожденными пороками сердца, такими как тетрада Фалло, наблюдаются аномалии развития черепно-лицевых структур в виде несращения твердого неба и верхней губы (расщелина неба и заячья губа).

В статье представлен клинический случай синдрома Ди Джорджи у ребенка 2 лет, и рассмотрена предложенная схема комбинированного хирургического лечения и иммунокоррегирующей терапии. У пациента с классической триадой, характерной для этого состояния (иммунодефицит, гипопаратиреоз и врожденный порок сердца). верифицирован синдромом Ди Джорджи, подтвержденный лабораторными и инструментальными методами диагностики. Особенностью данного клинического случая явилось то, что ребенку были успешно проведены два этапа открытой хирургической коррекции сочетанного порока сердца на фоне постоянной (ежемесячной) иммунокоррекции, однако, в связи ограниченным доступом к госпитальной медицинской помощи пациентам с иммунодефицитными состояниями в период пандемии COVID-19, пациент не смог своевременно получить плановую иммунокоррекцию в условиях стационара. По мнению авторов, данные ограничения спровоцировали развитие тяжелых инфекционных осложнений, приведших в итоге к летальному исходу. Залогом повышения выживаемости больных синдромом Ди Джорджи являются пренатальный скрининг, а также комбинация своевременной

хирургической коррекции аномалий и иммунозаместительной терапии, которые активно применяются в зарубежных странах. Также неполный курс лечения синдрома Ди Джорджи может быть ассоциирован с развитием серьезных осложнений.

Introduction

DiGeorge syndrome, or velocardiofascial syndrome, is associated with a deletion of chromosome 22q11.2 and is one of the most common deletions in the human genome, second only to Down syndrome, which is associated with a trisomy on chromosome 21. The prevalence of DiGeorge syndrome ranges from 1:1000 to 1:4000 - 1:6000 newborns according to different literature data. The chromosomal deletion 22q11.2 results in impaired development of the pharyngeal gut, which gives rise to the posterior part of the oral cavity, tongue, salivary glands, palatine tonsils, glands derived from the epithelium of the pharyngeal pockets (thyroid, parathyroid, thymus) and the cardiac outflow tract.

Clinically, full DiGeorge syndrome can be observed, which includes the full range of typical manifestations, namely congenital anomalies and severe immunodeficiency. It is also possible to observe partial DiGeorge syndrome, which includes only some of the manifestations without evidence of marked immunodeficiency. A diagnostic criterion to distinguish between complete and incomplete DiGeorge syndrome is the determination of the number of native T cells (CD4+CD45RA+ T cells). T-cell deficiency is often associated with B-cell deficiency and hypogammaglobulinemia.

DiGeorge syndrome was first described as a clinical triad: immunodeficiency, hypoparathyroidism and congenital heart disease (conotruncal anomalies). Further study of DiGeorge syndrome has led to the identification of a variety of clinical manifestations of the disease, including many congenital anomalies and pathological conditions, such as non-enlargement of the hard palate and upper lip (wolf's mouth and harelip), as well as later manifestations, such as gastrointestinal or renal anomalies, autoimmune diseases, and various manifestations of cognitive retardation.

Objective: To discuss the complexities of combination treatment of DiGeorge syndrome within the constraints of the COVID-19 pandemic.

Case presentation

A child, a boy aged 4.5 months, G4P4 uncomplicated pregnancy, with a birth weight of 2500g, with no family history of facial dysmorphism and other congenital anomalies, was admitted to a children's city clinical infectious disease hospital in September 2019 with signs of respiratory failure, rapid breathing, increased body temperature, cough, runny nose. The initial physical examination revealed skin cyanosis, decreased skin turgor, increased body temperature to 37.4°C, tachycardia 146 per minute, tachypnea 54 per minute. The child's weight at the time of the examination was 3500 g, which is below the age norm, and he was artificially fed, sucking weakly. The child's psychomotor development was also delayed.

In the cardiac region, a "heart hump" type bulge was visualized, and systolic tremor with widening of the cardiac borders in the cross section was noted on palpation. Auscultation of the lungs revealed dyspnea and dry wheezing rales. Auxiliary muscles were involved in breathing. Heart sounds were muffled and a coarse systolic "machine murmur" was noted at all sites. On initial physical examination, oxygen saturation was 85%, blood pressure was 72/46 mmHg, and heart rate was 150 beats/min. On the ECG, the cardiac axis was 100° to the right and there was evidence of hypertrophy of both ventricles.

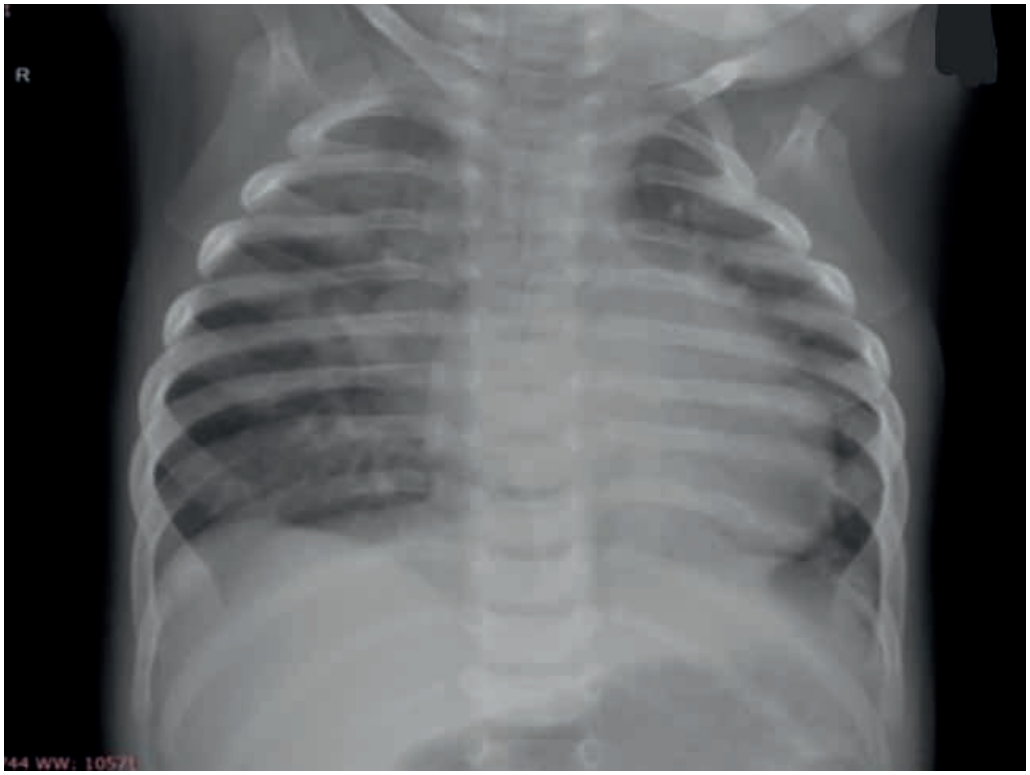


Figure 1.
X-ray shows signs of bilateral focal pneumonia. Cardiomegaly. Hypo/aplasia of the thymus gland.

