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CURRENT TOPIC

Gunshot Wound: Pathogenesis

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Abstract

Gunshot wounds remain one of the most complex types of combat injuries. A gunshot wound is a dynamic system in which the initial mechanical destruction of tissue is only the starting point of a complex and multi-level process. Subsequently, the wound site steadily transforms and the volume of non-viable tissue increases, spreading beyond the wound channel area. This review examines the pathogenesis of a gunshot wound, which is a chain of cause-and-effect changes in which each link is formed as a direct consequence of previous disturbances. The pathophysiological events that contribute to the chronic wound process are identified, which cannot be interrupted by natural mechanisms.

Key words: Wound, gunshot; Injuries; Molecular-cellular damage; Inflammation, chronic; Dysfunction, endothelium; Blood coagulation disorders; Perfusion, tissues; Microthrombosis.

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Introduction

Gunshot wounds remain one of the most complex types of combat trauma, as their pathogenesis combines mechanical tissue destruction, a barotraumatic component of damage caused by pressure fluctuations in the temporal pulsating cavity and a cascade of subsequent pathophysiological reactions.[1, 2] The high kinetic energy of the projectile forms a zone of primary necrosis surrounded by an extensive zone of molecular-cellular damage, where processes of coagulation necrosis, ischaemia, reperfusion stress and early uncontrolled inflammation are triggered.[3] These events "grow" out of a biologically expedient ancient universal algorithm: localisation/minimisation of damage, elimination of necrotic tissue, prevention of the spread of infection and initiation of regeneration. However, in the case of gunshot wounds, they quickly exceed the limits of adaptation and acquire significant damaging potential. This is why a gunshot wound is always a dynamic system in which the initial mechanical destruction of tissue is only the starting point of a complex, multi-level process. Over the following period, the wound site steadily transforms and the volume of non-viable tissue increases, spreading beyond the wound channel area.

Thus, the relevance of the problem is determined not only by the frequency of gunshot wounds in modern armed conflicts but also by their unique pathophysiological nature, which requires pathogenetically verified and standardised treatment approaches.

Pathophysiology of gunshot wounds

I. Moment of injury (seconds to minutes)

The kinetic energy of an injurious projectile causes direct rupture of capillaries and the precapillary network, resulting in massive local blood loss and haematoma formation in the cavitation zone.[1, 2] Simultaneous destruction of cell membranes leads to the rapid release of intracellular components, collectively referred to as damage-associated molecular patterns (DAMPs),[3] which normally do not come into contact with immunocompetent cells. The key ones are:

1. Mitochondrial DNA (mtDNA) is perceived by the immune system as a foreign molecular pattern, since mitochondria are evolutionarily fixed endosymbionts of bacterial origin and, as a result, have a nucleotide sequence in nucleic acids or an amino acid sequence in polypeptides similar to that of bacteria.[4] Once in the extracellular space, it binds to toll-like receptor 9 (TLR9), which is expressed by dendritic cells, B lymphocytes, monocytes/macrophages and neutrophils, leading to the production of type I interferons and proinflammatory cytokines, including tumour necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-1β, IL-12, interferon-α (IFN-α) and IFN-β.[4] Thus, mtDNA functions as an endogenous alarm signal marking tissue damage. In experiments and clinical settings, circulating mtDNA levels correlate with the severity of trauma and the risk of developing a systemic inflammatory response.[5, 6]
2. High-mobility group box-1 (HMGb1) is a nuclear non-histone protein that, in the event of necrosis or mechanical damage, is released into the extracellular space and becomes an alternative danger signal. It binds to toll-like receptors (TLR) on innate immune cells, TLR2/4 and receptor for advanced glycation end products (RAGE), enhancing the production of pro-inflammatory cytokines (IL-1β, TNF-α) and recruiting immune cells to the site of damage,[7] which collectively contribute to the development and persistence of inflammation.
3. Formyl peptides (FP) are short peptides with N-formylated methionine, typical for bacteria, which are also released from mitochondria and damaged cells. They are recognised by the FPR1/FPR2 receptor of neutrophils, monocytes and macrophages. Their binding triggers rapid chemotaxis, activation of oxidative burst and degranulation of neutrophils.[8] Formyl peptides are thus among the most potent chemoattractants.
4. Histones are nuclear proteins that package DNA into nucleosomes, regulate chromatin conformation and control the transcriptional activity of the genome. Once in the extracellular space, they act as DAMPs, activating TLR2 and TLR4 receptors in immune cells, which stimulates the production of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-8 and enhances haemocoagulation.[9]
5. Adenosine triphosphate (ATP) – extracellular ATP acts as a danger signal in the event of cell damage or necrosis. It binds to P2X7 purinergic receptors on macrophages, dendritic cells and neutrophils, activating the NLRP3 inflammasome. This leads to the release of pro-inflammatory cytokines, including IL-1β, IL-18 and TNF-α and the recruitment of immune cells to the site of damage,[10] thereby intensifying the local inflammatory response. Extracellular ATP serves as a marker of cellular damage.

