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Review article

Coronary no reflow

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ABSTRACT

The no-reflow phenomenon has been studied extensively in the basic science laboratory and has entered the clinical arena. No-reflow, which develops largely within the first 2 h of reperfusion, is primarily the result of ischemic endothelial cell injury that obstructs the capillary lumen. Additional contributing mechanisms in experimental models include neutrophil accumulation, reactive oxygen species, and the coagulation cascade. Atherosclerotic- and thromboembolism also contribute to no-reflow during percutaneous coronary intervention and clinical myocardial infarction. No-reflow is assessed using tracers, electrocardiography (ST segment resolution), angiography (thrombolysis in myocardial infarction [TIMI] flow grading and myocardial blush grading), Doppler guidewires, myocardial contrast echocardiography, and cardiac magnetic resonance imaging. No-reflow is a poor prognosticator for left ventricular remodeling and function, and acute and long-term clinical events and survival. No-reflow benefits from therapies initiated during coronary occlusion or during early reperfusion. Potential therapies include vasodilators, statins, antiplatelet agents, thrombus aspiration, distal protection devices, ischemic preconditioning, remote ischemic preconditioning and postconditioning, pharmacologic preconditioning, and hypothermia. This comprehensive review will cover the underlying mechanisms, methods of assessment, prognostic implications, and potential therapies for the no-reflow phenomenon. This article is part of a Special Issue entitled "Coronary Blood Flow".

Contents

Abbreviations: NR, no-reflow; MI, myocardial infarction; IS, infarct size; TF, tissue factor; PCI, percutaneous coronary intervention; MRI, magnetic resonance imaging; TIMI, Thrombolysis in myocardial infarction; MBG, Myocardial blush grade; MCE, myocardial contrast echocardiography.

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1. Introduction

The ominous phenomenon whereby tissue perfusion does not occur in the presence of patent epicardial coronary arteries is referred to as microvascular obstruction, slow flow, or "no-reflow" (NR). Flow disturbances were observed in a cat model of coronary occlusion followed by reperfusion without any residual intraluminal obstruction [1]. Occasionally after 30 min occlusions and often after 60–120 min occlusions reduced blood flow was observed in the subendocardium. Krug et al. [1], however, did not relate this disturbance to intraluminal vascular obstruction, but to an increase in intraventricular pressure, and did not call the disturbance "no-reflow" (although in retrospect, it probably was). NR and its associated ultrastructural abnormalities were first described in a canine model of coronary occlusion/reperfusion in 1974 [2] and the NR phenomenon has since become an area of great interest to basic scientists and to clinical cardiologists. The pathophysiology and evolution of NR has now been described in great detail as well as NR's adverse clinical consequences. Cardiologists are treating NR in the clinical arena. This review will describe the underlying mechanisms and evolution of NR, modalities of assessment, prognostic implications and therapies relating to NR.

2. Pathophysiology — in animal models

2.1. Ultrastructural damage

An understanding of the NR phenomenon begins with an appreciation of the cellular ultrastructure, which was first described in 1974 [2] by subjecting dogs to 90 min of coronary artery occlusion with different durations of reperfusion. Following 90 min of occlusion (Table 1; Fig. 1), damage to cardiac myocytes (within the ultimate area of NR) included cellular swelling, subsarcolemmal blebs, cytoplasmic membrane-bound vacuoles, swollen mitochondria, and nuclear chromatin clumping and margination [2]. Endothelial cells demonstrated nuclear chromatin clumping and margination, a decrease in number or absence of pinocytotic vesicles, and occasionally intercellular separation. Most importantly, endothelial cells were swollen and deformed with small intraluminal protrusions and large intraluminal membrane-bound bodies (blebs) were noted. Initially upon reperfusion the endothelial protrusions and blebs persisted, often filling capillaries and obstructing the lumen. Red blood cells were observed tightly packed within the lumen and within the extravascular space. After 5–10 min of reperfusion capillaries occasionally became compressed by adjacent subsarcolemmal blebs in addition to continued intraluminal obstruction by endothelial protrusions and blebs. Large gaps were now frequently observed in the endothelium, often with adjacent fibrin and platelet thrombi. The extravascular space contained fibrin tactoids, myocardial cell mitochondria, membranous debris, and numerous red blood cells [2]. Endothelial glycocalyx deterioration and reduction in thickness was noted [3]. Areas adjacent to NR zones were characterized by severe myocardial cell damage and minimal endothelial cell injury. Thus, it appeared that endothelial cell injury and obstruction of capillaries played a primary role in NR [2].

To investigate the sequence of events that culminate in NR a similar model of occlusion and reperfusion was used with different durations of occlusion [4]. Myocardial cell injury began occurring at 20 min of occlusion and worsened in severity with longer durations of occlusion. Ultrastructural evidence of endothelial cell injury was not observed until 60 min of coronary occlusion and was more prominent in areas of severe myocardial cell damage. Endothelial cell injury was apparent in approximately 20% of vessels at 60 min, and in 40% of vessels at 90–180 min with loss of pinocytotic vesicles in another 20% [4]. Red blood cell stasis was occasionally observed after 40 min of occlusion and became more prominent after 60–90 min of occlusion. Three-hundred and twelve biopsies were taken of ischemic myocardium: 58% contained myocardial, but not endothelial cell damage, 42% showed both myocardial and endothelial cell injury, and none showed endothelial injury in the absence of myocardial cell damage [4]. This study suggested that ultrastructural damage occurs first within the myocardial cells followed by damage to the microvasculature [4]. This sequence of injury first to myocardial cells then to endothelial cells was supported functionally in a study demonstrating normal endothelial-dependent vasodilation after 15 min of occlusion and reperfusion, suggesting intact endothelial cells in contrast to a significantly reduced vasodilatory response to acetylcholine after

Table 1
Ultrastructural damage observed in capillaries and endothelial cells in the area of no-reflow.
Data from [2,18].

- Swollen intraluminal protrusions (often filled capillaries and obstructed lumen)
- Large, clear, intraluminal membrane-bound bodies (blebs; often filled capillaries and obstructed lumen)
- Pinocytotic vesicles greatly decreased in number or absent
- Nuclear chromatin clumping and margination
- Occasionally diffusely swollen endothelial cells
- Occasionally capillaries compressed by adjacent subsarcolemmal bleb
- Capillaries contain masses of tightly packed red blood cells upon reperfusion
- Frequently large gaps in endothelium (intercellular separation)
- Numerous extravascular red blood cells
- Extravascular fibrin tactiods, platelet thrombi, myocardial cell mitochondria, membranous debris
- Intravascular neutrophil accumulation and clustering (and lumen obstruction)