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Review

The "no reflow" phenomenon following acute myocardial infarction: Mechanisms and treatment options

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ABSTRACT

If 'no reflow' is observed within 45 min of reperfusion using balloon angioplasty or stent, it is probably related to microthromboemboli, which may also contribute to the extension of the 'no reflow' zone by converting 'low reflow' areas into necrotic ones even when reperfusion is achieved more than 45 min after the onset of coronary occlusion. Since 'no reflow' is noted when 45 min of coronary occlusion has elapsed even in the absence of a thrombus, 'no reflow' late after reperfusion is predominantly due to tissue necrosis and unlikely to be resolved unless methods to reduce infarct size are used.

Attempts at reducing the intracoronary thrombus burden during a coronary procedure for acute myocardial infarction (AMI) have been shown to reduce 'no reflow' and improve clinical outcome, as has the use of potent antithrombotic agents. Drugs that can reduce infarct size, when given intracoronary or intravenous in conjunction with a coronary intervention during AMI can also reduce 'no reflow' and improve outcomes in patients with AMI.

The prognostic importance of 'no reflow' post-AMI is related to its close correspondence with infarct size. Although several imaging and non-imaging methods have been used to assess 'no reflow' or 'low reflow' myocardial contrast echocardiography remains the ideal method for its assessment both in and outside the cardiac catheterization laboratory.

Contents

Introduction

Following reperfusion therapy, myocardial tissue perfusion may not be restored in up to a third of the patients after acute myocardial infarction (AMI) despite thrombolysis in myocardial infarction grade 3 flow on coronary angiography. This phenomenon of myocardial tissue 'no reflow' in patients with AMI was first described by Ito et al. [1] and then confirmed by several others [2–6] using myocardial contrast echocardiography (MCE). Later, other imaging techniques also described the finding [7,8], but their validity for accurately assessing 'no reflow' is questionable and will be discussed later.

Many clinicians believe that the 'no reflow' phenomenon results solely from the micro-vascular obstruction caused by distal embolization of thrombi and plaque components during balloon angioplasty and stent placement. This review is meant to refute

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this notion and to demonstrate that the 'no reflow' phenomenon results principally from tissue and microvascular damage during myocardial ischemia and not from microembolization, particularly if coronary occlusion persists beyond 45 min. If the ischemic period is short (<45 min), infarction is likely to be minimal and if there is 'no reflow' after balloon angioplasty and stent placement, then it can be attributed to distal embolization.

When coronary occlusion has lasted for >45 min, the duration of ischemia determines the likelihood and the extent of 'no reflow' independent of whether there is additional distal microembolization. Furthermore, surrounding the 'no reflow' zone there is a 'low reflow' zone that can either survive as such or evolve into a 'no reflow' area after reperfusion therapy. The size of the 'low reflow' zone is principally determined by collateral blood flow. Finally there are potential treatment options for the 'no reflow' phenomenon.

Historical perspective

The 'no reflow' phenomenon was most probably first reported in 1959 in the kidney by Sheehan and Davis (the one of Sheehan's syndrome fame) [9]. The initial description in the heart was by Krug and colleagues [10] who showed interstitial edema and red cell packing of damaged capillaries. A year later, Majno and colleagues [11] reported their findings in the brain in a "Letter to the Editor" in *The Lancet* and the histological findings they described are those that are now deemed characteristic of the 'no reflow' phenomenon. These findings were later confirmed in the heart in much greater detail by Kloner et al. [12] in 1974. The hallmarks of the 'no reflow' phenomenon initially described by these authors are myocyte swelling, endothelial cell swelling with luminal protusions, and intravascular red blood cell aggregates [11,12]. Later findings included presence of capillary leukocyte plugging [13,14] and to a lesser extent, platelet and fibrin accumulation [15,16]. Myocardial damage always precedes the microvascular abnormalities in the presence of total coronary occlusion not caused by a coronary thrombus and not vice versa [17].