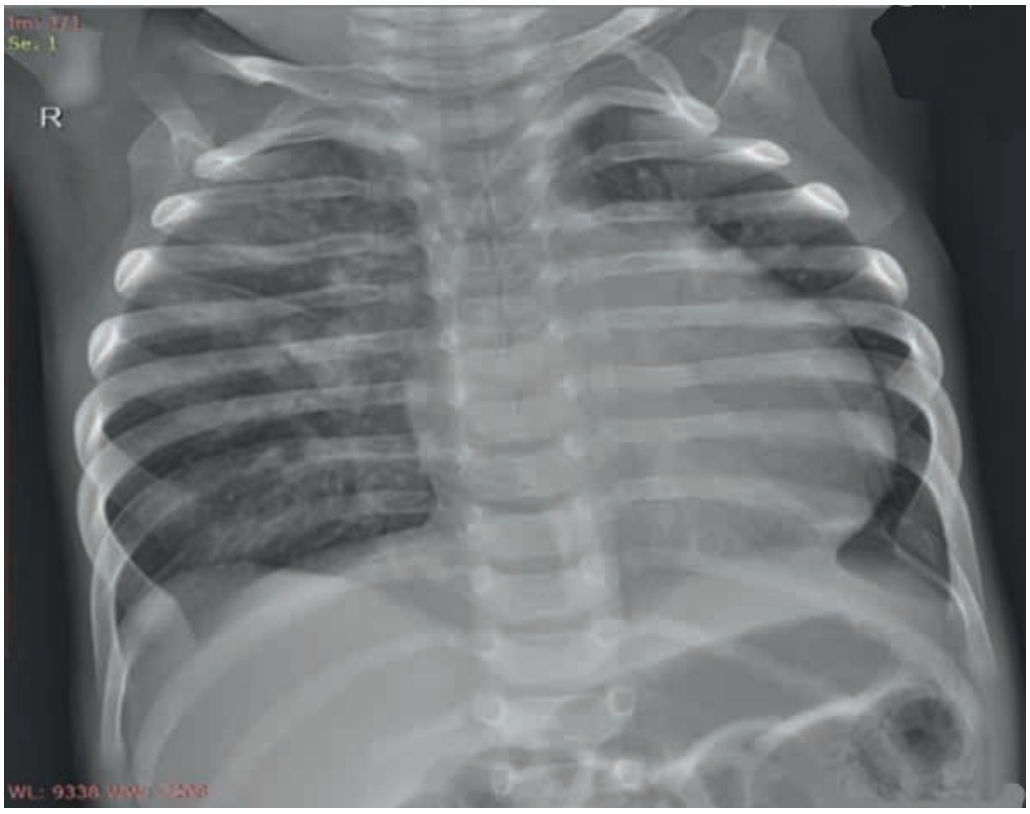
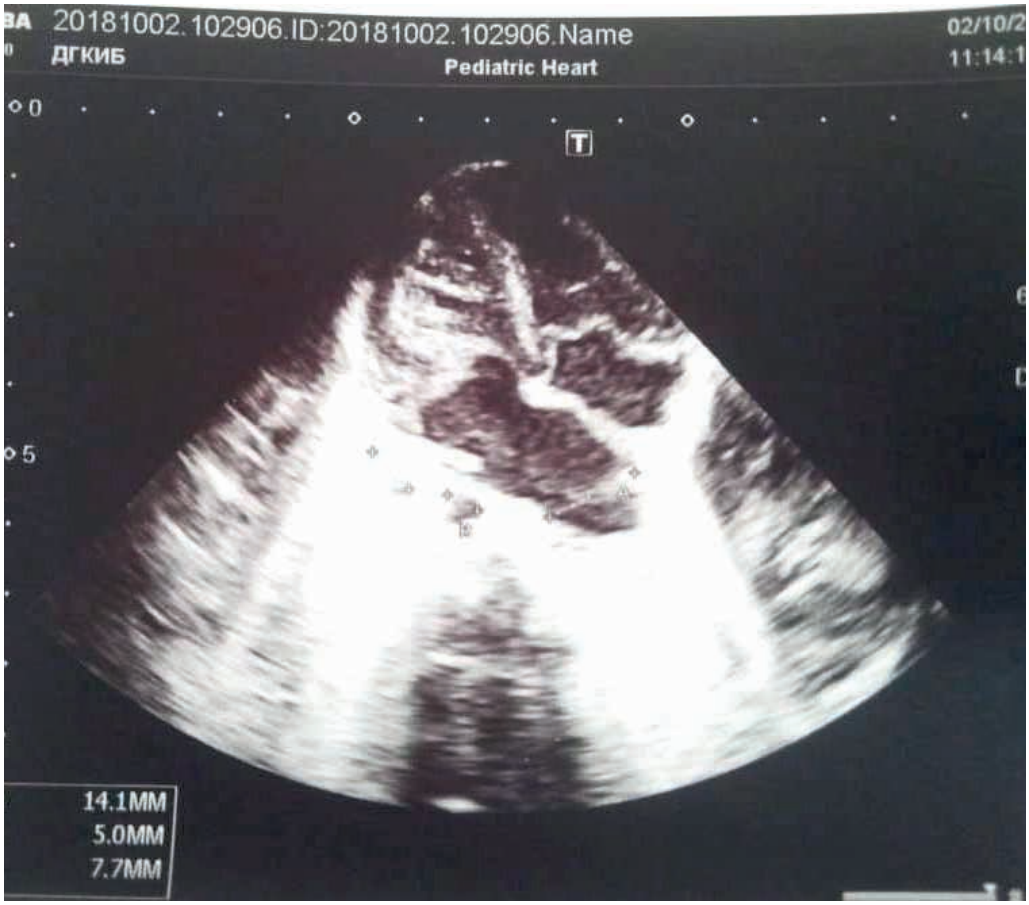


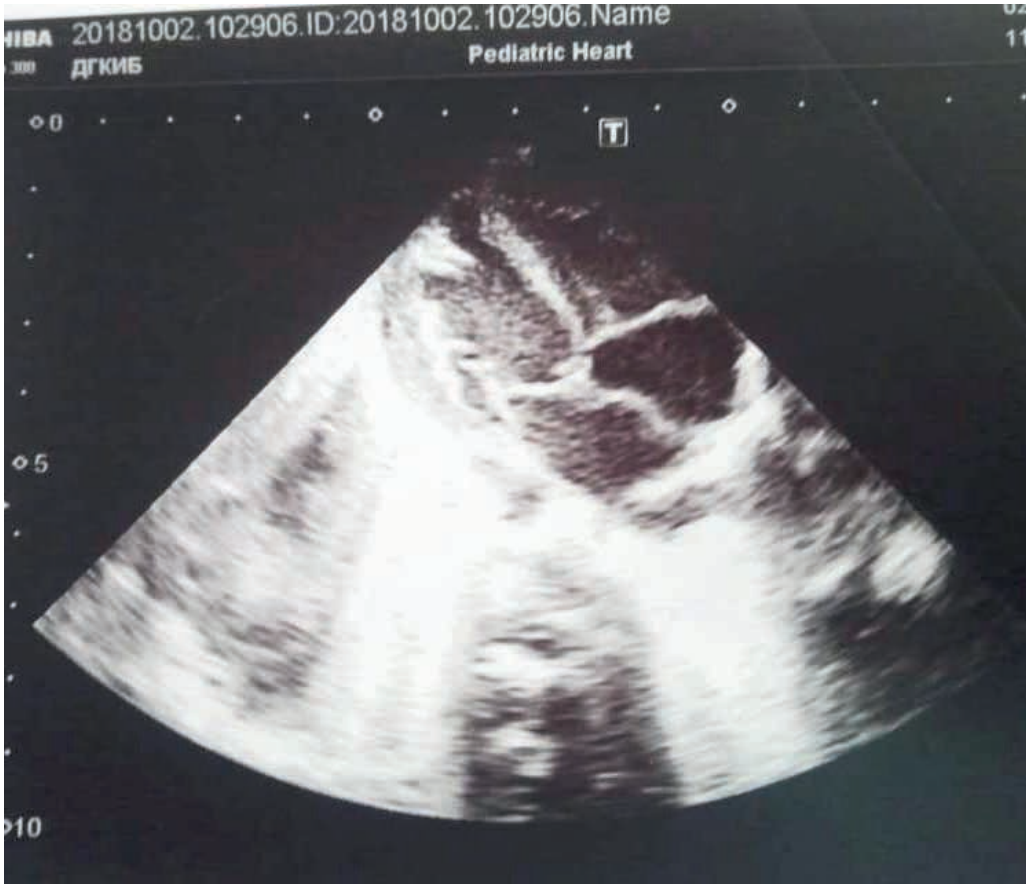
Figure 2.
Reconvalescence in dynamics after 10 days. Cardiomegaly, heart waist is smoothed.