   Events initiated by DAMPs are biologically expedient, as they act as “alarm molecules”, allowing the immune system to instantly detect damaged cells and mobilise local and systemic defence mechanisms, which is necessary to prevent the spread of microorganisms, ensure rapid haemostasis and attract innate immune cells to the site of damage.[3, 11]

However, these mechanisms can transform from an adaptive response into a factor of systemic damage. Gunshot wounds create conditions for a massive release of DAMPs, exceeding the physiological range by tens of times, accompanied by excessive stimulation of TLRs of innate immune cells, complement activation, systemic endothelial dysfunction and the development of uncontrolled inflammation, which can progress to a systemic inflammatory response (SIRS),[6, 12] triggering the development of multiple organ failure. Pathogen-associated molecular patterns (PAMPs) perform a similar role, activating the same signalling pathways of the innate immune system. This dual signalling (DAMPs + PAMPs) leads to synergistic amplification of the inflammatory response, accelerated complement activation and increased risk of sepsis.[13, 14] This explains the clinical frequency of infection and the

need for early, adequate primary surgical treatment and antimicrobial therapy.

II. Early period (minutes to first hours)

Endothelial activation

Almost simultaneously with the release of DAMPs, proinflammatory cytokines IL-1β, TNF-α and IL-6 activate microvascular endothelial cells, initiating shedding of the glycocalyx – a thin polysaccharide-protein coating on the surface of endothelial cells that plays a key role in regulating permeability, coagulation and leukocyte adhesion.[15]

Reactive oxygen species

The activation of NADPH oxidase in endothelial cells and recruited neutrophils leads to the formation of reactive oxygen species (ROS). ROS convert mechanical damage into an inflammatory signal, as they are secondary messengers in inflammatory signalling pathways.[16] ROS also has a bactericidal effect by destroying membrane lipids, oxidising proteins and fragmenting DNA. This causes tissue toxicity in the macroorganism, contributing to an exponential increase in DAMPs, which triggers a secondary cascade of damage and inflammasome activation.

Inflammasome

The inflammasome is a cytosolic multi-subunit protein complex formed in innate immune cells in response to the detection of PAMPs and DAMPs.[17] Its key function is to activate caspase-1, which ensures the proteolytic maturation of pro-IL-1β and pro-IL-18 to their biologically active forms in the cytosol of activated phagocytes and subsequently initiates their pyroptosis – an inflammatory form of programmed cell death, resulting in the rapid release of IL-1β/IL-18, expulsion of granule contents, release of DAMPs (of phagocytic origin), which enhances the local inflammatory response.[17, 18] The effects of inflammasome activation in a gunshot wound are:

- hyperinflammation (IL-1β, IL-18);
- pyroptosis of macrophages and monocytes, causing increased necrosis;
- endothelial dysfunction and increased its procoagulant activity;
- local thrombosis and microcirculation disorders;
- worsening of coagulopathy and transition of local inflammation to systemic inflammation.[17, 18]

The above effects potentiate necrobiotic changes in tissues. Therefore, an inflammatory reaction is inevitable even with a “sterile” gunshot wound. Thus, it is ROS that explains why the morphology of a gunshot wound is dynamic over time.[16]

ROS enables the modification of the inflammatory profile by altering the chemical structure of danger signals. For example, HMGb1 loses its pro-inflammatory activity when fully oxidised, but when partially oxidised, it enhances it.[7]

