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.

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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
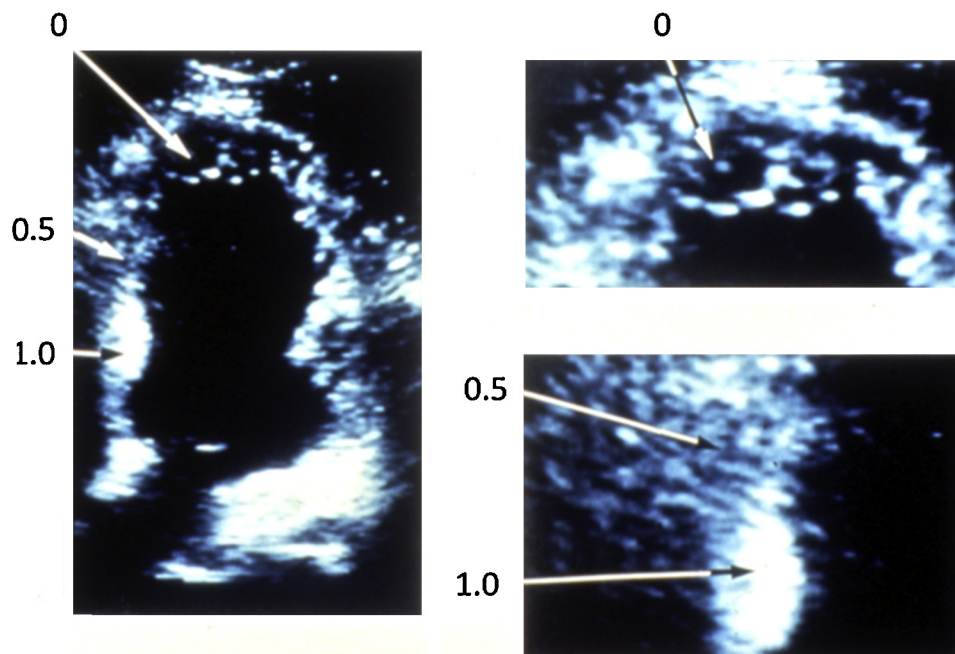

Fig. 1. Panel A illustrates a four-chamber view depicting three different contrast patterns in a patient with an antero-apical infarction and a patient infarct-related artery in whom microbubbles were injected into the left main coronary artery in the cardiac catheterization laboratory: 0 = no opacification; 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.
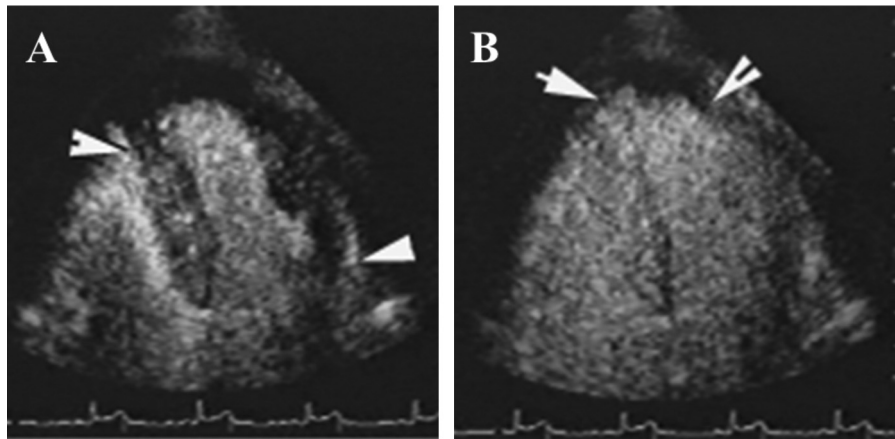
Fig. 2. Myocardium perfusion defect in a patient with chest pain and no electrocardiographic changes before (A) and after (B) coronary angioplasty. Panel A depicts risk area and panel B depicts a small area of residual 'no reflow' in the apex that did not improve function one month later.
Source: From Kaul S. [20], with permission from the American Heart Association.

the 'no reflow' phenomenon is capillary damage, the flow within the center of this area where the damage is most dense (mostly the endocardium) can be reduced compared to the normal bed. In areas of less dense damage, the hyperemic flow may be attenuated enough to be similar to or even higher than in normal tissue that is not experiencing hyperemia. In the 'low reflow' zone surrounding it, the actual flow is hyperemic [24–30], although not as high as would be expected in the normally hyperemic tissue.

