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Cardiac disorders in burn injury

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ABSTRACT

The presented review highlights the peculiarities of cardiovascular system damages in burn injury. The epidemiological data on the incidence of thermal injuries are reported. The pathogenic mechanisms of heart disorders during various periods of burn injury, as well as pathological changes in the myocardium are examined in detail. The main clinical manifestations of heart damage on the background of burn disease have been identified (heart failure, myocarditis, infectious endocarditis, cardiac arrhythmias and conduction disturbances, myocardial infarction). Special attention is paid to laboratory and instrumental methods for investigation of the heart with a discussion of the benefits and disadvantages of each method. The manuscript discusses the main therapeutic approaches for the management of burn patients with cardiac pathology, as well as the possibilities of using and the effectiveness of modern treatment methods aimed at improving survival, diminishing the severity of cardiovascular disorders and improving the prognosis of such patients.

Key words: thermic burns; burn injury, heart in burn trauma, heart failure; pathogenesis, pathomorphology, clinical picture; diagnosis, management.

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Поражение сердца при ожоговой болезни (обзор литературы)

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РЕЗЮМЕ

Обзор посвящен особенностям поражений сердечно-сосудистой системы при ожоговой болезни. Приведены эпидемиологические данные о распространенности термических поражений. Подробно рассмотрены патогенетические механизмы повреждения сердца в различные периоды ожоговой травмы, а также патоморфологические изменения миокарда. Выделены основные клинические проявления поражений сердца на фоне ожоговой болезни (сердечная недостаточность, миокардит, инфекционный эндокардит, нарушения ритма и проводимости сердца, инфаркт миокарда). Особое внимание уделено лабораторным и инструментальным методам исследования состояния сердца с обсуждением преимуществ и недостатков каждого метода. Рассмотрены основные терапевтические подходы ведения ожоговых больных с кардиальной патологией, а также возможности и эффективность использования современных методов лечения, направленных на улучшение выживаемости, выраженности сердечно-сосудистых нарушений и улучшение прогноза таких пациентов.

Ключевые слова: термические ожоги, ожоговая болезнь, сердце при ожоговой травме, сердечная недостаточность, патогенез, патоморфология, клиническая картина, диагностика, лечение.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Thermal damage is a serious medical, social and economic problem. It is related to the high frequency of burn injuries in everyday life, at work and during military conflicts, the complexity and duration of treatment of the patients, frequent disability and high mortality. According to the data, 11 million people worldwide sought medical care for burns in 2004. The risk of burns tends to increase with lower socioeconomic status, and up to 90% of burns occur in low- or middle-income countries. According to WHO, about 180 thousand cases of deaths caused by burns are registered annually worldwide [1]. In Ukraine, the overall incidence of thermal injuries is also quite high and accounts for 152 cases per 100 thousand inhabitants. In the Russian Federation, 251,480 burns were recorded in 2018, which is 171.2 cases per 100 thousand people [3].

With widespread and deep burns, a clinically pronounced generalized reaction of the body develops. It begins in the first hours after the injury and lasts not only the entire period of the wound existence, but also some time after the complete restoration of the skin covering. This complex set of interconnected pathophysiological changes and clinical manifestations that occurs in response to a burn injury is called a “burn disease” [4].

Thermal trauma is accompanied by a number of deviations and disorders in the activities of the body as a whole and, in particular, cardiac disorders. The diverse spectrum of morphological changes in the myocardium is observed in extensive burns. There are decrease in myocardial contraction, various rhythm and conduction disturbances, and development of heart failure (HF). Thus, according to some data, signs of myocarditis are revealed in 20–40% of cases, and signs of arrhythmia and heart block are seen in about 35% of cases of burn disease.

Heart damage in burn injury with underlying cardiovascular diseases can approach significant severity and not only be the cause of severe HF, but also the death of injured patients [5]. The initial presence of cardiopulmonary pathology in the burned patient increases the risk of developing myocardial infarction (MI) or death by more than 6 times. Nevertheless, despite the high occurrence of burns and common heart damage, special characteristics of cardiac pathology are poorly highlighted in the literature, and data on pathophysiological events, current diagnostic and treatment methods are revealed scantily.

