# Inflammation and vasomotry during reperfusion

Gourdin, Maximilien; Dubois, Philippe

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Chapter 2

# Inflammation and Vasomotricity During Reperfusion

Maximilien Gourdin and Philippe Dubois

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## 1. Introduction

Restoration of perfusion and reoxygenation of ischemic tissues restores aerobic metabolism and supports postischemic functional recovery but also generates significant damage related to the ischemia/reperfusion (I/R) phenomenon. At the level of a blood vessel, lesions of I/R are mainly characterized by the perturbation of vasomotion and endothelial dysfunction. Moreover, despite the fact that ischemia occurs in a sterile environment, reperfusion induces a significant activation of innate and adaptive immune responses: massive reactive oxygen species (ROS) production; activation of pattern-recognition receptors or toll-like receptors (TLRs); activation of complement, coagulation, cytokine and chemokine production; and inflammatory cell trafficking into the diseased organ.[1] I/R activates different programs of cell death (necrosis, apoptosis or autophagy-associated cell death) and generates a systemic inflammatory response that lasts several days and that can lead, in some cases, to multi-organ failure and death. [2-4]

## 2. Posthypoxic blood vessel motricity and posthypoxic endothelial dysfunction

Blood vessels, and especially endothelium located at the blood-organ interface, are particularly susceptible to ischemia-reperfusion injuries. Endothelial stunning or the loss of endothelial functions during reperfusion contributes to IR injuries and compromises the postischemic recovery. [5-7]

The basal vascular tone is a continual balance between vasoconstrictors and vasodilators acting on the blood vessel. Vascular smooth muscle cells (VSMCs) and endothelium play pivotal roles in this control.

Posthypoxic vasoconstriction, in response to vasoconstrictors, and endothelium-independent vasodilation, induced by direct vasodilators (direct action on VSMCs), are slightly affected by I/R, demonstrating the relative resistance of VSMCs. [8]-[10] In contrast, endothelium-dependent dilatation is deeply affected. Despite the fact that endothelial cells seem relatively more resistant than other cells types (cardiomyocytes, neurons, renal tubular cell), I/R modifies their phenotype: diminution of their anticoagulant properties, increased vascular permeability, increased leukoadhesivity and establishment of a proinflammatory state in the endovascular milieu.

The production of some bioactive agents decreases (e.g., prostacyclin, nitric oxide), while that of others increases during I/R (e.g., endothelin, thromboxane A2). [1],[11]-[16] These endothelial modifications are called endothelial dysfunction and are widely described in human and animals studies.[15],[17]-[21] IR-related endothelial dysfunction is mainly characterized by the loss of NO availability and seems to be related to the reperfusion more than to ischemia. [10] In normal situations, NO acts in numerous pathways: direct vasodilation, indirect vasodilation by inhibiting the influences of vasoconstrictors (e.g., inhibiting angiotensin II and sympathetic vasoconstriction), inhibiting platelet adhesion to the vascular endothelium (anti-thrombotic effect), inhibiting leukocyte adhesion to vascular endothelium (anti-inflammatory effect), and inhibiting smooth muscle hyperplasia by scavenging superoxide anion (anti-proliferative effect). The diminution of NO concentration jeopardizes these functions.

Multiple hypotheses have been proposed to explain postischemic endothelial dysfunction: massive ROS production by mitochondria, activation of immune cells, activation of xanthine oxidase and $NADPH_2$ oxidase by the ceramide/sphingosine kinase pathway, the depletion of dihydrobiopterin (an essential cofactor of nitric oxide synthase), increased arginine consumption in other intracellular pathways, the production of chemokines and cytokines (tumor necrosis factor-alpha (TNF-$\alpha$), interleukin-1, -6, and -8) or the activation of the complement system (C3a fraction, C5b-9 fraction). [21]-[31]