This is important because if one performs MCE immediately after reperfusion one might underestimate the size of the 'no reflow' and 'low reflow' zones [24–26]. The size of the 'no reflow'

zone also changes dynamically in the first several hours after reperfusion because of vasospasm, myocardial edema, etc. [24,29]. Panels A and B in Fig. 3 show relatively small perfusion defects at 45 min and 3 h after reperfusion in an infarct model, while the
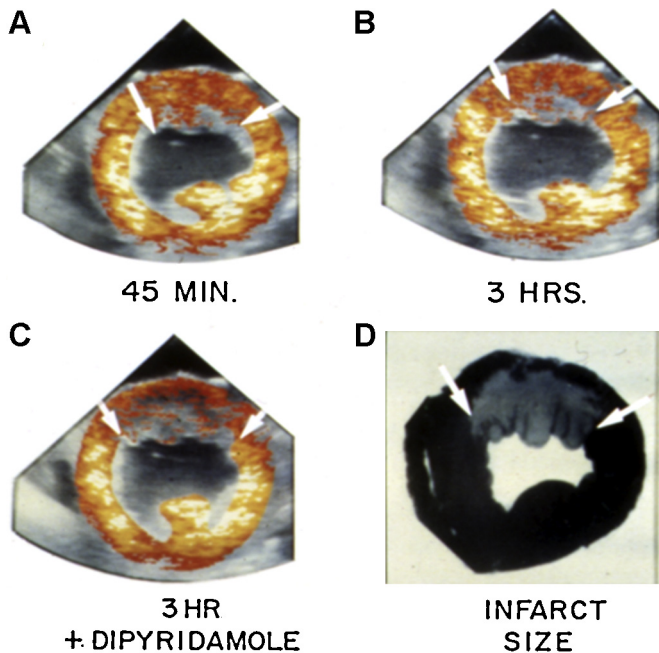

Fig. 3. Changes in perfusion patterns after reperfusion in a dog with a nearly transmural infarction caused by 3 h of coronary occlusion. After 45 min of reperfusion, a small relative color defect localized to the endocardium in the anterior wall is noted as shown by arrows in panel A. After 3 h of reperfusion, this defect was slightly larger as depicted by arrows in panel B. The addition of dipyridamole, resulted in a much larger relative contrast defect shown by arrows in panel C which closely delineated the true size and shape of the infarct on tissue staining with triphenyl tetrazolium chloride, which is indicated by arrows in panel D.
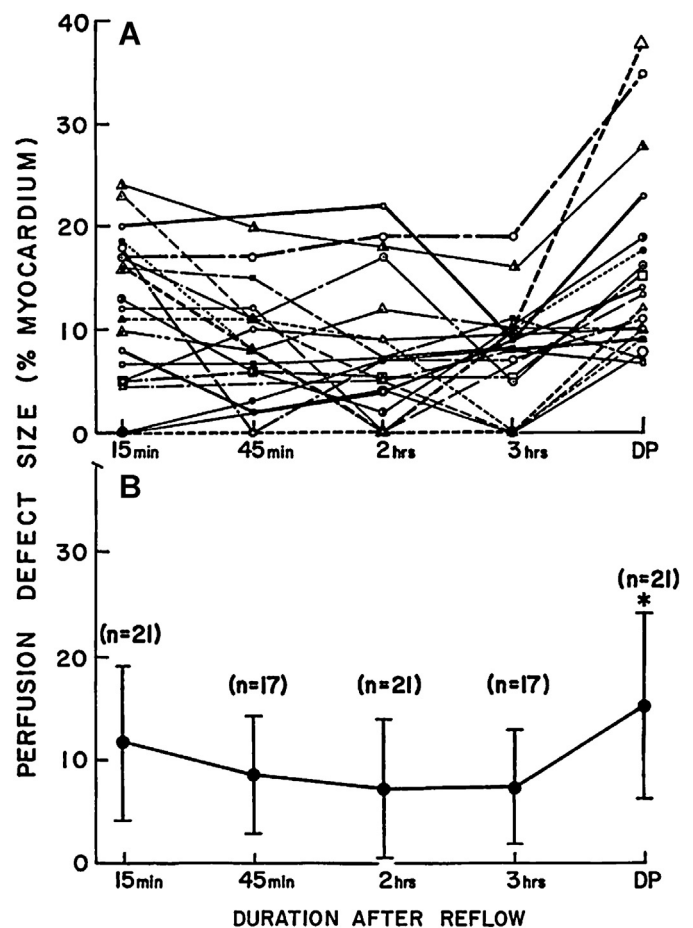*Source*: From Villanueva et al. [24], with permission of the American Heart Association.