Activated leukocytes and endothelial cells secrete metalloproteinases and serine proteases, thereby enhancing glycocalyx degradation. The release of glycocalyx components (syndecan-1, heparan sulphate, hyaluronate) occurs under the action of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), ROS and proteases, which increases vascular permeability, leads to interstitial oedema and loss of the physiological barrier between blood and tissue, as well as loss of the anti-adhesive and anticoagulant barrier properties of the endothelium. This phenomenon is observed in haemorrhagic shock, with the extent of glycocalyx shedding correlating with shock severity and outcome.[15] In addition, endothelial activation increases the expression of adhesion molecules (P-selectin, E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1)), which promotes the adhesion of neutrophils and monocytes.[19] During endothelial activation or damage (eg under the influence of IL-1β, TNF-α, ROS), von Willebrand factor (vWF) is released from Weibel–Palade bodies into the bloodstream. The released vWF promotes platelet adhesion to the subendothelium and their aggregation.[20] Thus, vWF is the link between endothelial activation and local thrombus formation in response to injury or inflammation. Together, these processes lead to regional disturbances in capillary blood flow (erythrocyte sludge, stasis and perfusion deficit) even when arterial pressure remains normal. Microthrombosis and endothelial dysfunction are important mechanisms in the transition from local damage to a systemic coagulopathic state.[20, 21]

Microthrombosis

The destruction of the endothelial glycocalyx in the first hours after trauma is biologically justified by the need to increase vascular permeability, facilitate the migration of leukocytes and plasma proteins to the site of injury and provide immune system cells with access to the wound

site. This is the basis of a rapid local immune response. Microthrombosis is one of the early responses of the innate immune system to local damage. In conditions of acute inflammation, it performs a clearly programmed, biologically appropriate function as a limiter.[21] Microthrombosis mechanically blocks the exit of microbes into the systemic bloodstream and retains cytokines within the focus, preventing them from causing a systemic inflammatory response. In gunshot wounds, the extent and rate of destruction of the glycocalyx are incomparably higher than physiological norms. As a result, interstitial oedema develops, microcirculation deteriorates, ischaemia intensifies and microthrombosis forms, leading to secondary tissue necrosis, which further exacerbates the inflammatory response.[21]

Complement/NETs

Complement activation is one of the most pathogenetically significant reactions in gunshot wounds. The classical (activated by DAMPs), alternative (initiated by endothelial damage and exposure of the subendothelium) and lectin (initiated by DAMPs and the entry of blood cells into the interstitium) pathways are activated simultaneously. Immune complexes, damaged endothelium and bacterial structures cause an immediate increase in C3a and C5a.[22] Their biological purpose is to eliminate microorganisms, opsonise necrotic masses and recruit neutrophils. However, C5a-mediated hyperactivation of neutrophils causes degranulation, release of proteases and formation of neutrophil extracellular traps (NETs), leading to further destruction of the endothelium, microcirculation disorders and microthrombosis.[23] At the same time, the membrane attack complex (MAC, C5b-9), which is necessary for fighting bacteria, contributes to the lysis of endothelial cells and the deterioration of the blood vessel barrier function.[22] Thus, the vicious circle closes at yet another level, transforming the key antibacterial mechanism into one of the mechanisms of secondary tissue damage.

III. Reperfusion period (hours – first day)

Reperfusion stress

When blood flow is restored, damaged tissues are subjected to reperfusion stress. Reperfusion is an adaptive process designed to eliminate oxygen debt. The fact is that the resumption of oxygen delivery to near-normal levels against a background of mitochondrial dysfunction following previous ischaemia causes a rapid synthesis of ROS.[24] ROS, together with activated neutrophils, trigger further damage to the endothelium.

Neutrophils/NETs

This process is carried out by NETs, which are a special form of antimicrobial activity of granulocytes based on controlled disintegration of the nucleus, unravelling of chromatin and its release into the external environment in the form of a fibrillar deoxyribonucleoprotein matrix saturated with enzymes of primary granules, which promotes the fixation of pathogens, but at the same time enhances hemocoagulation potential and endothelial damage, progression of ischaemia and necrobiotic changes.[23]

Apoptosis vs necrosis

Cell death at this stage follows two parallel pathways: apoptosis, which is controlled cell death aimed at removing irreversibly damaged cells without massive inflammation and necrosis, which is cell disintegration with the release of DAMPs. Apoptosis, as a regulated form of cell death, is biologically beneficial in the early phase of trauma. It allows damaged cells to be disposed of without their contents escaping into the intercellular space, limits inflammation and prevents the formation of chronic infectious-necrotic foci.[25]