PATHOPHYSIOLOGY

The burn disease has a complex multicomponent pathogenesis, the individual links of which become prevailing in different time periods after a burn injury. On the first day after injury, hypovolemia, hemodynamic shifts and disturbances of microcirculation develop. Then, severe intoxication occurs (the first 1–2 weeks) and later, infectious complications emerge. In this regard, four periods are distinguished during the burn disease: burn shock (first 3–5 days), acute burn toxemia (5–10 days), septicotoxemia (from 11 days to complete wound healing), and recovery.

In the first hours of the burn injury, even in the absence of massive shifts in the body's water spaces, the severity of the patient's condition is associated with pain syndrome and psycho-emotional stress, which serve as a trigger for the neuroendocrine response. The primary reaction occurs at the level of the spinal neural-reflex arcs with irritation of the sympathetic nervous system and the release of catecholamines into circulation, which leads to vasospasm, increased total peripheral vascular resistance, centralization of circulation, ultimately resulting in the occurrence of peripheral tissue hypoxia and acidosis.

These events are exacerbated by impairment of respiratory function (a decrease in the respiratory volume and vital capacity of lungs), which, in turn, leads to a decrease in blood oxygen saturation and tissue oxygenation, the accumulation of underoxidized metabolic products, and the development of respiratory and metabolic acidosis. Simultaneously, there is a short increase in the stroke and minute volume of the heart, an increase in blood pressure (BP), which subsequently drops as hypovolemia deteriorates.

An increase in blood coagulability, microthrombosis and alterations in microcirculation occur, which deteriorates tissue hypoxia and acidosis. In this setting, a paralytic expansion of capillaries emerges, and microcirculatory and electrolyte disturbances increase. Subsequently, pathological depolarization of the cell membranes of cardiomyocytes with alteration of their permeability develops.

Several hours post burn, a profound shock state develops due to the loss of preload as burn edema advances [6].

Immediately post burn, cardiac function is inhibited due to the pro-inflammatory effect of interleukin-1B and tumor necrosis factor-alpha (TNFα), which can be blocked by CD14 knockout or slowed down due to kappa B nuclear factor blockers [7]. In the 48 hours post burn, tachycardia develops with increasing cardiac output (CO) and myocardial inflammation occurs due to β-adrenergic influence [8]. The decrease in the right ventricular ejection fraction [9], observed after endotoxemia, can be mitigated by thromboxane blockade. Initially, after the increase in total vascular resistance in catabolic phase of systemic inflammation and sepsis, vasoplegia develops deteriorating cardiogenic and redistributive shock leading in turn to multi-organ failure.

It was established [10] that, in case of burn injury, acidosis causes the increase in the cytosolic calcium content in cardiomyocytes, the secretion of pro-inflammatory cytokines by these cells, and activation of the apoptosis and autophagy processes. Myocardial damage in a burn injury leads to an alteration of its contractility and the development of HF. Inflammatory cytokines (TNFα, interleukin-6) contribute to the development of diastolic dysfunction of the left ventricle (LV).

At the moment of thermal exposure to the skin, a huge number of cells are destroyed and damaged with the release of a bulk of various biologically active substances: inflammatory mediators (kinins, serotonin, histamine, acute phase proteins, complement factors, etc.). All of them have a vasoactive effect and significantly increase the permeability of the vascular wall. In burn patients, metabolic imbalance along with disorders of the endocrine, respiratory systems and psychoemotional status affect the cardiovascular system [11].

Another mechanism of myocardial damage in burn disease is the hyperproduction of reactive oxygen species and lipid radicals. An excess of free radicals causes cardiomyocyte membrane permeability disturbances, change in ionic homeostasis, damage to their genetic apparatus and activation of programmed mechanisms of cell death [12].

An imbalance in the acid-base state and the electrolyte content (in particular, hyper- or hypokalemia), specific to a burn disease, can lead to various disturbances in the cardiac conduction and heart rate, including life-threatening arrhythmias.