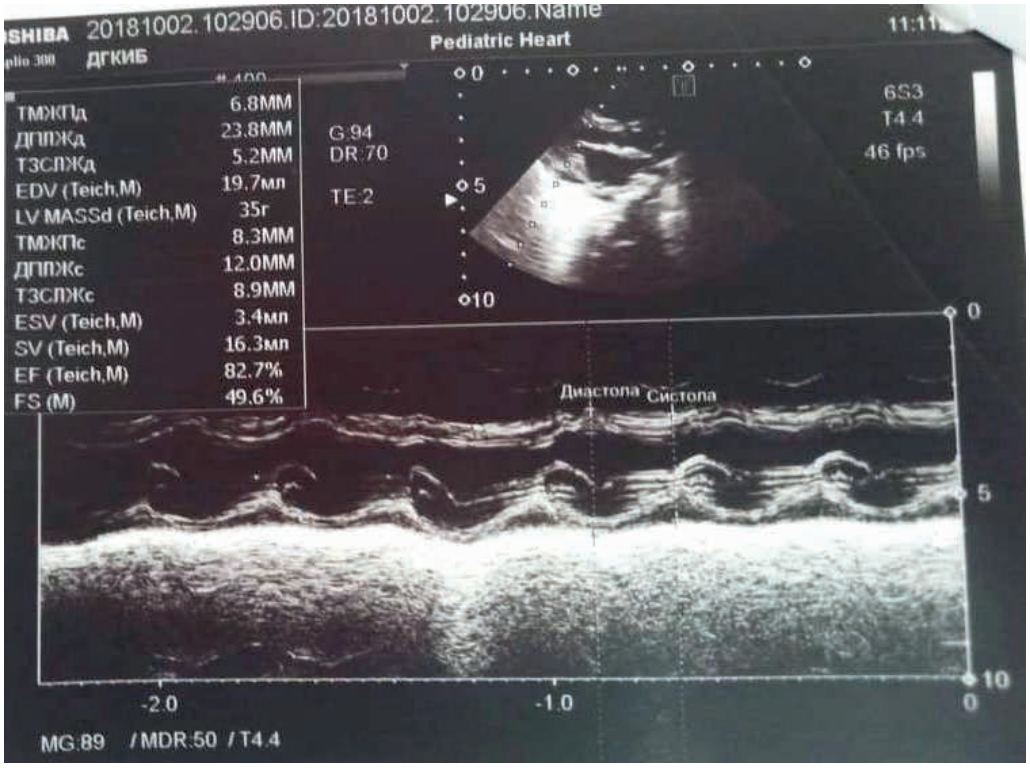
The patient was referred to a pediatric cardiac surgery center, where EchoCG revealed a wide open aortic duct, atrial septal aneurysm with an atrial septal defect, as well as an interventricular septal defect and left ventricular wall hypertrophy.

Echocardiography revealed a combined congenital heart defect (CHD) - Tetralogy of Fallot.

Figure 3 and 4.
Cardiac ultrasound revealed a congenital heart defect: Small anomalies of cardiac development (SACD). Interventricular septal defect, multiple moderate dilations of the right and left ventricles. Severe hypertrophy of the right ventricular walls.







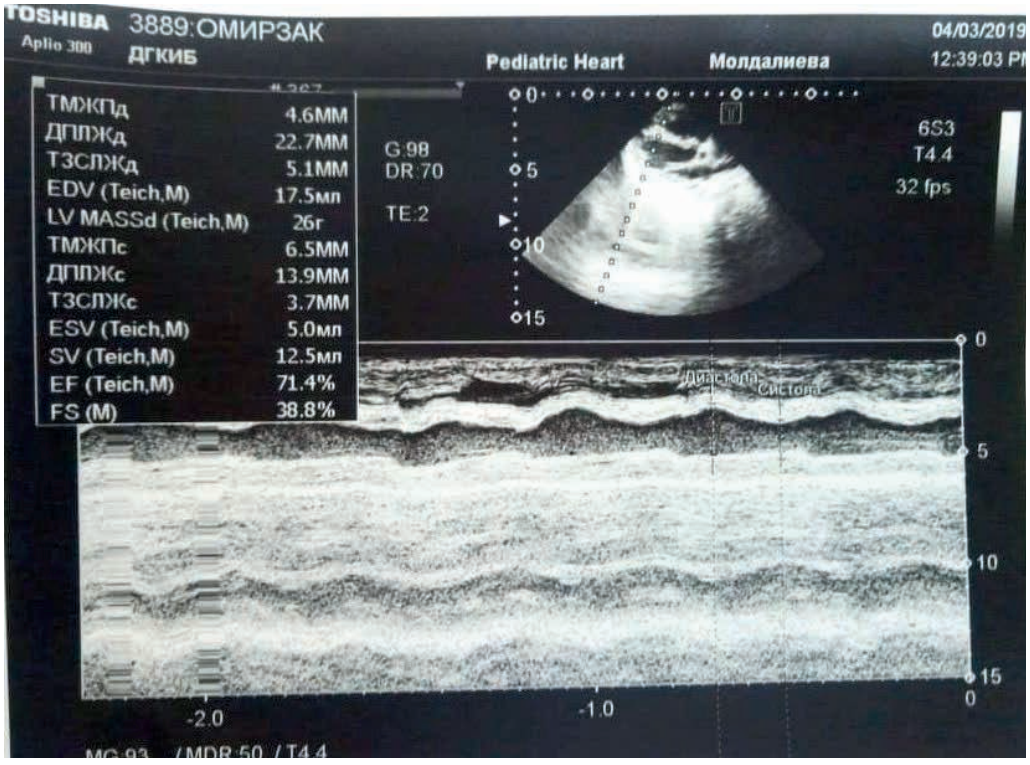


Figure 5 and 6.
Open ductus arteriosus. Signs of pulmonary hypertension. Additive papillary muscle group. Aneurysm of the sinuses of Valsava. Mitral and tricuspid valve insufficiency. Myocardial contractility is satisfactory.