Despite abundant basic science literature indicating that 'no reflow' occurs within minutes after release of total coronary occlusion, no attempts were made to study this phenomenon in humans in the early days of thrombolysis and balloon angioplasty for AMI. This was partly related to the lack of methods for and interest in assessing microvascular perfusion either outside or in the cardiac catheterization laboratory. Routinely used clinical techniques to assess myocardial perfusion at that time such as single photon emission tomography were thought to measure myocyte integrity, but not provide an independent assessment of microvascular perfusion. Ito and colleagues [1] were able to assess the 'no reflow' phenomenon after AMI in humans by using MCE, a technique that utilizes gas-filled microbubbles, which after intravascular administration remain entirely within the intravascular space and on ultrasound examination can delineate regions with and without microvascular perfusion [18,19]. Earlier studies used intra-coronary injections of microbubbles in the cardiac catheterization laboratory (Fig. 1) [1,2]. With the advent of commercially available microbubbles capable of trans-pulmonary passage, it became possible to assess myocardial perfusion with intravenous administration of these agents (Fig. 2) [4–6,20].

Myocardial blood flow in reperfused myocardium

In the absence of any tissue damage, restoration of coronary flow after prolonged coronary occlusion results in hyperemic myocardial blood flow (MBF). At this stage, because of the release of endogenous adenosine and other vasodilators during ischemia, the resistance vessels within the myocardium are fully dilated, resulting in reduced microvascular resistance and increased MBF. The hyperemia under these conditions is limited principally by the capillary number, size, and function [21–23]. Since the hallmark of

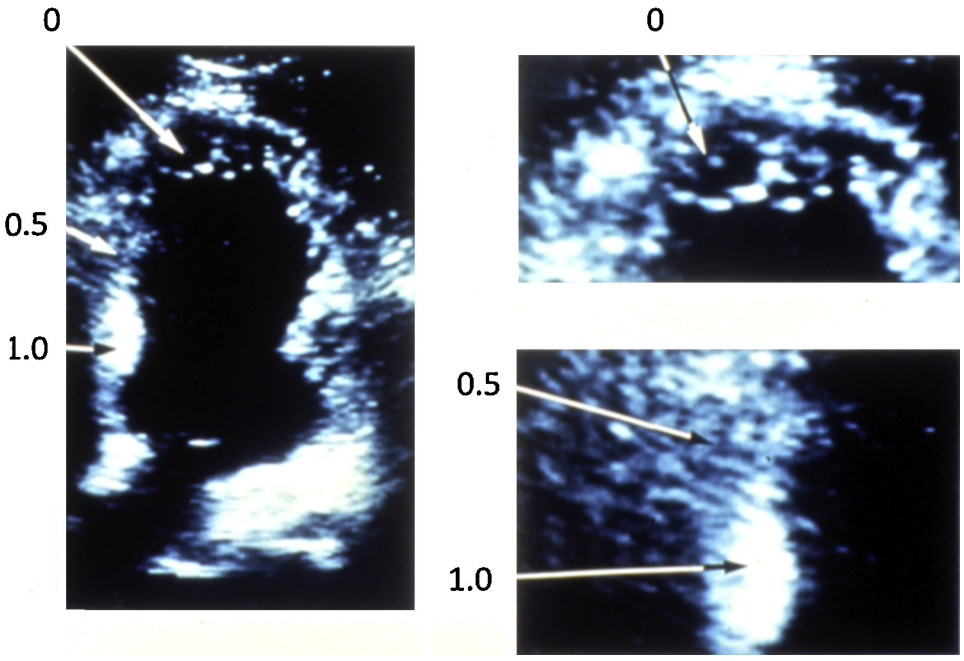

Fig. 1. Panel A illustrates a four-chamber view depicting three different contrast patterns in a patient with an antero-apical infarction and a patient infarct-related artery in whom microbubbles were injected into the left main coronary artery in the cardiac catheterization laboratory: 0 = no opacification; 0.5 = patchy opacification; and 1 = homogeneous opacification. These regions have been magnified to show a score of 0 in panel B and scores of 0.5 and 1 in panel C. Regions with scores of 1 improved their function fully after balloon angioplasty. Those with scores of 0.5 improved function partially and those with scores of 0 did not improve function.

Source: From Ragosta et al. [2] with permission of the American Heart Association.