RESEARCH REPORT

Reduction of “No-Reflow” Phenomenon by Intra-Aortic Balloon Counterpulsation in a Randomized Magnetic Resonance Imaging Experimental Study

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OBJECTIVES Intra-aortic balloon counterpulsation (IABC) can improve post-myocardial infarction (MI) outcomes, but the mechanisms of such effect remain unclear. We hypothesized that IABC augmentation reduces the extent of microvascular obstruction after acute infarction.

BACKGROUND Microvascular obstruction or “no-reflow” (MO) has been shown to negatively influence left ventricular (LV) remodeling after myocardial infarction (MI).

METHODS Seventeen dogs underwent 90 min of coronary artery occlusion followed by reperfusion. Animals were then randomized to either IABC (n = 9) or control (n = 8); IABC augmentation was performed for 24 h after MI. Microvascular obstruction and infarct size by first-pass and delayed contrast-enhanced magnetic resonance imaging (MRI) were measured at 1 and 24 h after reperfusion and compared with postmortem infarct size and MO by microspheres.

RESULTS Microvascular obstruction by MRI, expressed as percent LV mass, decreased significantly in IABC (4.9 ± 2.2% to 3.6 ± 1.5%) and increased in controls (3.4 ± 0.5% to 4.9 ± 1.1% from 1 to 24 h, respectively; p < 0.001). Similar results were found for MO defined by microspheres. In the control group, MO increased significantly, during 24 h of study (from 8.8 ± 1.7% to 43.2 ± 11.1% of infarcted myocardium; p < 0.05), whereas not important change was observed in the IABC group (from 21.3 ± 7.1% to 25.8 ± 14.7%; p < 0.05 vs. control at 24 h). Infarct size, measured by MRI, increased in both groups (13.2 ± 1.8 to 15.5 ± 2.1 from 1 to 24 h, respectively; p < 0.05).

CONCLUSIONS Intra-aortic balloon counterpulsation augmentation performed after reperfusion improves myocardial perfusion at the tissue level, and reduces the extent of no-reflow caused by microvascular obstruction. (J Am Coll Cardiol 2004;43:1291–8) © 2004 by the American College of Cardiology Foundation

Reperfusion therapy significantly improves survival after acute myocardial infarction (MI) (1). Yet, despite flow restoration in epicardial coronary arteries, limited reperfusion at the tissue level due to microvascular obstruction (MO) has been documented, and is also known as the “no-reflow phenomenon” (2). Previous work has also demonstrated that this is a progressive process, which evolves mainly within the first 48 h after reperfusion (3). At the same time, continued ischemia due to MO, even after successful reperfusion (4), has been proposed as a mechanism of myocardial infarct extension (3), and has a negative prognostic impact in patients with acute MI (5). This suggests that there might be a therapeutic window for intervention to limit infarct extension by reducing the extent of MO during the immediate reperfusion period. Such an intervention could, in theory, result in better functional outcomes and improved prognosis for post-MI patients.

Intra-aortic balloon counterpulsation (IABC) is a mechanical cardiac-assist device that significantly increases diastolic and mean blood pressure in the aorta and coronary arteries, while at the same time decreasing systolic pressure, thereby unloading the heart. Intra-aortic balloon counterpulsation has been shown to improve survival in patients with acute MI who present with cardiogenic shock (6). In patients with large acute infarcts, IABC has been shown to improve clinical outcomes (7–9). However, the mechanisms underlying the beneficial effects of IABC at the myocardial tissue level remain unknown. It is not known, for example, whether IABC has a direct impact on the adequacy of post-MI reperfusion, and whether such effects are mediated by reducing the progression of microvascular obstruction, infarct size, or both.

In this study, we tested the hypothesis that IABC augmentation has a beneficial effect on microvascular function after acute MI and epicardial coronary flow restoration. We performed a randomized trial in a canine model of reperfused MI using contrast-enhanced magnetic resonance imaging (MRI) to measure the impact of IABC therapy on
the progression of MO (“no-reflow phenomenon”) and infarct size during the first 24 h after reperfusion.