Fig. 4. The temporal sequence of perfusion defects defined by myocardial contrast echocardiography in 21 dogs undergoing 3 h of coronary occlusion followed by reperfusion. The y-axis depicts perfusion defect size as a percentage of the left ventricular myocardium in the short-axis slice, while the x-axis represents the interval after the onset of reperfusion, except the last stage (DP – dipyridamole) which could have followed either a 2-h (4 dogs) or a 3-h period of reperfusion (17 dogs).
Source: From Villanueva et al. [24], with permission of the American Heart Association.

infract size measured at 3 h is significantly larger. Fig. 4 illustrates perfusion defect sizes from a large group of dogs undergoing ischemia followed by reperfusion. It is clear that the defect sizes at rest change dynamically between 15 min and 3 h after reperfusion. Although no clinical study has measured the 'no reflow' zone at repeated intervals after AMI, the ideal time to measure 'no reflow' at rest in order to determine the extent of myocardial necrosis is probably after 48 h following reperfusion [30]. At that time dynamic changes in resting tissue perfusion have subsided and the extent of no reflow correlates well with infarct size and denotes a region of irreversible tissue damage. Also any transient contribution of microthromboemboli to the 'no reflow' zone have reversed by that time.

Since the ischemic zone that will ultimately demonstrate 'no reflow' has reduced MBF reserve immediately after reperfusion [24–26,31–33], administration of a vasodilator such as dipyridamole unmasks the regions of abnormal flow reserve that will ultimately develop necrosis and no reflow [24,25]. Panel C in Fig. 3
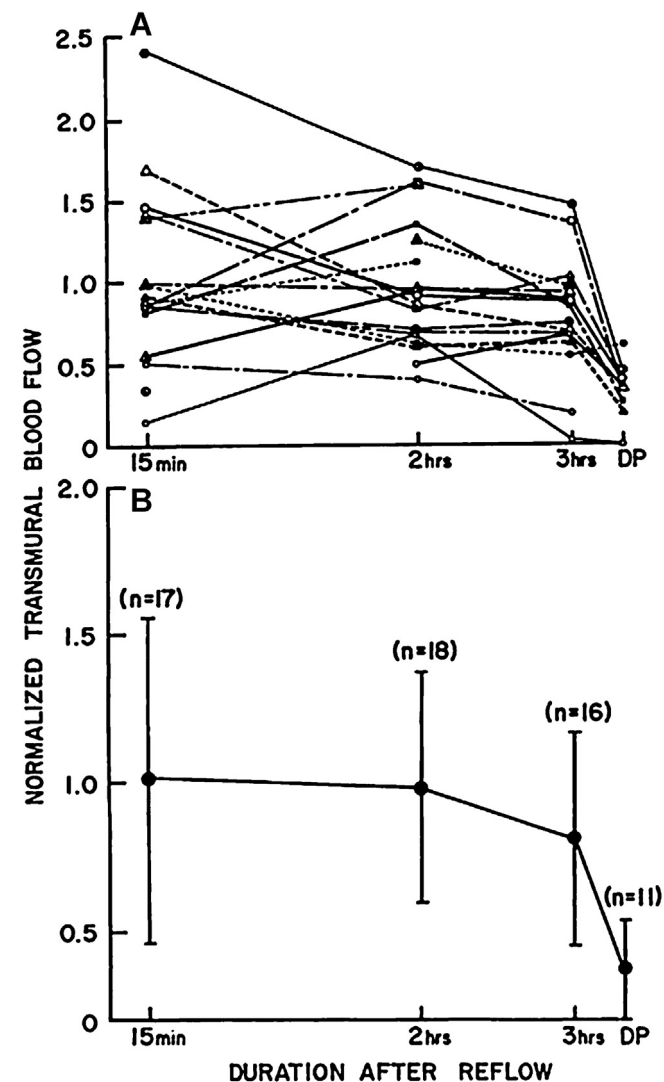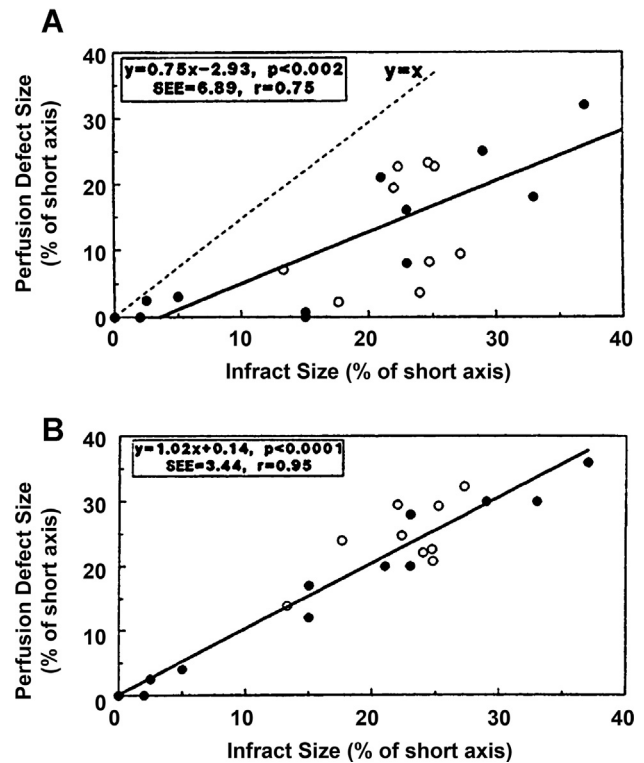
Fig. 6. (A) Relation between myocardial contrast echocardiography (MCE) defect size 15 min after reperfusion in the absence of adenosine (y-axis) and infarct size (y-axis) measured either at 15 min (filled circles) or 3 h after reperfusion (open circles). (B) Relation between MCE defect size 15 min after reperfusion in the presence of adenosine (x-axis) and infarct size (y-axis) measured either at 15 min (filled circles) or 3 h after reperfusion (open circles).