In normoxic conditions, the endothelium permits only restricted diffusion. During hypoxia, the modifications of the cytoskeleton of endothelial cells, induced by hypoxia and low intracellular cyclic adenosine monophosphate phosphate (cAMP) concentration, increase vascular permeability, leading to capillary leakage and perivascular interstitial edema.[1] Complement system activation, leukocyte endothelial adhesion and platelet-leukocyte aggregation increase after reperfusion.[1],[32] A clinical example is the acute respiratory failure with hypoxia and pulmonary edema observed in several surgeries. Acute respiratory distress syndrome is caused by heart failure but also by a disruption of the alveolar-capillary barrier.[33]-[36]

## 3. The inflammatory response

Ischemia-reperfusion induces a vigorous inflammatory reaction including activation of the complement system; activation of the innate and adaptive immune systems; increased ROS, cytokine, chemokine and other proinflammatory metabolite production; and activation of programmed cell death. If inflammation concerns mainly ischemic organs, its effects will

extend to the whole body and, particularly, the organs with a high capillary density, such as lung, brain and kidney. [1],[12],[37],[38]

### 3.1. Activation of the complement system

Reperfusion injury is characterized by autoimmune responses, including natural antibodies recognizing neoantigens and subsequent activation of the complement system (auto-immunity). [1] Locally produced and activated, the complement system amplifies inflammation during ischemia and reperfusion through complement-mediated recognition of damaged cells and anaphylatoxin release. The anaphylatoxins C3a, C4a and C5a lead to the recruitment and stimulation of immune cells, which promotes cell-cell interactions by increasing the expression of adhesion molecules (vascular cell adhesion molecule-1, ICAM-1, E-selectin and P-selectin) on the surface of the endothelial cells and neutrophils. [12],[39] Moreover, C5a is a chemotactic factor that directly stimulates leukocytes to synthesize and secrete cytokines such as interleukin (IL)-1, IL-6, monocyte chemoattractant protein-1 (MCP-1) and TNF-$\alpha$. iC3b is implicated in neutrophil-endothelium interactions. C5b-9, known as the final cytolytic membrane attack complex complement, is a powerful chemotactic agent that causes direct lesions to the endothelial cells, stimulates the endothelial production of IL-8, MCP-1, and ROS and inhibits endothelium-dependent vasodilatation. [12],[39]

### 3.2. Cell-cell interactions during reperfusion

#### *3.2.1. Neutrophil–endothelium interaction*

During reperfusion, neutrophils play a central part in the inflammatory response and in the genesis of the I/R injuries. Activated neutrophils produce high amounts of cytokines, chemokines, and ROS in the vascular lumen but also in the parenchyma that directly contacts cells. These neutrophils and endothelial cells activated by cytokines (e.g., IL-6, TNF-$\alpha$, IL-8, IL-1$\beta$) and other proinflammatory mediators (e.g., platelet-activating factor, ROS) promote a close interaction between these cell types that will result in a significant concentration of activated neutrophils in the interstitium. [1],[13],[15],[17],[32],[40]-[43] This complex process can be summarized in four steps: chemoattraction, weak neutrophil adhesion to the endothelium, followed by a stronger adhesion and, finally, neutrophil migration (Figure 1). Three families of sarcoplasmic adhesion molecules are implicated in the neutrophil-endothelium interaction: selectins, $\beta$2-integrins and immunoglobulins.

- Chemoattraction:

Upon reperfusion, the endothelium, parenchyma and resident immune cells (mainly macrophages and neutrophils) release cytokines such as IL-1, TNF-$\alpha$ and chemokines, inducing the production of selectins by endothelial and immune cells. Circulating leukocytes are concentrated towards the site of injury by the concentration gradient of chemokines.