In conditions of tissue destruction caused by burns, proteins of the injured patient acquire the properties of autoantigens. In this case, antibodies produced by the patient's body interact with both pathologically altered and normal tissue components, cardiomyocytes, in particular. One of the mechanisms responsible for the development of autosensitization is the formation of tissue and microbial antigen associations, in which the microbial part acts as an adjuvant. All these pro-

cesses can lead to the development of burn myocarditis.

In the period of burn toxemia and septicotoxemia due to the initiation of the secondary bacterial infections, various cardiac infective complications are also possible. In this setting, myocarditis, pericarditis and infectious endocarditis (IE) may develop.

PATHOMORPHOLOGY

Morphological examinations also indicate heart damage in case of the burn disease. Those who died in the first days of the burn injury the section show signs of circulatory disorders, edema of the interstitial and perivascular tissue, foci of protein and fatty degeneration. During autopsy during the period of septicotoxemia in the burn disease, heart sizes were enlarged in the transverse direction, its walls became flabby, the cavities were extended and were filled with massive variegate blood clots. Histological examination of such myocardium revealed widespread dystrophic changes, especially pronounced in the LV wall, small damage areas and small-focal myocyte necrosis.

Pathological cardiac changes during septicotoxemia of the burn disease are characterized by widespread dystrophic lesions and edema of the interstitial and perivascular myocardial tissue. In persons of young and middle age, injuries of this nature occurred most often in the setting of sepsis. In older people with a previous heart disease, extensive dystrophic myocardial lesions were detected without generalization of the infection.

CLINICAL PICTURE

Heart failure (HF) plays a significant role in the clinical picture of heart damage in burn disease. In small lesions (up to 10% of the total body surface area (TBSA)), only moderate tachycardia and slight increase in BP can be observed in the injured. In more extensive and deeper burns (over 10–15% of TBSA) in the first period of the burn disease, dyspnea, palpitations and chest pain often occur. Acrocyanosis, tachycardia and diminishing of the first sound at the cardiac apex are clinically detected. BP rises slightly during the erectile phase of burn shock and decreases in the torpid phase. In some cases indicating an unfavorable prognosis, refractory arterial hypotension develops in the early stages after thermal injury. In patients with initial arterial hypertension, BP during shock usually drops to normal values and often remains at the same level throughout the subsequent period of the disease [4].

In toxemia phase injured may remain shortness of breath, palpitations and chest pain. Due to tachycardia, systolic murmur at the apex, the decrease in BP and expansion of the heart borders are often determined.

In the period of septicotoxemia, pericarditis and endocarditis often develop which may be one of the reasons for the development and progression of HF. In these cases, the fluid infusion in large volumes used in the treatment of burn injured can deteriorate their condition due to the significant increase in pre- and afterload.

Electrolyte imbalance (hyper- or hypokalemia), myocardial ischemia and MI, myocarditis or underlying cardiac pathology can cause various rhythm and conduction disturbances in burn injured patients. These changes can occur within 6–8 hours after the injury, therefore, the sooner the measures will be taken to prevent and compensate them, the greater is the likelihood of a favorable course of the burn disease and the lower incidence of its serious complications [4].

A relatively rare, but very severe complication of the burn disease is acute coronary syndrome, including the development of MI. Vasospastic forms of acute coronary insufficiency in burn disease are described, in the origin of which the release of endogenous nickel possessing a powerful vasoconstrictor effect is considered [13]. M. Caliskan et al. [14] have demonstrated that vasoconstriction of the coronary arteries and arterioles are caused by stress factors and increased activity of the sympathetic tone attributable to the burn injury. Moreover, the authors found that vasoconstriction causes a worsening of systolic and diastolic LV function, a decrease in the reserve of coronary blood velocity reflecting microvascular dysfunction in the absence of obstruction or narrowing of the coronary arteries lumen [14].