Source: From Villanueva et al. [25], with permission of the American Heart Association.

Fig. 5. The temporal sequence of radiolabeled microsphere-derived transmural blood flow within the risk area in 21 dogs undergoing 3 h of coronary occlusion followed by reperfusion. Transmural blood flow within the risk area is expressed as a percent of transmural blood flow in the normal posterior wall on the y-axis and the interval after reperfusion is depicted on the x-axis. DP represents measurements made during the infusion of dipyridamole after 3 h of reflow.

Source: From Villanueva et al. [24], with permission of the American Heart Association.

illustrates the perfusion bed size at 3 h after reperfusion during administration of dipyridamole. In comparison to panels A and B in the same figure, the defect size closely approximates the infarct size (panel D) [24] and this corresponds to the increase in perfusion defect size after administration of dipyridamole (panel B in Fig. 4). The obvious increase in defect size is related to the relative hypoperfusion within the infarct bed compared to the normal bed caused by dipyridamole and not an absolute decrease in MBF. Fig. 5 depicts MBF (measured with radiolabeled microspheres) within the reperfused myocardium compared to the normal myocardium, highlighting the heterogeneity in MBF during the first 3 h of reperfusion. In the presence of dipyridamole the heterogeneity in MBF as well as MBF compared to the normal bed are both markedly reduced allowing delineation of the 'no reflow and low reflow' zones.

The examples shown above are in the presence of dipyridamole 3 h after reperfusion, but the same results can be obtained immediately after reperfusion [25]. Fig. 6 illustrates the relation between actual infarct size and perfusion defect size on MCE at both 15 min and 3 h after reperfusion. Panel A shows the marked underestimation of infarct size by the perfusion defect size in the absence of dipyridamole, while panel B shows the results after dipyridamole administration. Therefore, with dipyridamole the perfusion defect size predicts infarct size accurately no matter when it is measured after reperfusion.

Influence of collateral blood flow

Since 'no reflow' occurs exclusively within the infarcted tissue, its extent as that of the infarction is determined by the level
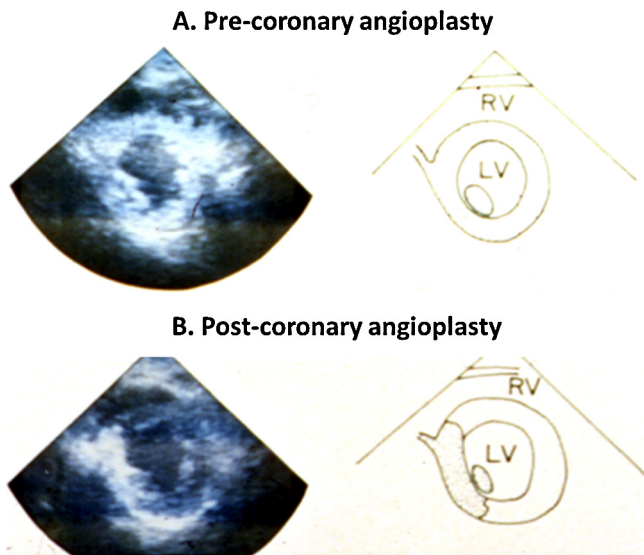
A. Pre-coronary angioplasty