Discussion

DiGeorge syndrome is caused by a chromosomal microdeletion 22q11.2 and is characterised by a wide range of clinical manifestations. Congenital heart disease occurs in 80% of cases, with the most common manifestations being coarctation of the aorta, common arterial trunk and tetralogy of Fallot. Lesions of the nasopharyngeal apparatus occur in about 70% of cases and manifest as velopharyngeal anomalies, cleft palate, cleft lip, cleft frenulum of the palate, nasal tone of voice, olfactory

dysfunction and hearing loss. There may be various signs of dysembryogenesis stigma, characteristic facial features such as elongated face, macrognathia, broad nasal bridge, small teeth. Delayed physical, speech and psychomotor development is observed in 70-90% and manifests itself with age. Immunological disorders occur in 77% of cases. Infections due to immunodeficiency occur not from birth but throughout the course of the disease. T-cell deficiency may predispose to autoimmune disease, which may be as high as 8.5%, especially in patients with CD4+ deficiency.[2]

DiGeorge syndrome is not uncommon in adults in the form of various variants of CHD: Tetralogy of Fallot, unilateral absence of the pulmonary artery, and others. Among patients with CHD, 55% had chromosomal abnormalities, 71% of patients with chromosomal abnormalities had cardiac CHD, four of whom had the triad: congenital laryngeal membrane, deletion of chromosome 22q11 and congenital cardiovascular anomalies.[3]

Surgical correction and complete repair of Tetralogy of Fallot consists of repair of the interventricular septal defect by patch placement, dilation of the right ventricular outflow tract by muscle resection, pulmonary valvuloplasty and, if necessary, enlargement of the pulmonary trunk patch. If there is significant hypoplasia of the pulmonary valve annulus, a transannular patch is placed. Surgery is usually elective at 2-6 months of age, but can be performed at any time if symptoms are present or if there is severe right ventricular outflow tract obstruction.[4]

Prophylaxis against infection is recommended for most patients with DiGeorge syndrome who are incompletely immunodeficient, and thymic transplantation (TT) is recommended for those who are fully immunodeficient.[5]

Therefore, the next important treatment tactic for DiGeorge syndrome is TT. TT is a promising treatment strategy for complete DiGeorge syndrome. According to the literature, 71 infants with complete DiGeorge anomaly were identified, of which 59 infants underwent TT. After TT, 12 (20%) infants required emergency admission to the intensive care unit (ICU). Of these, 7 (58%) of the 12 infants survived to discharge from ORIT and six survived 6 months after TT. 42 (71%) of the 59 infants who underwent TT had CHD, of whom 9 (75%) were treated in the ORIT. There was a correlation between days without mechanical ventilation and age at transplantation (R 0.17; p = 0.423). Age at transplantation and the presence of CAD were not associated with the risk of ORIT hospitalisation (odds ratio 0.95; 95% CI 0.78-1.15 and odds ratio 1.27; 95% CI 0.30-5.49, respectively) or ORIT mortality (odds ratio 0.98; 95% CI 0.73-1.31 and odds ratio 0.40; 95% CI 0.15-1.07, respectively).[6]

The causes of early post-transplant mortality were viral infections in the absence of thymopoiesis and late death due to autoimmune thrombocytopenia, septic shock with graft rejection and the need for repeat TT. Signs of thymopoiesis developed in 5-6 months, also at 12 and 24 months after TT in 10 patients there was observed a dynamic increase in the level of circulating naive CD4 and T cells. Although the age norm is not always reached, the risk of new infections is reduced. On average, prophylactic antimicrobials and immunoglobulin replacement therapy are discontinued after 49 months. Histological confirmation of thymopoiesis has been observed in patients who have undergone biopsy of the transplanted tissue, with complete maturation to the formation of terminal Hassall's corpuscles and expression of autoimmune regulators.[7,8]

However, autoimmune complications have occurred after TT. Untimely therapy, namely correction of cardiac CHD and TT of the thymus gland, may lead to an unfavourable outcome, as occurred in our clinical case.[9]

Recent studies following the COVID-19 pandemic have shown that many respiratory viruses are more severe in people with T-cell immunodeficiency. Patients with 22q11.2 deletion syndrome were at risk for a severe course of COVID-19.[10]

Conclusion

Patient A underwent the first stage of surgical correction of CHD. The presented clinical case coincided with the period of COVID-19 pandemic. Restrictive measures were introduced during the period

of disease incidence (May-June 2020), including limited planned hospitalisation of immunocompromised patients. As a result, Patient A was unable to receive planned monthly immune-replacement therapy to correct primary immunodeficiency, which led to the development of infectious complications of viral infection of unclear genesis during the COVID-19 outbreak and ultimately to death.

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COMPLICATIONS OF USING A DOUBLE-LUMEN ENDOTRACHEAL TUBE AND THEIR TREATMENT

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Authors declare that they have no conflicts of interest

Keywords:
Iatrogenic tracheal injury, double-lumen endotracheal tube, tracheal rupture treatment, artificial lung ventilation, laryngeal mask, fibrobronchoscopy in tracheal injuries.

Annotation

A 46-year-old woman, withheight 161 cm and weight 75 kg, underwent endoscopic resection of the esophagus with reconstruction of the gastrointestinal tract with a gastric tube (McKeown procedure). During the surgery a tracheal injury with a rupture of the membranous part revealed, which was considered as a complication regarding a double-lumen endotracheal tube installation. Clinically, the rupture remained asymptomatic during two hours of single-lung ventilation of the left lung and was visualized during the thoracoscopic stage of the surgery. The tracheal rupture was promptly repaired. In the postoperative period, the patient required prolonged lung ventilation through a laryngeal mask. Frequentbronchial fibroscopy was performed to verify the condition of the tracheal suture, its continuity, and to provide tracheobronchial sanitation in the intensive care unit. The application of a multidisciplinary approach to diagnose and treat a life-threatening complication as tracheal rupture in a short time allowed us to stabilize the patient's condition and avoid the development of further complications.

Қос қуысты эндотрахеальды түтікті қолданудың асқынулары және оларды емдеу

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Түйінді сөздер:
кеңірдектің ятрогенді зақымдануы, қосқуысты эндотрахеальды түтік, кеңірдектің жыртылуын емдеу, механикалық өкпе желдетуі, ларингеальды маска, кеңірдек жарақаттарына арналған фибробронхоскопия.

Түйіндеме

46 жастағы әйелге, бойы 161 см және дене салмағы 75 кг, асқазан-ішек жолдарының тұтастығын қалпына келтіру үшін жасалған өңештің эндоскопиялық резекциясы кезінде (McKeown отасы) кеңірдектің мембраналық бөлігінің жыртылуы байқалды. Зақымдануды қос қуысты эндотрахеальды түтікті орнату нәтижесінде дамыған деп болжадық. Кеңірдектің жыртылуы 2 сағат ішінде бір өкпенің сол жақ жел-

детуінде байқалмады және отаның торакоскопиялық кезеңінде визуальды анықталды. Кеңірдектің жыртылған бөлігі қалпына келтірілді. Отадан кейінгі кезеңде науқасқа ларингеальды маска арқылы ұзартылған өкпе желдетуі қажет болды. Қарқынды емдеу бөлімінде кеңірдек тігісінің күйін, оның тығыздығын және трахеобронхиалды ағаштың (ТБА) санациясы үшін бірнеше рет фибробронхоскопия жасалды. Кеңірдектің жыртылуы сияқты өмірге қауіп төндіретін асқынуды қысқа уақыт ішінде диагностикалау мен мультидисциплинарлы тәсілмен емдеу науқастың жағдайын тұрақтандыруға және одан әрі асқынулардың дамуын болдырмауға мүмкіндік берді.