There are also descriptions of cases of the development of stress-induced cardiomyopathy (Takotsubo) with severe hemodynamic abnormalities in setting of the burn injury. Results of studies confirm the basic concept of post-traumatic heart damage as stress-induced cardiomyopathy and have demonstrated the potential importance of stress in accelerating fatal outcome in patients with injuries and thermal burns.

DIAGNOSIS

Laboratory tests. It is known that during the first 3–4 days in burn injured, there is most often an increase in potassium in blood, which can be the cause of the development of various cardiac rhythm and conduction disturbances including life-threatening ones.

Estimation of troponin levels is currently used as a standard biomarker for diagnostics MI and acute coronary syndrome [15, 16]. In case of the burn disease, an increase in blood levels of myocardial damage markers, such as cardiac troponins and creatine phosphokinase MB-fractions is observed. Moreover, the degree of their elevation reflects the severity of myocardial damage.

In this context, it should be noted that an increase in troponin levels occurs under the influence of a wide range of non-cardiac and cardiac factors, such as physical endurance training, sepsis and other serious diseases, including stroke, pulmonary embolism [17], pericarditis, myocarditis, Takotsubo syndrome [18], acute coronary syndrome, acute HF, tachyarrhythmias, etc. It is suggested that TNFα increases the permeability of the cell membrane under stress or inflammation and is considered a possible mechanism responsible for increasing troponin levels [15].

Due to the above mentioned non-cardiac causes, many authors have shown that troponin levels can be increased in burns of significant areas. The increase in troponin levels usually occurs in patients with burns affecting ≥15% of TBSA and during the first 72 hours after injury. In one study, no patients with burns <20% of TBSA showed the increase in troponin, despite matched age, weight, and gender characteristics with those whose burn area exceeded 20% of TBSA. Data from the prospective study that found correlation between elevated troponin T levels and regional abnormalities of LV wall movement in patients with the burn area > 20% of TBSA were presented. None of the patients with identified regional impairment of LV wall movement showed the normal level of cardiac troponin. It is noteworthy that in experimental studies and in burn injured, the decrease in the troponin level was revealed after surgical escharotomy (surgical excision of an eschar) [15].

The concentration of brain natriuretic peptide and its precursor (NT-proBNP) in blood plasma reflects the degree of hemodynamic load on the heart. There are suggestions that these indicators can be used to assess the prognosis of burned patients in extremely serious conditions. Thus, the level of NT-proBNP closely correlates with the size of the burn area, the degree of fluid retention, the severity of organ failure, and mortality rates. In addition, the determination of the level of brain natriuretic peptide in the blood serum is considered to be a simple and informative method for detecting HF in patients with severe burns during resuscitation procedures in the setting of shock.

Electrocardiography (ECG). On the ECG records, a decrease in voltage, sinus tachycardia, various rhythm disturbances (atrial fibrillation and atrial flutter, premature cardiac beats, supraventricular and ventricular tachycardia, ventricular fibrillation), conduction disturbances and pathological changes in the initial and final parts of the ventricular complex can be determined. There is often an increase in the QT dispersion with close correlation of this indicator with severity of the heart damage. Concerning the heart rate variability determined by 24-hour Holter ECG monitoring, it was found that abnormal heart rate variability during the immediate postburn period is strongly predictive of death [19, 20]. In burn injury, the inhibition of the wave structure of the heart rhythm and the total spectrum power indicators are observed [21]. S.Y. Joo et al. [20] revealed a sympathetic predominance during daytime and a decreased parasympathetic activity during nighttime in burn injured patients.