- Rolling adhesion

Endothelial L-selectin interacts with the P-selectin and the E-selectin-specific ligand-1 (ESL-1) expressed by neutrophils. [44],[45] The activation of TLR-2, ROS production, the complement

system and thrombin and a high intracellular calcium concentration promotes the expression of endothelial P-selectin from the Weibel–Palade bodies. Its peak of expression occurs 10–20 min after the beginning of reperfusion.[40],[46] P-selectin interacts with P-selectin glycoprotein ligand-1 (PSGL-1) expressed by neutrophils. These interactions are weak and reversible, providing transitory neutrophil adherence, slowing down leukocytes and allowing them to "roll" along the endothelial surface. During this rolling motion, transitory bonds are formed and broken between selectins and their ligands. This phase prepares the neutrophils and the endothelium for the following stage.

- Tight adhesion

At the same time, chemokines released by endothelial and immune cells activate the rolling neutrophils. Stimulated by ROS, platelet-activating factor (PAF), IL-1, TNF-α and leukotriene B4 (LTB4), neutrophils present CD11a/CD18, CD11b/CD18 and CD11c/CD18 from intracellular granules. These sarcoplasmic proteins interact with the iC3a fraction of the complement system and ICAM-1, an endothelial protein whose expression is reinforced by TNF-α and IL-1.[47],[48] This interaction switches from a low-affinity link to a high-affinity state and firmly attaches the neutrophil to the surface of the endothelial cell, despite the shear forces of the blood flow.

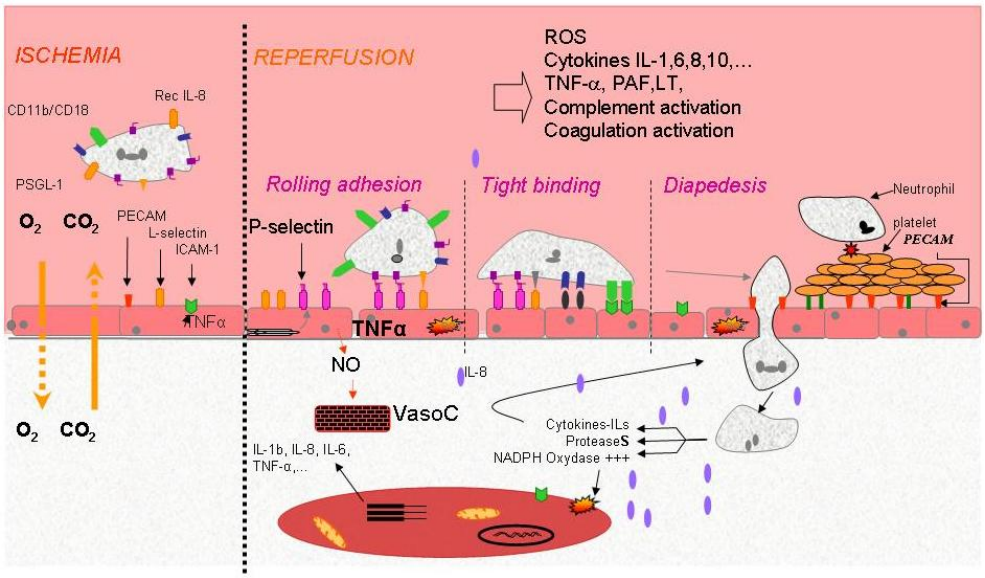


**Figure 1.** Ischemia–reperfusion-induced neutrophils accumulation in the interstitium is a mechanism described in three phases implicating specific complementary proteins. CD11b/CD18, sarcoplasmic neutrophil integrin; $CO_2$, carbon dioxide; ESL-1, E-selectin-specific ligand-1; I/R, ischemia– reperfusion; $O_2$, oxygen; PECAM, platelet–endothelial cell adhesion molecule-1; PSGL-1, P-selectin glycoprotein ligand-1; Rec IL-8, neutrophil IL-8 receptor; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-a; WPB, Weibel–Palade body.