Осложнения применения двухпросветной эндотрахеальной трубки и их лечение

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Аннотация

У женщины 46 лет, ростом 161 см и массой тела 75 кг во время эндоскопической резекции пищевода с восстановлением целостности желудочно-кишечного тракта желудочной трубкой (операция McKeown) произошло повреждение трахеи с разрывом мембранозной части, которое расценено как осложнение в результате установки двухпросветнойэндотрахеальной трубки. Клинически разрыв не проявлялся в течение двух часов однолегочной левосторонней вентиляции легких, и был выявлен визуально во время торакоскопического этапа операции. Разрыв трахеи был ушит. В послеоперационном периоде пациенту была необходима продленная вентиляция легких, которая осуществлялась через ларингеальную маску. Неоднократная фибробронхоскопия проводилась для верификации состояния трахеального шва, его герметичности и санации трахеобронхиального дерева в отделении интенсивной терапии. Применение мультидисциплинарного подхода к диагностике и лечению такого жизнеугрожающего осложнения как разрыв трахеи, позволил в короткое время добиться стабилизации состояния и избежать развития дальнейших осложнений.

Introduction

The double-lumen endobronchial tube is often used for a single-lung ventilation method in thoracic surgery. However, its use can lead to tracheal rupture due to large external diameter and the frequently used stylet.[1,2] Tracheal rupture after intubation is a rare complication, but it is a life-threatening condition, and the prognosis directly depends on the timeliness of diagnosis and treatment. It is important to ensure airway patency before and after treatment.

In addition, early extubation is recommended to prevent complications due to increased airway pressure. However, in most cases, mechanical ventilation is required after surgery for tracheal rupture.[3]

Using the example of a 46-year-old female patient who had a tracheal rupture caused by intubation with a double-lumen endobronchial tube during esophageal extirpation, the authors discuss the management of a tracheal rupture discovered during surgery, the use of a laryngeal mask airway as an alternative for prolonged ventilation in the

postoperative period and the role of fiberoptic bronchoscopy to verify the restoration of tracheal rupture.

Clinical case

A female patient, 46 years old, height 161 cm and body weight 75 kg, was prescribed extirpation of the esophagus for squamous cell keratinizing cancer of the middle third of the esophagus, an infiltrative-ulcerative form with invasion into the muscle layer. A McKeown operation is planned - in which resection of the esophagus and formation of a gastric tube is performed using laparoscopic and thoracoscopic methods, and esophagogastroanastomosis is performed through a cervical approach. During the preoperative examination, including blood tests, electrocardiography, chest CT (computed tomography) and bronchoscopy, we identified nonspecific cardiomyopathy, endometriosis of the uterine body and varicose veins of the lower extremities without circulatory disorders in them, and no other specific abnormalities were found. According to clinical lab results: total protein levels were reduced - 55.9 g/l, minor microalbuminuria - 30 mg/l, leukocyturia - 14 cells/ml, erythrocyturia - 15 cells/ml were detected in the urine.

The patient was examined by an anesthesiologist before the surgery, ASA risk class 2 was determined, and general multicomponent endotracheal anesthesia was planned.

The patient was taken to the operating room without premedication wearing compression stockings on the lower extremities. Basic monitoring has been established. Initial vital signs were stable: blood pressure 135/65 mm Hg, heart rate 78 per minute, blood oxygen saturation 97%. A peripheral venous cannula was inserted into the cubital vein.

Induction of anesthesia was performed intravenously: Propofol 150 mg, fentanyl 0.2 mg. Myoplegia with pipecuronium 4 mg and suxamethonium 100 mg. The trachea was intubated with a double-lumen left-directed endotracheal tube, size 35Fr, without a stylet. Intubation proceeded without technical difficulties using the classical technique. The tube was passed into place without resistance. The position of the tube was verified by auscultation, and complete isolation of both lungs was achieved. Two-lung ventilation was established by volume mode with a tidal volume of 450 ml, respiratory rate 14 per minute, inhalation-exhalation ratio 1:2, FiO2 45%. In this case, the peak pressure in the respiratory tract was 14 cm H2O, the plateau pressure was 10 cm H2O, and the end-expiratory pressure was 3 cm H2O. Compliance was 55-60 ml/cm H2O, EtCO2 32-37 mmHg, SpO2 99-100%.

Maintenance of anesthesia: Sevoflurane 0.6-1 MAC, fentanyl 1 mg. The duration of the operation was 425 minutes, the duration of anesthesia was 495 minutes.

Monitoring of the patient's vital functions was expanded, and the radial artery and internal jugular vein on the right were cannulated. Invasive monitoring of blood pressure and central venous pressure was started. A thermistor is installed in the nasopharynx to continuously monitor core body temperature. The bladder was catheterized with a Foley catheter to monitor hourly urine output. To prevent induced hypothermia, infusion of warm (39°C) infusion solutions was used using the EnFlow infusion media warmer, as well as convection air heating of the patient's torso using the Equator device. The antibiotic ceftriaxone 1 g was administered. and pantoprozole 40 mg.

The patient was placed in a prone position, and single-lung ventilation of the left lung was started. FiO2 increased to 60%, tidal volume decreased to 300 ml, respiratory rate increased to 20 per minute. At the same time, the peak pressure in the respiratory tract was 17 mmHg, the plateau pressure was 14 cmH2O, and the end-expiratory pressure was 0 cmH2O. Compliance was 22-30 ml/cm H2O, EtCO2 35-40 mmHg, SpO2 97-98%. The thoracoscopic stage of the operation began in the conditions of right-sided carbothorax and carbomediastinum. After opening the mediastinal pleura along the esophagus, the esophagus is gradually mobilized using sharp and blunt routes with the intersection of the azygos vein. At the 115th minute of the operation, during mobilization of the esophagus in the upper thoracic region, there was a sudden decrease in SpO2 to 79%, an increase in heart rate to 128 per min-

ute, a decrease in peak pressure to 10 cm water column, plateau pressure to 7 cm water column, etCO2 increased to 99 mm Hg, a leak appeared in the anesthesia machine circuit to 700 ml/min. Both channels of the double-lumen endotracheal tube were sanitized, and a small amount of blood-streaked mucus was aspirated from the right channel. Arterial and venous pressure werestable.

During inspection of the mediastinum, surgeons identified a linear rupture of the membranous part of the trachea, which began 1 cm above the tracheal bifurcation and continued proximally; the tracheal cuff of the tube was visualized in the lumen of the trachea. The trachea and esophagus were separated. A longitudinal rupture of the membranous part of the trachea over 10 cm was detected.