Necrosis, on the contrary, is accompanied by membrane rupture and the release of large amounts of DAMPs, leading to prolongation/escalation/generalisation of inflammation.[26]

Clinical implications

In gunshot wounds, these two processes are in a reciprocal relationship: kinetic energy and cavitation cause instantaneous massive necrosis, while local hypoxia, reperfusion stress and ROS suppress apoptotic pathways, forcing cells to undergo necrotic death. Under conditions of oxygen deficiency, caspase activity decreases and apoptosis is "cancelled", making necrosis the dominant pattern of damage,[26] which lies at the root of secondary necrosis, necessitating repeated surgical procedures.

IV. Subacute period (1–7 days)

The subacute period is characterised by a transition from early inflammatory response to repair,

but in gunshot wounds, this transition is disrupted due to massive necrosis, microbial contamination and persistent local hypoperfusion. During this period, three key pathological processes develop: immune modulation, biofilm formation and coagulopathy.

Immune modulation

Immune modulation is a change in the phenotype of innate immune effector cells, particularly macrophages. Normally, there is a transition from the M1 phenotype (producers of TNF-α, IL-1β, IL-6) to the M2 phenotype (producers of transforming growth factor beta (TGF-β), IL-10, vascular endothelial growth factor (VEGF)), which is necessary for the transition from inflammation to proliferation during the wound healing process.[27] In gunshot wounds, against the backdrop of a constant influx of DAMPs due to secondary necrosis, hypoxia, local acidosis and microbial PAMPs, the M1 phenotype remains dominant, which ultimately prolongs inflammation, proteolysis and destruction of the extracellular matrix.[28] It should be added that, due to the above-mentioned characteristics of gunshot wounds, the process of neutrophil elimination through efferocytosis is blocked, leading to the accumulation of NETs,[23] which induce microvascular thrombosis through the activation of coagulation factor XII. As a result, tissue ischaemia intensifies, creating pathophysiological conditions for the development of secondary necrosis.[23] In addition, continuous complement (C3a, C5a) activation persists, leading to secondary tissue destruction.[22] C5a is the most dangerous in the context of secondary tissue destruction.[29]

Biofilm formation

Persistent necrosis and infection contribute to the formation of biofilms. These are complex, structurally organised microbial communities encapsulated in a self-produced extracellular matrix consisting of polysaccharides, proteins and nucleic acids, which protects bacteria from phagocytosis, complement activity and NETs and also significantly reduces the penetration of antibiotics, forming resistance even in initially sensitive strains.[30] It is noteworthy that microorganisms within the biofilm function as a quasi-multicellular system with pronounced functional differentiation, that is, surface cells actively divide, interact with the immune system and antibiotics, deep cells transition to a state of low metabolic activity and cells at the base form a dense matrix and participate in attachment.[30] Thanks to the biofilm matrix, stable gradients of oxygen and substrates are created, which form different ecological niches within a single structure (similar to a multicellular organism): on the outside, there is plenty of oxygen, nutrients and antibiotics; deep inside, there is hypoxia, accumulation of acidic products and low metabolism.[30] In addition, thanks to the coordination of behaviour through signalling mechanisms, biofilm bacteria are capable of synchronously switching gene expression, regulating biofilm density, modifying virulence and cooperatively resisting immune attacks.[31] In the context of wound infection, biofilms form predominantly in areas of persistent necrosis, which serve as a substrate for bacterial adhesion and subsequent colonisation.[32] This process initiates chronic infection and recurrent low-intensity inflammation, degradation of the endothelial glycocalyx and increased vascular permeability, blocking of the proliferation phase and delayed maturation of granulation tissue.[33, 34] This highlights the need for aggressive surgical control of the lesion and adjuvant antimicrobial therapy.

Coagulopathy

Coagulopathy during this period is associated with the destruction of the glycocalyx. The release of syndecan-1 and heparan sulphate, combined with an excess of DAMPs, especially extracellular histones and HMGB, leads to the activation of factor XII, platelets and the formation of multiple microthrombi in the capillaries.[9, 21] The presence of NETs enhances these processes, as NET-associated DNA and histones act as attractants for fibrin and platelets.[23] Fibrinogen is capable of adsorbing onto DNA strands through electrostatic interactions. The overall mechanism of NETs' effect on hemocoagulation can be represented as follows:

- Neutrophils release NETs (DNA + histones);
- DNA adsorbs fibrinogen and retains it in the wound;
- Thrombin converts fibrinogen into fibrin directly on DNA strands;
- Histones activate platelets and enhance their adhesion to NETs;
- A DNA–histone–platelet–fibrin complex is formed, typical of immunothrombosis;
- A dense, lysis-resistant clot is formed.