B. Post-coronary angioplasty

Fig. 7. Short-axis view of a patient with a totally occluded right coronary artery after acute myocardial infarction. The upper panel depicts a myocardial contrast echo-cardiography image after microbubble injection into the left main coronary artery prior to angioplasty of the right coronary artery showing contrast enhancement of the entire left ventricular myocardium. The bottom panel depicts the same view after successful angioplasty of the right coronary artery and injection of microbubbles directly into it, showing the perfusion bed of the right coronary artery. At the time of coronary occlusion this bed was supplied by collaterals from the left system (top panel).
Source: From Sabia et al. [34], with permission of the New England Medical Society.

of nutrient MBF at the time of coronary occlusion. Hence, collateral blood flow is a major determinant of the size of the 'no reflow' zone. Consequently, MCE performed at the time of coronary occlusion can predict the ultimate size of 'no reflow' even if the coronary occlusion is not reversed. In the early days of MCE, collateral flow was measured by injecting microbubbles directly into non-occluded coronary arteries. The top panel in Fig. 7 is an example of a patient with an inferior AMI and occluded right coronary artery who demonstrates adequate myocardial perfusion after left main injection of microbubbles. After the artery was opened and microbubbles were injected directly into it (bottom panel), there was no evidence of 'no reflow' in the previously occluded bed [34].

After introduction of commercially available microbubbles capable of myocardial opacification from a peripheral venous injection, it became possible to quantify MBF with MCE. For this approach a dilute solution of microbubbles is administered intravenously as a constant infusion using a pump device. In a few minutes, steady state is achieved, when the concentration of microbubbles in the myocardium and other organs is constant. Then high-energy ultrasound is used to destroy microbubbles in the myocardium after which their rate of myocardial replenishment is measured (Fig. 8 Panel A). Time versus acoustic intensity (AI) curves can be generated from different myocardial regions and fitted to an exponential function: $y = A(1 - e^{-\beta t})$, where y is AI at a pulsing interval t, A is the plateau AI, and β is the rate constant which represents the rate of rise of AI (and thus mean microbubble velocity, Fig. 8, Panel B) [35].

The beam width of an ultrasound probe represents the thickness of the ultrasound image and is approximately 5 mm. Microbubbles, which have an intravascular rheology similar to that of erythrocytes [36,37], travel at 1 mm s^{-1} at rest within the myocardial capillaries. Thus, after microbubble destruction, the beam width fills within 5 s in the presence of normal MBF. When MBF is reduced it takes a longer time to fill the beam and the time it takes to fill the beam is inversely proportional to MBF. Myocardial tissue is
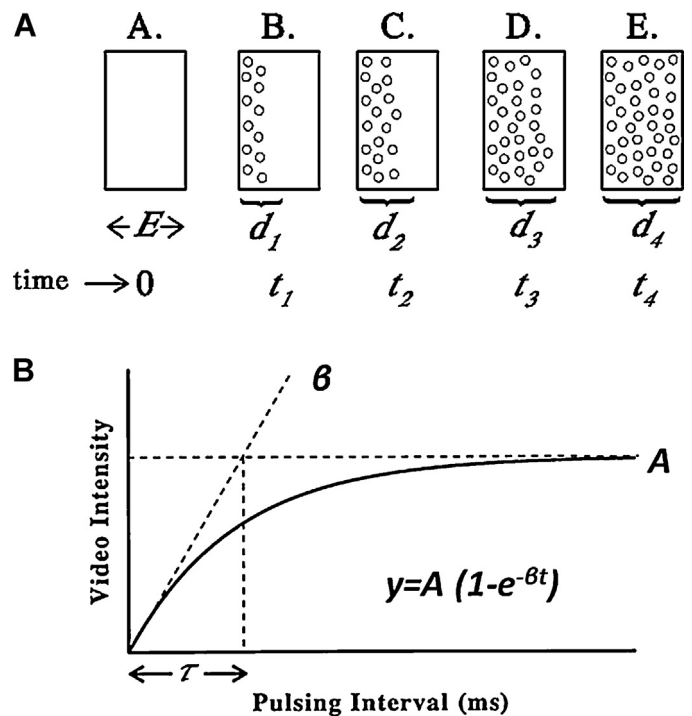