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- Migration into the interstitium or diapedesis

Intercellular adhesion molecule-1 (ICAM-1) and platelet-endothelium adhesion molecule-1 (PECAM-1) are sarcoplasmic adhesion molecules belonging to the superfamily of the immunoglobulins. They are implicated in the transfer of neutrophils towards the interstitium, termed diapedesis. Leukocytes extravasation comprises many stages, which are not fully understood. Nevertheless, it seems that PECAM-1, found on neutrophil and endothelial cell membranes, is necessary for diapedesis. [1],[49] It interacts with several sarcoplasmic proteins of neutrophils. The cytoskeleton of the neutrophil is reorganized to allow the projection of pseudopodia between endothelial cells. This transfer is facilitated by inflammatory mediators, the CD11/CD18–ICAM-1 interaction and ROS, which combine to decrease the expression of cadherin and induce the phosphorylation vascular endothelial-cadherin and catenin, components of the intercellular junctions. [50]-[53] There is controversy concerning the mechanisms underlying this transfer through the basal membrane of the endothelium. Once into the interstitium, the neutrophil migrates along a chemotactic gradient towards the site of injury, where it causes considerable damage.

The neutrophil-related injuries in the interstitium are mainly related to the massive ROS production, proteases from the intracellular neutrophilic granules and the metabolites of arachidonic acid (PAF and LTB4). PAF and LTB4 are powerful chemoattractants that stimulate neutrophil degranulation. The neutrophil granules contain proteases, collagenases, elastases, lipoxygenases, phospholipases and myeloperoxidases that digest the protein network of the extracellular matrix. For example, elastase digests substrates such as collagen types III and IV, immunoglobulins, fibronectin and proteoglycans. Several cells, such as cardiomyocytes, stimulated by IL-6, express ICAM-1. The neutrophil binds to its receptor and empties its granules directly near the cell. [54],[55]

#### *3.2.2. Neutrophil-platelet interaction*

The role of platelets in ischemia-reperfusion injuries is unclear. However, it seems that they participate directly and indirectly in posthypoxic endothelial injury. [32],[56] Platelets affect neutrophil activation by releasing thromboxane A2, platelet-derived growth factor, serotonin, lipoxygenase products, proteases and adenosine. During reperfusion, approximately 25% of the fixed platelets are directly bound to the endothelium and the remaining 75% to neutrophils linked to the endothelium. [32],[57] This platelet-neutrophil interaction potentiates the neutrophils' capacity to produce superoxide and platelet-activating factor. [58],[59] Moreover, the neutrophil-platelet aggregates contribute to the no-reflow phenomenon and jeopardize the quality of the microcirculation. 60

### 3.3. Reactive oxygen species or oxygen free radicals

Reactive oxygen species, such as superoxide anion ($O_2^{-\bullet}$), hydrogen peroxide ($H_2O_2$) and hydroxyl radical ($OH^-$), are highly reactive and able to oxide all cellular constituents, includ-

ing proteins, DNA, phospholipids and other biological structures. During reperfusion, PAF, TNF-$\alpha$, IL-6, IL-1$\beta$, granulocyte-macrophage colony-stimulating factor, complement fraction C5a and the ROS themselves stimulate endothelial and neutrophil ROS production. [49], [61],[62] On the other hand, ROS activate nuclear factor-κB, promote cytokine production (e.g., TNF-$\alpha$, IL-6, PAF), and induce the synthesis and expression of endothelial and leukocyte adhesion molecules. [15],[41],[63]

In the reperfused tissue, the principal sources of ROS are neutrophil NADPH-oxidase, xanthine oxidase, mitochondria and the arachidonic acid pathways. [64]-[66] The massive ROS production quickly exceeds the capacity of cellular defense systems (catalase, superoxide dismutase, glutathione peroxidase and vitamins C and E). ROS directly cause much structural damage, increase the susceptibility to the opening of the mitochondrial permeability transition pore, activate immune and endothelial cells and induce apoptosis. [67]