Microthrombosis leads to increased ischaemia and secondary necrosis, increasing the depth of tissue damage.[21, 23] All of the above are characteristic of local microcirculatory coagulopathy.

Massive tissue damage activates the mechanism of trauma-induced coagulopathy, which is an early post-traumatic dysfunction of haemostasis, as an integral result of the interaction of tissue damage, perfusion insufficiency, endothelial dysfunction and modification of the fibrinolytic system.[35] The modern concept of key links in pathogenesis, their sequence and mutual connections are presented as follows:

1. Initiating factors and early dynamics of haemostasis

Normally, the endothelium completely isolates tissue factor (TF; also known as factor III, thromboplastin, or CD142) from the bloodstream. As long as the vessel remains intact, TF is not accessible to blood and coagulation is not activated. Massive tissue destruction leads to exposure of TF, its contact with circulating coagulation factors FVII/FVIIa and the formation of the TF–VIIa complex, which initiates increased thrombin generation, which in turn causes the formation of a fibrin matrix at the site of injury[36] through the formation of fibrin monomers, which then spontaneously polymerise. In persistent hypoperfusion, compensatory-adaptive mechanisms (activation of the sympathetic-adrenal system) and pathophysiological reactions (cell hypoxia, acidosis, increased lactate concentration, ischemic endothelial damage) alter the endothelial phenotype by increasing the expression of thrombomodulin, adhesion molecules (ICAM-1, VCAM-1, P-selectin), tissue plasminogen activator (tPA), protease-activated receptors (PAR) and inflammatory mediators.[37] This leads to a rapid transformation of the endothelial surface from anticoagulant to procoagulant-activated. First, this occurs at the site of injury (TF exposure, local thrombin generation, local fibrin formation) and in the case of prolongation, the transformation becomes systemic. That is, the coagulation cascade is activated systemically, plasma factors (V, VIII, fibrinogen) are depleted, thrombin synthesis initially increases, then decreases due to consumption and activation of protein C, fibrinolysis becomes uncontrolled (hyper- or hypo-fibrinolysis), microthrombosis is combined with bleeding, which clinically manifests as consumption coagulopathy.[35, 37]

2. The role of the endothelium and glycocalyx

The endothelium and its glycocalyx are central regulators of the balance between procoagulant and anticoagulant potentials. During shock and ischaemia, the glycocalyx degrades and the expression of thrombomodulin, adhesive molecules and receptors increases, accompanied by a loss of the barrier and anticoagulant properties of the vascular surface.[15] Degradation of the glycocalyx contributes to the release of syndecan-1 and other markers of endotheliopathy into the serum, correlating with the severity of coagulopathy and outcome.[15] Thus, endotheliopathy integrates local tissue trauma with generalised dysfunction in the haemostasis system.

3. Activation of protein C

As a result of the conjugation of thrombin with thrombomodulin on the surface of the endothelium, protein C is activated, which has two key effects: it inactivates factors Va and VIIIa and reduces thrombin generation. The biological rationale for this event is to prevent the spread of thrombin beyond the site of injury, which is a local antithrombotic protection that prevents systemic coagulation.[38]

In cases of massive trauma and shock, the situation changes dramatically. Excessive activation of protein C contributes to the excessive expression of thrombomodulin in the endothelium. Thus, thrombin switches from a procoagulant to an anticoagulant vector, resulting in abnormally high levels of activated protein C, which leads to the accelerated inactivation of Va and VIIIa, suppression of thrombinogenesis, insufficient fibrin formation and the inability to form a stable fibrin clot, ultimately leading to the formation of consumption coagulopathy.[39] Thus, in the absence of coagulation factors, activated protein C becomes a factor of decompensation.