Fig. 8. Panel A shows the ultrasound beam elevation (thickness) represented as 'E' in A. If all the microbubbles in the elevation are destroyed by a single pulse of ultrasound at t0, then replenishment of the beam elevation (d1–d4, B–E), will depend on the velocity of microbubbles and time of imaging. Panel B shows the pulsing interval (x-axis) versus video-intensity (y-axis) plot where myocardial blood volume is shown as A and rate of microbubble replenishment is shown as β. The function used to fit the relation is also depicted.
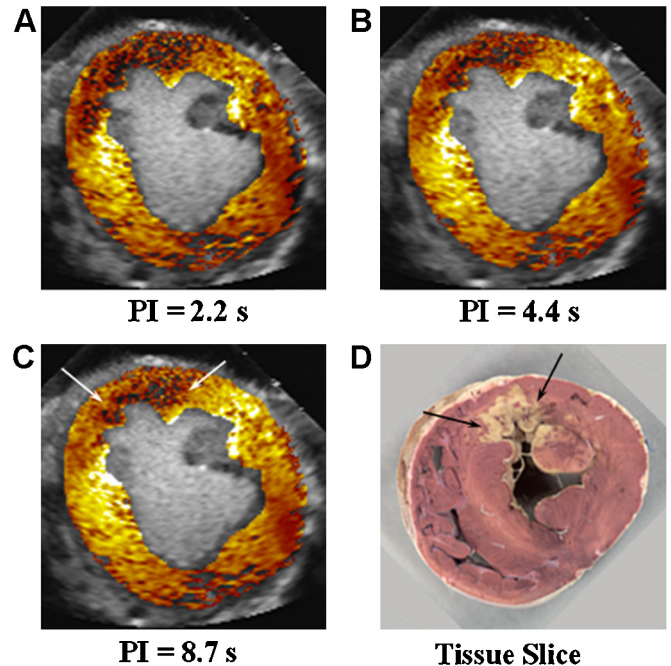
Fig. 9. Perfusion defects at various times after microbubble destruction and the ultimate infarct size (by tissue staining) in a dog undergoing 6 h of left anterior descending artery occlusion. In this example, although the risk area (A) is large at 2.7 s after bubble destruction, the infarct size on post-mortem tissue staining is moderate because of modest collateral-derived myocardial blood flow (D). The epicardium is spared from necrosis and the infarct size is accurately predicted at 30 min after coronary occlusion at 8.7 s after microbubble destruction (C), where assessment of epicardial perfusion is slightly better that at 4.4 s after bubble destruction (B) because of more collateral filling.
Source: From Coggins et al. [40], with permission of the American Heart Association.

unlikely to undergo necrosis if MBF is >0.25 mL min^{-1} g^{-1} (normal being 1 mL min^{-1} g^{-1}) [38,39]. Thus, we can define the amount and extent of collateral MBF that is likely to prevent myocardial necrosis and 'no reflow' by measuring the time it takes to fill an occluded myocardial bed.

Fig. 9 is an example of MCE images at various times after microbubble destruction. Although the region with reduced perfusion is delineated 2.7 s after bubble destruction, the final size of perfusion defect at 8.7 s is much smaller because of collateral flow with the margins and epicardium, and the infarct size (panel D) corresponds to the perfusion defect size at this time [40]. These images were taken 30 min after coronary occlusion while the infarct size was measured 6 h after occlusion. Thus the ultimate infarct size (and thus 'no reflow' area) was predicted at the time of coronary occlusion. This obviously has great potential import in clinical decision-making, including urgency of providing reperfusion options.

Conversion of 'low reflow' to 'no reflow'

As previously stated, there is a 'low reflow' zone surrounding the 'no reflow' zone. The 'no reflow' zone exists even in the absence of reperfusion and its spatial extent is determined by the absence of adequate collateral blood flow. However, after reperfusion, the 'low reflow' zone can either persist as viable myocardium or become subject to necrosis. The fate of this 'low reflow' zone after reperfusion is determined either by the degree of persistent microemboli from the thrombus/plaque in regions undergoing stent placement and/or from reperfusion injury.