Ventilation parameters were adjusted based on the patient's condition and the leak. The patient resumed double-pulmonary ventilation with a tidal volume of 600 ml, respiratory rate 20 per minute, inhalation-exhalation ratio 1:2, FiO2 100%. In this case, the peak pressure in the respiratory tract was 17 cm H2O, the plateau pressure was 14 cm H2O, and the end expiratory pressure was 3 cm H2O. Compliance was 45-50 ml/cm water column. The leakage was 580-720 ml/min. Gradually, within 4 minutes, EtCO2 decreased to 42-49 mmHg, and SpO2 increased to 93-95%. Blood pressure was 100/60 mm Hg, heart rate decreased to 100 per minute.

After a multidisciplinary intraoperative consultation, it was decided to close the tracheal rupture endoscopically and intensify antibacterial therapy with meropenem, which was administered intravenously at a dose of 1 g. The defect in the membranous part of the trachea was sutured with a continuous suture, and a hydrotest was performed, which showed complete tightness of the trachea. The operation continued.

The thoracic stage was completed after complete stabilization of respiratory function. In dynamics, the ventilation parameters were changed taking into account the eliminated leak, the tidal volume was reduced to 450 ml, the respiratory rate was reduced to 14 per minute to achieve normal ventilation at EtCO2 35-38 mm Hg. After suturing the trachea, gas exchange was stabilized and improved in dynamics. Tachycardiaregressed.

At the end of the thoracic stage, the patient was rotated to the "supine" position and the endoscopic abdominal stage of the operation began, which went without any complications. After the abdominal stage of the operation, against the background of the relative stability of the patient's vital functions, the operation was completed with the application of esophago-gastroanastomosis from the cervical approach.

At the end of the operation, the patient in medicated sleep with stable vital signs was transported to the intensive care unit.

Upon admission to the intensive care unit the patient was examined, including chest x-ray, blood tests for acid base, gas composition, electrolytes, coagulation status and standard biochemical composition. A consultation was held to determine further tactics of the patient's management, at which it was decided to continue double-lung ventilation through a double-lumen endotracheal tube with deep sedation. If respiratory function is stable and there are no other complications from the airway, lungs or chest frame, after 6-8 hours it was recommended to remove the double-lumen endotracheal tube and replace it with a supraglottic airway to continue ventilation. A disposable #4 laryngeal mask was chosen as the supraglottic airway. In case of difficulties in providing ventilation through the supraglottic airway, it was suggested to replace it with a single-lumen endotracheal tube.

6 hours 40 minutes after the patient's admission to the intensive care unit against the background of deep sedation with dexmedetomidine and fentanyl, prolonged artificial ventilation, the patient's condition was stable, gas exchange was satisfactory, there were no accumulation of mucus in the respiratory tract, there were no pneumothorax or pneumomediastinum. A double-lumen endotracheal tube was removed from the trachea under the influence of an ultra-short-acting muscle relaxant (suxamethonium). Laryngeal mask No. 4 was installed, the cuff was inflated until a tight seal was achieved. Artificial

ventilation of the lungs was continued through the laryngeal mask using the same parameters. Oxygenation was satisfactory. A diagnostic and sanitation fibrobronchoscopy was performed, which revealed that the suture on the membranous part of the trachea is intact, no defects were found, no accumulations of mucus and blood were detected, and there was no bronchial obstruction.

Subsequently, the depth of sedation was reduced, spontaneous breathing restored, and the ventilation mode was changed to auxiliary with pressure support. At the same time, the parameters of respiratory support were dynamically selected so that the peak pressure in the respiratory tract did not exceed 12-15 cm of water column, and at the same time, PaO2 was not lower than 70 mm Hg, and PaCO2 was within 35-45 mm Hg. The patient was gradually awakened. A state of wakefulness of 10 points on the Aldreth scale has been achieved.

5 hours 30 minutes after installation of a laryngeal mask airway and prolonged assisted ventilation, the patient was gradually adapted to spontaneous breathing, and pressure support was reduced to zero. In this case, the respiratory rate was 18 per minute, up to 300-450 ml. SpO2 94-97% with FiO2 35%. The laryngeal mask was removed, and the patient was inhaled with humidified warm oxygen through nasal cannulas with a flow of 4 l/min. SpO2 after removal of the laryngeal mask was 96%, respiratory rate was 18 per minute.

Subsequently, the patient received complex intensive therapy, including enhanced antibacterial therapy, pain relief, parenteral nutrition, infusion therapy, mucolytic inhalations, sanitation fibrobronchoscopy, verticalization and activation. The medical staff of the intensive care unit was highly suspicious of infectious complications in the form of mediastinitis.

The course of the early postoperative period passed without any complications. The patient experienced mild respiratory failure and a systemic inflammatory response. Respiratory failure was mild and regressed within 3 days after surgery. Signs of the systemic inflammatory process completely regressed on the fifth day. On the sixth postoperative day, the patient was transferred to a specialized surgical department in stable condition. On the 14th postoperative day, the patient was discharged from the hospital in satisfactory condition.

Discussion

In pulmonary and mediastinal surgery, the double-lumen endotracheal tube is widely used for lung separation because of its ease of placement and the ability to quickly switch between single- and double-lung ventilation. Its correct position during single-lung ventilation can be verified by auscultation without the use of a fiberoptic bronchoscope, and if it is positioned correctly, its inadvertent dislocation is quite rare during surgical interventions. However, intubation and positioning may be difficult because the length and outer diameter of this type of tube are relatively large. Long-term artificial ventilation using such tubes is impractical.[4,5] In addition, tracheal intubation with a double-lumen tube may result in tracheal injury, as well as tracheitis, pharyngitis, and sometimes tracheal or bronchial rupture. According to the literature, the incidence of tracheal rupture due to intubation with a double-lumen tube is less than 1%.[2] This mainly occurs in the form of a longitudinal rupture of the membranous part of the trachea and left bronchus.[6]

The main risk factors for tracheal rupture are the inexperience of the specialist performing tracheal intubation with a double-lumen tube, repeated attempts at intubation, incorrect use of the stylet, excessively inflated cuff, incorrect choice of tube size, incorrect placement of the tube, sudden movements of the patient, severe cough, impaired structure of the membranous part of the trachea due to for steroid or radiation therapy, chronic obstructive pulmonary disease and tracheomalacia. In addition, risk factors include short stature, obesity, patient age over 50 years, and much more. In addition, tracheal injuries are more common in women.[7,8] The choice of 35Fr double lumen tube can be considered appropriate, due to the height and gender of the patient.[9]

Although tracheal rupture is a rare complication, it is a life-threatening condition. Mortality due to tracheal ruptures can reach, according to some authors, up to 40%.[10] Immediate detection and

adequate treatment are very important in such a situation. A high level of suspicion based on clinical manifestations is important in diagnosis.[2] If the rupture is caused by tracheal intubation, after the start of mechanical ventilation, clinical symptoms of subcutaneous emphysema, pneumomediastinum and pulmonary hemorrhage reveal quickly, and if the pleura is damaged, pneumothorax may develop. However, in this clinical case, clinical symptoms appeared 2 hours after the start of anesthesia and mechanical ventilation during the surgical phase, which may also be associated with damage to the membranous part of the trachea.