ROS can also be produced by monoamine oxidase (MAO) of the outer mitochondrial membrane. MAO transfers electrons from amine compounds with oxygen to produce hydrogen peroxide. [68] p66Shc, a cytosolic adaptor protein for tyrosine kinase receptors that has been implicated in signal transduction, translocates to the mitochondrial matrix during reperfusion and oxidizes the reduced cytochrome *c*, which generates oxygen peroxide. [67],[69]

### 3.4. Ischemia-reperfusion-induced apoptosis

Reperfusion is vital for the functional recovery of an ischemic organ but also initiates the apoptosis pathways. [70],[71] Apoptosis is an active mechanism of cellular death, is genetically programmed, consumes energy, requires the expression or activation of specific enzymes, and can be induced by the oxidative stress of reperfusion. Reperfusion-induced apoptosis occurs in many organs, including heart, brain, kidney and liver. The reperfusion of an organ can induce apoptosis in other, distant organs. For example, reperfusion of a lower limb or the small bowel can induce apoptosis of cardiomyocytes or lung cells, respectively. [72],[73] The TNF-$\alpha$ production by the reperfused organ seems to play a crucial part in the induction of apoptosis. [70],[74]-[76] TNF-$\alpha$ initiates a receptor-dependent death pathway by activating downstream caspases. [70],[76],[77] Other causes of reperfusion-induced apoptosis are also important: mitochondrial depolarization, high intracellular calcium, mPTP opening and the release of some mitochondrial proteins into the cytoplasm, such as cytochrome *c*. When this protein is released from mitochondria into the cytoplasm, it interacts with apoptotic protease activating factor-1 (Apaf-1) and ATP to form the apoptosome, a large oligomeric protein complex that can activate caspase 9, which activates the caspase-dependent apoptosis pathway.

Endothelial cell apoptosis precedes and influences the apoptosis of the subjacent parenchymal cells. For example, a reduction in endothelial apoptosis decreases the apoptosis of subjacent cardiomyocytes. This suggests that signals emanating from the endothelium during apoptosis can induce or reinforce that of the cardiomyocytes.

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## 4. Integration of different aspects of ischemia-reperfusion

### 4.1. Blood vessel

According to the level of the vascular system considered (small arteries, capillaries and post-capillary veins), the repercussions of I/R are identical, but the clinical pictures differ.

*4.1.1. At the arteriolar level*

The principal manifestation of I/R in arterioles is a loss of the vasodilatation-dependent endothelium and the appearance of spasms. [78] Widespread endothelial lesions decrease the production of nitric oxide and do not counterbalance the arterioles' tendency toward vasoconstriction. This tendency is highlighted in several tissues, such as skeletal muscle, heart, lung and brain. [79]-[82] The combined effects of IR and inflammation on arteriolar vasomotricity are well documented. The increase in the contractile response of the pulmonary and mesenteric microcirculation after cardiac surgery predisposes the patient to the development of pulmonary shunt or mesenteric ischemia, particularly during the administration of vasopressive drugs in the postextracorporeal circulation. [83 ],[84]

*4.1.2. At the capillary level*

The posthypoxic recovery of an organ depends on the quality of its microcirculation and the resultant nutrient delivery and gaseous exchange. However, the microcirculation is the site of a paradoxical phenomenon called "no reflow", characterized by a major reduction in the capillary density. Despite the reestablishment of complete blood flow, an incomplete and heterogeneous perfusion of microcirculation persists. [85],[86] The capillaries are blocked by the parenchymatous and endothelial edema and the adhesion of the neutrophils and platelets to the surface of the endothelium, aided by the reduction in the production of nitric oxide. [15],[81], [85]-[87] Increased ROS and the depletion of ATP modify the cytoskeleton and the intercellular junctions, contributing to the loss of liquid from the vascular bed towards the interstitium. [88], [89] The phenomenon of no reflow persists several weeks after reperfusion. [85]

*4.1.3. At the postcapillary vein level*

The postcapillary veins are the sites of the inflammatory reaction. The margination and extravasation of the leukocytes are facilitated by the slower blood flow. Venous blood, arriving from the reperfused zones, is rich in proinflammatory mediators and activated neutrophils. These cause lesions both directly and indirectly through their interactions with platelets. [15],[90] Endothelial lesions prevent the intravascular oncotic pressure from recovering the excess liquid from the interstitium, thereby increasing the edema and contributing to the phenomenon of "no reflow".