In an animal model where coronary thrombosis was produced and then the thrombus was labeled with a ^{99m}Tc agent, it was observed that microthromboembolism occurred during balloon angioplasty [41,42]. The 'no reflow' zone was also larger in dogs with coronary thrombosis undergoing angioplasty than in those simply undergoing coronary ligation [42]. The spatial extent of microthromboemboli assessed in these studies was larger than the 'no reflow' zone. This phenomenon is again related to collateral vessels. The microemboli that travel down a vessel will extend beyond the risk area through collaterals [43]. Other investigators have also implicated microthromboemboli in the development of 'no reflow' phenomenon [44,45]. However, these results should be construed with caution. While, as in our study, it is possible that part of the initial 'no reflow' may be from microthromboemboli, these are most likely to dissipate with the use of thrombolytics and other anti-platelet therapy. Contrariwise, if cholesterol crystals and other debris are embolized peripherally during balloon angioplasty and stent placement, they may cause permanent microvascular obstruction and contribute to the 'no reflow' phenomenon [46,47].

While the importance of reperfusion injury in influencing the ultimate infarct size remains controversial [48], it is possible that the 'low reflow' zones are more susceptible to injury and may undergo necrosis after reperfusion compared to normally perfused regions. This can result from additional myocardial edema, inflammation, and leukocyte as well as platelet activation caused by the release of oxygen-free radicals. Whereas in our studies we did not find a reduction in resting MBF or increase in the 'no reflow' zone up to 3 h of reperfusion, others have reported the opposite [29,49]. These discrepancies may result from the different animal models used. In dogs, there is abundant collateral flow that might preserve the 'low reflow' zone, while rabbits do not have this protection, which might explain a greater susceptibility to reperfusion injury [49].

Other methods of assessing no reflow

Imaging techniques such as coronary angiography, cardiac magnetic resonance imaging (MRI), and cardiac computed tomography (CT) have been used to assess myocardial 'no reflow' [7,8]. Coronary angiography was used because of its availability at the time of coronary intervention and most laboratories did not have the know-how to perform MCE studies. All these techniques use dyes that do not remain within the intravascular space and thus cannot in principle define the status of the microcirculation. On MRI for example, the same area that shows low 'perfusion' early after reflow (deemed the 'no reflow' zone') shows hyper-enhancement several minutes later because of dye extravasation into the extravascular space where it gets lodged as a result of low perfusion. Coronary angiography is also a planar technique and cannot determine the 3D spatial extent of myocardial perfusion. The inferiority of other techniques compared to MCE for assessing 'no reflow' was confirmed in a multicenter study [50].

The Doppler wire has also been used to characterize 'no reflow.' Studies in TIMI grade 2 patients, most of whom have no reflow, show systolic flow reversal, reduced anterograde systolic flow, and anterograde diastolic flow with a rapid deceleration slope [51]. Because of the reduced anterograde flow and the presence of flow reversal, coronary inflow to the myocardium is reduced. The Doppler wire, however, remains an indirect way to assess the 'no reflow' phenomenon.

Prognostic implications for the 'no reflow' phenomenon

Some literature suggests that the 'no reflow' zone is smaller than the infarct zone, whereas our studies show that it corresponds to infarct size. The differences can be attributed mostly to methodological factors. For example, if the model studied is total coronary occlusion, then the infarct size is somewhat smaller than the 'no reflow' zone. In our studies we measured the infarct size after reperfusion, which is more relevant to the clinical situation. We also measured the infarct size by tissue staining with triphenyl tetrazolium chloride, while others performed a microscopic examination. In any case, there is a strong correlation between the size of 'no reflow' and that of infarction. As a consequence, the 'no reflow' zone size predicts systolic left ventricular function, remodeling, infarct expansion, ventricular arrhythmias, and thus the outcome [2–6,52–58].

Treatment options for 'no reflow'

As stated previously, if during AMI the duration of ischemia is <45 min before reperfusion is attempted and there is the presence of 'no reflow', it is most likely from distal thromboembolization. In that instance, any maneuver to reduce microthromboemboli will reduce 'no reflow'. In addition, if the microthromboemboli contribute to the conversion of the 'low reflow' zone to 'no reflow' even after longer duration of coronary occlusion, then reducing the incidence or quantum of distal embolization will also reduce 'no reflow'. Therefore, randomized studies that have utilized manual thrombus aspiration have shown better microvascular perfusion and long-term outcome compared to control patients undergoing a coronary intervention during AMI [59–62]. Similar results have been obtained with a distal occlusive protection device not with a thrombectomy device [62–64].