Fiberoptic bronchoscopy is one of the main methods for diagnosing tracheal rupture, with which it is possible to determine the depth and extent of the lesion, in addition, it is necessary in a treatment plan development for verifying complications after treatment, such as granulation or tracheal stenosis.[11] In our example, before clinical signs of tracheal damage appeared (subcutaneous emphysema, pneumothorax, pulmonary hemorrhage), the surgeon directly noticed the tracheal rupture itself, from which an air leak was observed. In addition, deterioration of gas exchange, increased leakage from the breathing circuit, decreased tidal volume, and decreased saturation during mechanical ventilation also indicated tracheal rupture.

Maintaining a patent airway during tracheal rupture repair requires safe ventilation and adequate surgical access. First of all, there should be no additional damage to the trachea by the tidal volume during inspiration. There are several methods of ventilation, including manual jet ventilation, high-frequency positive pressure ventilation, high-frequency jet ventilation, distal tracheal intubation, spontaneous breathing and cardiopulmonary bypass.[9,12,13] When suturing tracheal defects, the technique of placing the tube distal to the rupture is recommended. The tube is advanced distal to the rupture site with the cuff minimally inflated, which will not create pressure on the damaged tissue. At this time, a small air leak is acceptable.[1,14] However, in our case, because the rupture site was located directly above the bifurcation and extended to almost the entire trachea, we were concerned about additional damage that could occur when removing the double-lumen tube and reintubating the trachea with a single-lumen endotracheal tube and passing it distally. Thus, we came to the conclusion that it was necessary to deflate the tracheal cuff of the tube to provide surgical access and the ability to suture the damaged membranous part of the trachea without removing the tube. At this time, respiratory acidosis was observed due to air leakage, but vital signs, oxygenation, and end-tidal gas concentrations remained acceptable. It should be noted that anesthesia was maintained with the inhalational anesthetic sevoflurane. Since we did not use the bispectral index monitoring device during the operation, we could not check the depth of anesthesia using electroencephalography data, but we did not observe any signs of awakening during the operation.

Because the tracheal rupture was discovered during the thoracoscopic phase of the operation, we were able to visually record the level and extent of the injury. To check the tightness of the tracheal suture, we performed a hydrostatic test. No air leaks into the mediastinum were detected. Since the sutured trachea wrapped the endotracheal tube quite tightly, there was no air leakage into the oral cavity; therefore, we left the tracheal cuff of the tube in a deflated state.

After surgery for tracheal rupture, early extubation with spontaneous ventilation is recommended, as there is a possibility of damage to the tracheal mucosa due to movement of the endotracheal tube and cuff pressure. However, in many cases, prolonged mechanical ventilation is required after surgery[3] and patients remain intubated. Because this patient's respiratory acidosis progressed during surgery, we could not ignore the possibility of reintubation in the early postoperative period. In addition, we were concerned about re-rupture during emergency intubation in the intensive care unit, so we decided to perform prolonged ventilation through a double-lumen endotracheal tube with dynamic monitoring of the patient in the intensive care unit.

After stabilizing the patient's vital functions, taking into account the possibility of tracheal rupture in the larynx, the next day we replaced the endobronchial double-lumen tube with a laryngeal mask No. 4 and performed a fiberoptic bronchoscopic assessment. The laryngeal mask airway did not increase airway resistance and provided adequate ventilation. During fiberoptic bronchoscopic examination, the larynx and trachea were visually intact.[5,15] Subsequently, the laryngeal mask was also removed, while spontaneous breathing remained adequate.

Conclusion

Tracheal rupture after intubation with a double-lumen endobronchial tube is rare but a life-threatening complication. The clinical picture of tracheal rupture can appear after quite a long time. Timely and accurate diagnosis of this kind of complications with immediate restoration of the integrity of the trachea is necessary. If prolonged ventilation of the patient is necessary in the postoperative period, a laryngeal maskof the appropriate size can be used. Frequent and careful fibrobronchoscopy allows timely identification of additional injuries to the tracheobronchial tree and rehabilitation of the respiratory tract. Thanks to the timely and correct treatment tactics in this clinical situation, it was possible to avoid the development of further complications and fairly quick rehabilitation of the patient.

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Профессор Тоқсанбаевқа Ә. Т. 85 жас

Тоқсанбаев Әшім Тоқсанбайұлы, 1939 жылы қыркүйектің 12 жұлдызында Оңтүстік Қазақстан облысы, Шәуілдір ауданы, Көксарай ауылдық кеңесі, Ызакөл ұжымшарында дүниеге келген. Оңтүстік Қазақстан облысы, Киров ауданы, Жеңіс атындағы орта мектепті бітіргеннен кейін, Қазақ мемлекеттік медицина институтының емдеу факультетіне түсіп, оны 1964 жылы бітірді. Медициналық институтты бітіргеннен кейін Оңтүстік Қазақстан облысы, Шардара аудандық ауруханасында хирург-дәрігер болып жұмыс істеді. 1965 жылы ҚазОжРҒЗИ - кіші ғылыми қызметкері лауазымына конкурспен өтіп, онда Қазақстан Республикасының жетекші онкологтары мен радиологтарының жетекшілігімен, ғылыми-практикалық қызметпен айналыса бастады. Профессор М. Т. Таукенов пен доцент А. С. Ермоленконың жетекшілігімен, 1971 жылы "Қуық қатерлі ісігіндегі Уретероцистонеостомия" тақырыбында, кандидаттық диссертация қорғады.

1972 жылдан бастап 1973 жылдың сонына дейін, Алматы қаласының 2 қалалық клиникалық ауруханасының урологиялық бөлімшесінің меңгерушісі болып жұмыс істеді, сонымен қатар АММИ урология және оперативті нефрология кафедрасының ассистенті ретінде, жарты ставкадағы жұмысты қоса атқарды. 1974 жылдың қаңтарында АММИ урология және оперативті нефрология кафедрасының ассистенті болып сайланды, 1991 жылы конкурстың қортындысы бойынша доцент болды. 1999 жылы "Ятрогенді несеп-жыныс жыланкөзі" тақырыбында докторлық диссертация қорғады. 2004 жылдан бастап ҚазҰМУ урология және оперативті нефрология кафедрасының профессоры болып тағайындалды. Конкурстың нәтижесі бойынша 2008 жылдың қыркүйегінен бастап, С.Ж Асфендияров атындағы ҚазҰМУ урология және оперативті нефрология кафедрасының меңгерушісі атанды.

Урология мәселелері бойынша профессор Ә. Т. Токсанбаевтың перспективалық зерттеулерінсіз отандық операциялық урологияның заманауи жетістіктерін елестету қиын: онкоурологиялық ауруларды диагностикалау мен емдеудің заманауи мәселелері, сары фосфордың және оның бейорганикалық қосылыстарының жыныс жүйесіне әсері, әйелдердегі зәр шығару жүйесінің ятрогендік жарақаттарын диагностикалау және емдеу, шұғыл урология шартындағы қуық асты безінің қатерсіз гиперплазиясына байланысты жедел аденомэктомияны әзірлеу және енгізу. Қуық ісігінің пайда болу себебтері мен даму барысындағы құрылымын, сонымен қатар сары фосфордың еркектердің жыныс-жүйесіне әсерін зерртеулерінің мағынасы зор. Осы жұмыстарының нәтижелері бойынша төрт докторлық және сегіз кандидаттық диссертация қорғалды. Екі монографиясы «Несеп-жыныс жыланкөздері» 1988-жылы; «Әйелдердің несеп жүйесіннің ятрогенді жарақаттары» 2003 жылы, он бір оқу құралдары, жүз қырықтай ғылыми еңбектері баспа бетінде жарияланды. Өнертабыстары урологиядағы қалпына келтіру, қайта құрау оталарының өзекті сауалдарына арналған.