Transthoracic and transesophageal echocardiography (TEE) has important diagnostic value in severe patients, since it allows evaluate the myocardial structure and function, clarify causes of HF. According to the results of a systematic review regarding the importance of using TEE in 128 burn patients, the main pathological findings were deterioration of systolic and diastolic LV function, detection of vegetation on the heart valves, pulmonary hypertension, pericardial effusion and right ventricular HF. The advantages of TEE over transthoracic echocardiography are the possibility of a more accurate assessment of valve function, myocardial contractility and, perhaps most important, monitoring the adequacy of acute hemodynamic recovery and preload in the acute phase of resuscitation. TEE is especially informative in assessing the structure of heart valves to confirm or exclude IE and its complications, due to the proximity of the location of the high-frequency ultrasonic transducer to the heart. Given the susceptibility of burn injured to local and general infectious complications, IE can develop in any patient, regardless of the burn area. Nevertheless, thorough discussion of the indications for TEE is necessary considering the relative invasiveness of the method, the frequent thermal damage to the oral cavity and pharynx, the infrequent but existing probability of rupture of the esophagus and the risk of bacteremia.

Coronary angiography is used in patients with a clinical picture of acute coronary syndrome or acute myocardial infarction, which, as already noted, can develop against a background of the burn injury.

MANAGEMENT

In addition to the appropriate treatment of burn wounds during a shock period, the burn disease treatment includes the management of pain and patient exaltation, hypovolemia amelioration, replacement of the circulating blood volume, hemodynamic stabilization, metabolic disorders correction and infection control [22].

Procedural pain complicates the patient management and leads to the use of aggressive methods to combat it such as administration of potent opioids, ketamine, and regional or general anesthesia. Unfortunately, high doses of opioids are associated with several serious adverse effects such as depressed consciousness and the risk of developing delirium, hypotension, respiratory depression and not infrequently obstipation. Therefore, there is an obvious need to reduce the number of doses of opioid administrating throughout treatment, and at the same time to provide a tolerable level of pain [23].

It was shown that intravenous infusion of lidocaine starting with a bolus dose (1 mg/kg) and then in the form of a continuous infusion (180 mg/hour) is not accompanied by adverse effects and had a 25% opioid sparing effect [23].

Given massive volumes of solution transfusions during this period, it is recommended to provide inotropic myocardial support with dopamine at a dose of 5–10 mg/kg/min. At this dosage dopamine improves myocardial contractility and increases CO. When signs of congestive HF appear, the volume of infusion therapy should be reduced and diuretics should be administered.

Detoxification, the infection control and the correction of homeostasis are the main targets in the treatment of burn toxemia [22]. It is necessary to conduct timely and adequate correction of the acid-base state and electrolyte imbalance emerging in patients with severe burn injury. With the development of life-threatening disorders of cardiac rhythm and conduction (ventricular fibrillation, ventricular tachycardia, asystole, electromechanical dissociation, some forms of supraventricular tachycardia), active antiarrhythmic therapy is indicated and emergency resuscitation measures are fulfilled.

Non-emergency antiarrhythmic therapy is prescribed in cases where arrhythmia or heart block do not influence significantly a patient's condition. Therefore, in sinus tachycardia, β-blockers (propranolol, bisoprolol) or calcium antagonists (verapamil, diltiazem) are usually used.

For the treatment of hemodynamically relevant sinus bradycardia, atropine (0.5–2.0 mg), isoprenaline (2–20 μg/min by intravenous administration) or pacing are applied.

Extrasystoles usually do not require active antiarrhythmic therapy, since the prognosis for this form of arrhythmia depends entirely on the basic underlying process and the degree of structural damage of the heart. Class II and III of antiarrhythmic drugs, omacor are used to terminate extrasystoles of high grades (coupled, salvos, early) that cause hemodynamic disturbances in people with severe cardiac pathology (MI, myocarditis, severe LV dysfunction).

With the aim to terminate atrial fibrillation (AF) or flutter, electric cardioversion (ECV) or antiarrhythmic drugs (propafenone, procainamide, amiodarone or sotalol) are administered. If it is impossible to terminate AF, digoxin, verapamil or β-blockers are used to control the ventricular rate. Due to the high risk of thromboembolic complications, the treatment by anticoagulants is considered.

Paroxysms of atrioventricular tachycardia are stopped by vagal tests, intravenous infusion of adenosine triphosphate (10–30 mg), adenosine (6–12 mg) or verapamil. Transesophageal pacing and ECV are also effective. Radiofrequency catheter ablation is considered as a radical way to treat this arrhythmia.