4. Phenotypes of fibrinolysis

The key determinant of clinical variability in trauma-induced coagulopathy is the state of fibrinolysis. Severe trauma, accompanied by hypoperfusion, activation of the sympathetic-adrenal system, excessive expression of proinflammatory mediators and endothelial activation, induces the release of tPA into the systemic circulation, resulting in accelerated fibrin degradation and the development of hyperfibrinolysis.[40] In addition, elevated tPA levels cause excessive activation of plasmin, which is responsible for fibrin degradation, fibrinogen destruction, destabilisation of early thrombus, cleavage of coagulation factors (V, VIII, XIII, prothrombin), weakening of platelet aggregation and increased endothelial permea-

bility. The clinical equivalent of these events is bleeding that is resistant to conventional haemostatic treatment.[40]

An opposing variant of fibrinolysis has been described, in which the plasminogen activator inhibitor-1 (PAI-1), the primary physiological inhibitor of tPA, suppresses the conversion of plasminogen to plasmin, resulting in the inhibition of fibrinolysis and an increased risk of microthrombosis and organ dysfunction.[40]

Thus, in severe trauma, two opposing phenotypes of fibrinolysis are possible: hyperfibrinolysis (tPA-dominant) and fibrinolytic blockade (PAI-1-dominant). A key clinical goal is to identify the type of fibrinolytic response early on, as the choice of treatment depends on which fibrinolysis phenotype is dominant in the patient.

5. Microcirculatory disorders

Microcirculatory disorders include stasis, aggregation of erythrocytes and platelets, adhesion of leukocytes and sequestration of plasma in the interstitium due to increased endothelial permeability.[41] These processes exacerbate local thrombosis, impair regional perfusion and promote the spread of DAMP signals that sustain systemic inflammation and secondary coagulation activation.[41, 42] NETs and complement activation further modulate coagulation and endothelial dysfunction.[22, 23]

6. Integration: positive feedback loops

A combination of key pathophysiological processes (tissue factor exposure and enhanced thrombogenesis, protein C activation, fibrinolytic imbalance, endothelial dysfunction and microcirculatory disorders) forms several mutually reinforcing positive feedback loops.[39] These mechanisms lead to rapid progression of haemostasis disorders and a decrease in their regulatory stability. The presence of such feedback loops leads to a high probability of irreversible coagulation decompensation and subsequent exacerbation of multiple organ dysfunction, even with minimal delay in diagnosis and pathogenetically oriented intervention.[35, 43] Gunshot wounds typically involve a combination of local thrombosis and systemic hypocoagulation, leading to prolonged bleeding, impaired tissue oxygenation and delayed granulation tissue formation.[43]

V. Late stage of the wound healing process (> 7 days)

Persistent necrosis

This period in gunshot wounds is characterised by a transition to the remodelling phase, which becomes impossible due to persistent necrotic changes, foreign bodies and microbial contamination. The persistence of necrobiotic changes provides a constant source of DAMPs and PAMPs, which maintain local proinflammatory activity, preventing the transition to inflammation resolution and repair.[3, 44]

The destruction of the endothelial glycocalyx and the release of its fragments are accompanied by the loss of anticoagulant and barrier properties of the vascular surface, activation of platelet adhesion and local microthrombosis.[15, 35] Activation of the complement cascade with the generation of anaphylatoxins C3a and C5a enhances neutrophil chemotaxis and hyperactivation. C5a-mediated stimulation of neutrophils causes increased release of proteases (elastase, cathepsins), ROS and formation of NETs, which contribute significantly to secondary tissue destruction and further endothelial damage.[22, 23, 29]

Biofilms

Chronic microbial colonisation of the wound surface in the form of biofilms provides sustained saturation of PAMPs, resistance to phagocytosis and mechanical cleansing, antibiotic resistance and maintenance of local immune-inflammatory activation, which is a key factor in the transition from acute to chronic wounds.[30]

Immune dysregulation

Prolonged exposure to DAMPs/PAMPs and prolongation of the pro-inflammatory response systemically leads to marked changes in immune status. Prolonged activation of innate immunity is associated with subsequent dysfunction of the adaptive branch (decreased antigen presentation, lymphopenia, impaired functional activity of T lymphocytes), forming a state similar to immunoparalysis, which increases the risk of late infectious complications and predisposes to the development of multiple organ failure.[45]

Remodelling

Connective tissue remodelling is a physiological process aimed at replacing granulation tissue

with an ordered collagen matrix, organising vascularisation (VEGF-mediated angiogenesis) and restoring mechanical strength. During remodelling, VEGF is released, endothelial cells are activated, mature capillaries are formed and vessels are stabilised by pericytes, ensuring adequate perfusion.