### 4.2. Organs

In pulmonary transplantation surgery, I/R-induced lung injury is characterized by non-specific alveolar damage, lung edema and hypoxemia. The most severe form may lead to

primary graft failure and remains a significant cause of morbidity and mortality after lung transplantation.[91] Pulmonary microvascular permeability appears to have a bimodal pattern, peaking at 30 min and 4 h after reperfusion. [92] Mechanical ventilation, cardiopulmonary bypass during cardiac surgery and lung resection can also induce apoptosis and I/R-induced lung injury. [93]-[96]

Perioperative acute renal failure is associated with a high incidence of morbidity and mortality. According to the type of surgery, IR injuries in the kidney are direct or indirect. [97] For example, acute renal failure is the most important complication of remote tissue damage following abdominal aortic surgery. [98] I/R induces renal tubular injuries and contributes to the decrease of glomerular filtration. Recent data suggest that 13% of patients with acute kidney injury (AKI) evolve to end-stage renal disease within 3 years. In the case of patients with preexisting renal disease, the progression to end-stage renal disease rises to 28% within the same period. [98] These results suggest that AKI predisposes to chronic renal complication. I/R reduces blood vessel density and promotes renal fibrosis. The mechanisms mediating vascular loss are not clear but may be related to the lack of effective vascular repair responses. [99]

In cardiac surgery and in myocardial ischemia, cell death following I/R has features of apoptosis and necrosis. The loss of cardiomyocytes, which can hibernate in “no reflow” zones, and stunning, led by free radicals and calcium overload, explain the contractile posthypoxic dysfunction. The stunned cardiomyocytes can take several hours and days to recover. Intracellular ionic perturbation favors ventricular arrhythmias, such as ventricular fibrillation, ventricular tachycardia or ventricular extrasystole. [10 ]0 During ischemia, cardiomyocytes express ICAM-1. Neutrophils bind to this receptor and empty the contents of their granules onto the cells. [54],[55]

The mechanisms of I/R-induced brain injury have many similar aspects compared with those of I/R-induced myocardial injury. Many mediators and cytokines upregulated by I/R, such as bradykinin, purine nucleotides, nitric oxide and ROS, increase blood–brain barrier permeability and induce cerebral edema. [10 ]1 Although leukocyte infiltration into the ischemic brain increases cerebral damage, leukocyte accumulation in the microcirculation reduces reperfusion and increases the “no reflow” phenomenon.

The indirect repercussions of I/R on organs remote from the reperfused site are much more insidious. Neutrophils, complement activation, and massive production of cytokines and chemokines install a proinflammatory state that affects the functioning of other organs. During abdominal aortic surgery, I/R injuries are not only limited to the lower extremities but also cause damage to remote organs such as the lungs, kidneys, heart and bowel. [36],[97],[102]-[104] Lung injuries following abdominal aortic aneurysm surgery are characterized by progressive hypoxemia, pulmonary hypertension, decreased lung compliance and nonhydrostatic pulmonary edema, consistent with adult respiratory distress syndrome. [36],[103] In comparison with surgery, endovascular abdominal aortic aneurysm repair decreases I/R and I/R-induced-intestinal mucosal, renal and pulmonary dysfunction. [104]

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## Author details

Maximilien Gourdin and Philippe Dubois*

Department of Anaesthesiology, Université Catholique de Louvain, University Hospital of Mont Godinne, Belgium

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