Other ways to reduce the thrombus burden can also have beneficial effects on microvascular perfusion. For example, routine use of platelet inhibitors during coronary interventions for AMI can benefit myocardial perfusion; IIb/IIIa inhibitors, abciximab and tirofiban are examples of such agents [65,66]. Intracoronary administration of abciximab seems to have less 'no reflow' than intravenous administration [65]. An investigational drug, CP-4715 that inhibits both IIb/IIIa and $\alpha_v\beta_3$ has been shown to dramatically reduce 'no reflow' and the infarct size in a canine coronary
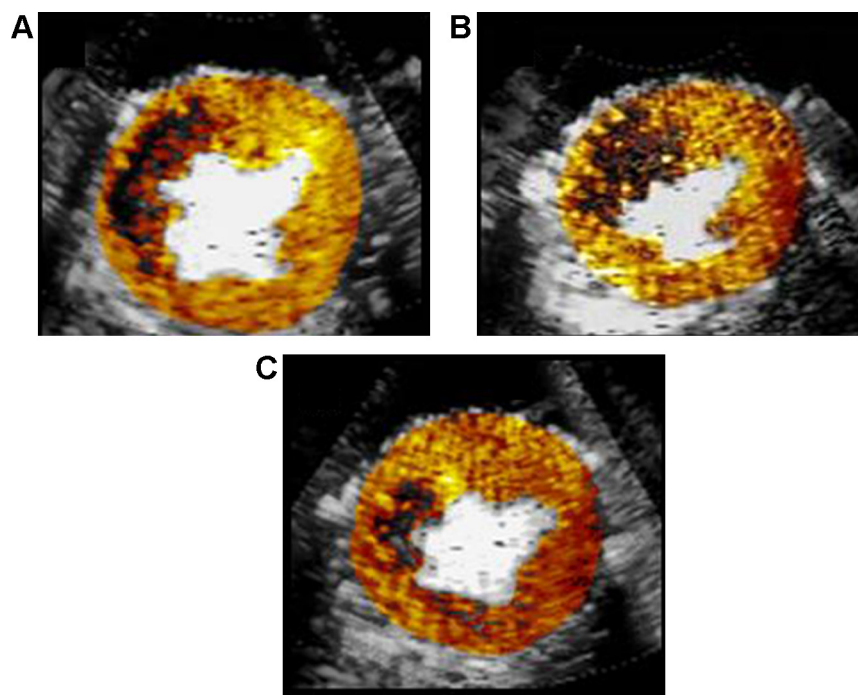
Fig. 10. Myocardial contrast echocardiography-derived 'no reflow' images from dogs receiving (A) saline, (B) tirofiban (a IIb/IIIa inhibitor), and (C) CP-4715 (both a IIb/IIIa and a $\alpha_v\beta_3$ inhibitor) in a model of reperfusion after angioplasty of a thrombus-occluded coronary artery.
Source: From Sakuma et al. [67] with permission of the European Society of Cardiology.

thrombosis model undergoing balloon angioplasty (Fig. 10) [67]. The inhibition of $\alpha_v\beta_3$ resulted in less inflammation, which may have contributed to less leukocyte plugging and less 'no reflow'.

Other than reducing distal thromboembolization, any maneuver that will reduce the infarct size will also reduce 'no reflow,' particularly if ischemia exceeds 45 min. Thus pharmacological interventions with adenosine (both intracoronary and intravenous) [68–70], nicorandil (intravenous and combination of intravenous and intracoronary) [71,72], and verapamil (intracoronary) [73,74] have all been shown to have salutary effects on the 'no reflow' size. Whereas nitroprusside was shown in a pilot study [75] to have a beneficial effect on 'no reflow' a randomized study failed to demonstrate this effect [76].

Adenosine has been shown to reduce the infarct size principally through coronary vasodilation and its anti-inflammatory effects through different adenosine receptors. Nicorandil reduces calcium overload and inflammation, the latter through its anti-oxidant and neutrophil inhibiting properties. Verapamil reduces flow heterogeneity in the ischemic bed and also inhibits platelets that can be activated due to low shear during ischemia. GP-531, an investigational drug that has no basal effect but increases adenosine levels during ischemia, was also shown to reduce the 'no reflow' zone and the infarct size in an animal model [77].

A recent animal study from Kloner's group that has been active in this field for 40 years reported a decrease in 'no reflow' from hypothermia late after reperfusion despite no change in the infarct size [78]. This intriguing finding is contrary to their original concept that microvascular dysfunction during coronary occlusion results from tissue damage and not vice versa [17]. Studies in animal models other than rabbit using in vivo assessment of myocardial perfusion will be needed to confirm these findings. Obviously, if myocardial cooling is instituted early during coronary occlusion, it will reduce the infarct size and hence the size of the 'no reflow' zone after reperfusion [79].

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