At the molecular level, this is accompanied by a change in the cytokine profile towards TGF-β-mediated fibroblast proliferation with their subsequent differentiation into myofibroblasts, synthesis of collagens I/III and regulation of matrix remodelling through matrix metalloproteinases (MMPs)/tissue inhibitors of metalloproteinases (TIMPs) balance.[46] Excess MMP leads to matrix destruction and scar instability, while TIMP prevalence leads to excessive fibrosis, contractures and pathological dense scars. Normal remodelling is only possible with a dynamic equilibrium between MMP and TIMP, which is regulated by TGF-β and mechanical tissue stimuli.

Pathological remodelling

However, with inadequate wound cleansing and persistent ischaemia, the cellular and metabolic environment remains unfavourable: hypoxia and acidosis induce stabilisation of hypoxia-inducible factor-1 alpha (HIF-1α), which modifies the functional profile of fibroblasts towards myofibroblastic transdifferentiation with excessive collagen production and matrix contraction, as well as increased activity of lysyl oxidase (LOX) enzymes, which enhance collagen cross-linking, making it denser.[47] Under such conditions, remodelling loses its orderliness and becomes pathological, forming dense fibrous scars, contractures and chronic fistulas.

Conditions for successful remodelling

Thus, successful physiological remodelling is only possible if two conditions are met. First, complete mechanical and/or physicochemical cleansing of the wound from necrosis, biofilms and foreign bodies. Secondly, restoration of adequate tissue perfusion and oxygenation, which ensures normalisation of cell metabolism, switching of inflammatory stimuli in the microenvironment to reparative ones and restoration of the MMP/TIMP balance. If these conditions are not met, molecular signalling cascades remain programmed for inflammation and destruction, which clinically manifests itself in chronic wound healing and an increased likelihood of late systemic complications.[47, 48]

Conclusion

1. The pathogenesis of a gunshot wound is a chain of cause-and-effect changes, in which each link is formed as a direct consequence of previous disturbances. Primary mechanical tissue damage and the instantaneous release of DAMPs trigger a hyperactivated inflammatory response that goes beyond physiological adaptation. At this stage, the foundation is laid for further events, including endothelial activation and microcirculatory disorders, deterioration of tissue perfusion, progressive ischaemia and the generalisation of inflammation.

2. Reperfusion, which is biologically necessary for restoring oxygenation, exacerbates damage. Excess ROS, NETs formation and uncontrolled complement activation lead to secondary necrosis, expansion of the lesion area and exacerbation of endothelial dysfunction. This creates a vicious cycle: ischaemia → reperfusion → ROS → endothelial damage → microthrombosis → worsening ischaemia.

3. In the subacute period, these processes transform into stable pathological cycles, circulus vitiosus. The dominance of the M1 macrophage phenotype, NETs persistence, constant supply of DAMPs and PAMPs, biofilm formation and progressive coagulopathy maintain chronic inflammation and prevent transition to the repair phase. These are the natural consequences of a single pathophysiological logic: the longer necrosis and microbial colonisation persist, the more actively inflammatory and coagulation cascades are sustained, creating a self-perpetuating system of damage.

4. The late period, which is normally characterised by remodelling and restoration of the matrix, becomes a phase of failed repair in gunshot wounds. Persistent necrosis, biofilms, chronic complement activation and destruction of the glycocalyx prevent the resolution of inflammation. Fibroblasts function in an environment of hypoxia and acidosis, which shifts their activity towards the formation of pathological fibrosis, hypercollagenosis and the formation of dense scars and contractures. Thus, disruption of the transition to repair not only delays healing but also

radically changes the quality and direction of remodelling.

5. All pathophysiological events, regardless of time frame, follow a common pattern: repeated damage initiates inflammation, accompanied by endothelial dysfunction and coagulation disorders, which in turn trigger a new cascade of damage. This cycle creates a chronic wound condition that cannot be broken by natural mechanisms.

6. The only way to change the course of the healing process of a gunshot wound is to break the key links in the pathological cycle: complete removal of necrotic tissue, elimination of biofilms, restoration of adequate perfusion and stabilisation of immune status. Without fulfilling these conditions, any attempt at healing will be futile, as molecular signals of damage continue to determine the vector of the wound process at all its stages.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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