The most effective treatment for acute coronary syndrome and MI is an urgent percutaneous coronary intervention with the maximally rapid restoration of coronary blood flow.

In recent years, the effectiveness of various approaches to the prevention of myocardial damage and dysfunction arising from burns has been actively studied. The possibility of using angiotensin-converting enzyme inhibitors, drugs that modulate ion channels, anti-inflammatory agents, antioxidants, metabolic drugs and cardioprotectors, has been considered for this purpose.

The issue of prescribing propranolol to adult patients who suffered thermal injury is being actively debated in order to reduce the hypermetabolic response [24–27]. Propranolol is being successfully used to block the effects of endogenous catecholamines which are involved as the first mediators of the hypermetabolic response. In the first stages of the burn injury, the level of catecholamines in the blood is increased by 10 times. The hyperdynamic type of circulation, an increase in the level of basal metabolism and the catabolism of skeletal muscle proteins taken together produce distinctly negative effect on the patient's

organism. The effects of propranolol in the burn patient include a decrease in thermogenesis, terminating or slowing down tachycardia, a decrease in CO and energy consumption at rest. The dosage used is individual for each patient, however, a reduction in heart rate by 20% causes a decrease in heart load and fatty infiltration (secondarily to a decrease in peripheral lipolysis). It has been shown that propranolol enhances the intracellular circulation of amino acids, which leads to a decrease in atrophy of muscle tissue, thereby increasing muscle mass. Carvedilol may have additional advantages due to its ability to block α-adrenergic receptors and remove free radicals [6].

The use of ozone therapy is scientifically grounded for the treatment of thermal lesions. Medical ozone has bactericidal and analgesic effects. It improves microcirculation, normalizes immunity and the oxidative-antioxidant state of blood and cells. There is the evidence that, during ozone therapy of patients with severe thermal injuries, the functional activity of the myocardium and CO increase. Moreover, an antiarrhythmic effect is observed, myocardial ischemia decreases (with an improvement in the processes of myocardial repolarization on the ECG), hemodynamic parameters improve.

A number of studies have shown that early surgical intervention (necrotomy, necrectomy, dermabrasion with xenoplasty, autodermoplasty), optimization of the wound process using a culture of fetal human embryonic fibroblasts, stem cells [28, 29], adequate transfusion and antibacterial therapy can reduce complications of the burn disease and decrease mortality.

The beneficial effect of listening to music on the course of a burn disease is shown. Thus, according to a meta-analysis [30], which covered 17 randomized controlled trials and 804 patients with burn injury, listening to music helped alleviate pain, decrease in anxiety and reduce heart rate.

PROGNOSIS

Although the most obvious consequences of thermal injury are associated with damage of the skin, systemic reactions that occur during burn disease affect many organs and tissues, including the heart, often causing an unfavorable outcome at the onset of the disease and having a negative effect in the long term. Therefore, according to data provided by J.M. Duke et al. [31] who compared individuals without a history of burns, patients with burn injuries over the age of 45 years were 1.46 times more often (95% confidence interval (CI): 1.36–1.56) and almost 3 times longer (95% CI: 2.60–3.25) were hospitalized due to pathology of the cardiovascular system. Patients with a history of burns were more often hospitalized for coronary heart disease (1.21, 95% CI: 1.07–1.36), HF (2.29, 95% CI: 1.85–2.82), cerebrovascular pathology (1.57, 95% CI: 1.33–1.84), and had higher mortality rates from cardiovascular diseases (1.11, 95% CI: 1.02–1.20). Similar data were obtained among pediatric patients under the age of 15 years who suffered from thermal trauma [32]. According to L. Knowlin et al. [5] derangements in cardiac function can last for two years in pediatric patients post burn.

CONCLUSION

In summary, it should be emphasized that timely diagnosis of heart damage in burn disease, treatment and prevention of its occurrence, including correction of electrolyte disorders, adequate antibiotic therapy, and the use of cardiovascular drugs can improve the quality of treatment and reduce the mortality of such patients.

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