Профессор Тоқсанбаев Әшім Тоқсанбайұлы Қазақстан Республикасының уролог-хирургтар мектебі құрушыларының бірі болып саналады, ол тек елімізде ғана емес, одан тыс жерлерде де танымал. Профессор Ә. Т. Тоқсанбаевтың жетекшілігімен қазақ тілінде алғашқы диссертация жазылды (профессор Сенгирбаев Д.И.- 2002 ж.). Профессор Ә. Т. Тоқсанбаев қазақ тіліндегі "Урология" оқулығының авторларының бірегейі. Профессор Ә. Т. Тоқсанбаевтың дәрістері мен баяндамалары ғылыми практикалық медицинада қазақ тілінің сарқылмас мүмкіндіктерін айқын көрсетті.

Профессор Ә. Т. Тоқсанбаев Қазақстанда Акушерлік және гинекологиялық араласу кезінде ятрогендік несеп-жыныс жыланкөздерін, сондай-ақ зәр шығару жүйесінің өткір жарақаттарын емдеу тактикасын әзірлеудің негізін қалаушы. Хирург-уролог ретінде ол несеп-жыныс жүйе мүшелеріне

11000-нан астам операция жасады, соның ішінде: қайта құрау, қалпына келтіру оталарын жасады. Олар бүгінгі күні – даму және тәжірибеге жаңа технологияларды кеңінен енгізу дәуірінде өзекті болып табылады.

Әшім Тоқсанбайұлының, ғалым және педагог қабілеті хирургия және урология саласына үлкен үлес қосты, емдеудің, студенттерді оқытудың прогрессивті әдістерін енгізді және оқу-әдістемелік әзірлемелерді жетілдірді. Ерен қабілетінің арқасында оқу-әдістемелік құралдарды жыл сайын өмірдің талабына сай мазмұнын жетілдіріп тереңдетіп оқытудың арқасында, көптеген дәрігер-урологтар базалық және күрделі, терең білім алып, денсаулық сақтау саласында табысты еңбек етіп жүр. Көпжылдық дәрігерлік ұстаздық қызмет барысында оқушылар мен жас дәрігерлерге консервативті және оперативті урологияның негіздерін игеруге көмектесті, жас ассистенттерді ұстаздық шеберлікке тәрбиеледі. Қазіргі таңда шәкірттері еліміздің бетке ұстар азаматтары. Профессор Ә. Т. Тоқсанбаев берген нәрмен сусындап, сіңірген еңбегін ақтап жоғары оқу орындарында, ғылыми орталықтарда, клиникаларда жемісті еңбек етуде.

Көптеген жылдар бойы Урология ғылыми орталығы жанындағы кандидаттық және докторлық диссертацияларды қорғау жөніндегі диссертациялық кеңестің мүшесі, С.Д. Асфендияров атындағы ҚазҰМУ Ғылыми кеңесінің, Еуропалық урологтар қауымдастығының мүшесі, Қазақстан урологтары ғылыми қоғамының құрметті мүшесі. Ұзақ жылдар бойы ана мен бала денсаулығын қорғау республикалық ғылыми-зерттеу орталығының кеңесшісі болды.

Профессор Ә. Т. Тоқсанбаевтың жетекшілігімен 2009 жылы "онкоурологиялық ауруларды диагностикалау мен емдеудің заманауи мәселелері" атты «Халықаралық ғылыми-тәжірибелік конференция» өткізілді, конференция аясында отандWық (Б. У. Шалекенов, А. И. Ізбасаров, С. М. Құсымжанов) және шетелдік (А. З. Винаров, Н. А. Григорьев, М. А. Газимиев) профессорларының қатысуымен "Урологияға аз инвазивті эндоскопиялық араласулар" мастер-классын өткізді.

Профессор Ә. Т. Тоқсанбаевтың ҚазҰМУ урология және оперативті нефрология кафедрасының меңгерушісі болып жұмыс істеген кезеңінде, кафедра Қазақстан Республикасында ғана емес, ТМД елдерінде де өзінің ғылыми-зерттеу және оқу-әдістемелік жұмыстарымен танылды. Кафедра құрамына 18 маман кірді, оның ішінде 4 профессор, 2 ғылым докторы, 2 доцент және 10 ассистент.

Профессор Ә. Т. Тоқсанбаев асқақ талантымен, еңбекқорлығымен, қажырлы күш-жігерімен білім ғылым саласына бергені аз емес. Мамандыққа деген сүйіспеншілік арқылы өзіндей парасатты, рухы биік ізбасарларын (профессор Кусымжанов С.М., профессор Сенгирбаев Д.И.,[профессор Хамзин А.А]., м.ғ.д Жантелиева Л.А., аға ғылыми қызметкер м.ғ.к Еремьянц Г.А., медицина ғылымының кандидаты Байдувалиев А.М Түркістан облысының денсаулық сақтау департаментінің басшысы , ассистент м.ғ.к Перепелица В.В., ассистент м.ғ.к Нисанбаев А.Д., ассистент Испосунова Г.А. және т.б.) тәрбиеледі.

Көпжылдық дәрігерлік ұстаздық қызмет барысында шәкірттері мен ізбасарларына консервативті және жедел урологияның негіздерін игеруге көмектесті, жас ассистенттерді педагогикалық шеберлікке үйретті. Қазіргі уақытта профессордың оқушылары жоғарғы оқу орындарында, ғылыми-зерттеу орталықтарында және клиникаларда табысты жұмыс істеп жүр.

Профессор Тоқсанбаев Әшім Тоқсанбайұлының барлық жарқын және жан-жақты кәсіби қызметі ғылымның заманауи жетістіктерін практикалық урологияға енгізуге арналған. Керемет хирург, классикалық клиниканың барлық жақсы принциптерін және медициналық практикадағы заманауи ғылыми-техникалық прогресті керемет біріктірді. Урология және оперативті нефрология, урогинекология саласында танымал әрі беделді маман. Медицина әрқашан жоғары жауапкершілікті, тәртіпті және адалдықты білдіреді, сонымен қатар үлкен эмоционалды және физикалық күшті қажет етеді. Профессор Ә. Т. Тоқсанбаевтың өмірі медицинаға шабыт берген қызметтің жарқын үлгісі болып табылады. Әріптестерінің құрметтілігі, студенттері мен ізбасарларының арасындағы жоғары беделі профессордың кәсібилігі мен мамандыққа деген адалдығы үшін марапатына айналды. Ұстаздық даму сатысының кезеңдерін түгелдей өткен. Жалпы еңбек өтімі-53 жыл,ғылыми-ұстаздық өтімі-50 жыл, ұстаздық өтімі-43 жыл.

Медицина жұртшылығы профессор Ә. Т. Тоқсанбаевты көрнекті ғалым, талантты ұстаз және тамаша хирург ретінде біледі.

Құрметті Әшім Тоқсанбайұлы, 85 жасқа толуыңызға орай, зор денсаулық, бақыт,баянды ұзақ өмір тілейміз!

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