METHODS

Experimental protocol. All animal studies were approved by our institutional animal care and use committee and comply with the “Guide for the Care and Use of Laboratory Animals” (NIH Publication no. 80-23, revised 1985). Seventeen mongrel dogs (25 to 30 kg) were anesthetized, intubated, and mechanically ventilated. During the 24-h period of study, all animals received prophylaxis with antibiotics (cefazolin, every 4 h) and were maintained under general anesthesia with isofluorane 1% or 2%.

Experimental MI. Catheter sheaths were placed in the right femoral artery (10 F) and right carotid artery (8 F). Subsequently, the animals were heparinized (5,000 IU intravenously). A 6 F pigtail catheter was advanced through the femoral artery into the left ventricular (LV) cavity for injection of radiolabeled microspheres and pressure monitoring. A coronary angioplasty balloon (3.5 F, 20 mm) was advanced through the right carotid artery into the proximal left anterior descending artery or left circumflex artery. Myocardial infarcts were created by inflating the angioplasty balloon for 90 min, after which time the balloon was deflated and the artery reperfused. After reperfusion, the catheter sheath in the carotid artery was removed, and the carotid artery permanently closed. The catheter sheath in the femoral artery was maintained throughout the entire study in every animal, regardless of the randomization group. No problems related to excessive bleeding or hematoma formation on the site of the incision was observed.

IABC randomization. After angioplasty balloon inflation but prior to reperfusion, each animal was randomized to either the “control” or the “IABC” group. To achieve the best augmentation with this device, a pilot study was conducted, using intra-aortic balloons containing no ferromagnetic materials, especially designed for this study. In four animals, different balloon sizes and different methods of pumping were tested. As a final result from the pilot study, the IABC group received an intra-aortic balloon (40 cc, Datascope, Mahwah, New Jersey) inserted under X-ray fluoroscopy via the femoral sheath immediately before reperfusion. The tip of the intra-aortic balloon was placed distal to the left subclavian artery, and IABC augmentation commenced immediately after reperfusion for 24 h (triggered on electrocardiogram, 1:1). To avoid any interference from the intra-aortic balloon augmentation, all data acquisition (imaging acquisition and microspheres blood sample) was done with IABC off. All animals were heparinized (100 IU/h) and sedated throughout the entire study period.

Radioactive microspheres. Myocardial blood flow (MBF) was measured at baseline, during occlusion, and at 1 and 24 h after reperfusion, prior to euthanasia. For each measurement, ~2 × 106 radioactive microspheres (15 to 16 μm diameter) labeled with 113Sn, 46Sc, 57Co, and 114Ru (PerkinElmer Inc., Wellesley, Massachusetts) were injected into the LV while an arterial blood sample was withdrawn.

MRI protocol. Images were performed at 1 and 24 h after reperfusion, using a 1.5-T magnetic resonance scanner (CV/i, GE Medical Systems). Animals were placed in right decubitus with a phased array surface coil wrapped around the chest.

First-pass perfusion imaging. Eight to 10 contiguous short-axis scout images were acquired covering the entire LV, using an electrocardiogram-gated, interleaved, saturation recovery gradient echocardiogram echoplanar imaging pulse sequence (EFGRE-T) (10). Images were acquired continuously for 1 min with intermittent breath-holds (~30 s duration), after an intravenous bolus of Gd-DTPA (0.1 mmol/kg, Magnevist, Berlex Inc., Montville, New Jersey). An entire short-axis stack was acquired every 2 to 4 heartbeats. After completion of first pass image acquisition, a second bolus of Gd-DTPA (0.1 mmol/kg) was injected.

Delayed perfusion imaging. Images were acquired 15 min after the second contrast injection using an electrocardiogram-gated, breath-hold, interleaved, inversion recovery, fast gradient echocardiogram pulse sequence (11). Images were acquired in the identical short-axis locations as the first-pass perfusion images in mid-diastole.

MRI data analysis. Magnetic resonance images were transferred to a SUN workstation (Sun Microsystems Inc., Santa Clara, California) and analyzed using a custom software package (MASS, Leiden, the Netherlands). No-reflow regions were defined as regions that showed persistent hypoenhancement for at least 1 min during the first 3 min after contrast injection (first-pass perfusion images) (3). The magnitude of MO was estimated by measuring the largest hypoenhanced area within the first minute after contrast injection. The decision was made by an agreement of two observers blind to the randomization.

Hyperenhanced regions were defined as those having distinct myocardial brightness on delayed images. The workstation window and level were set to full width and half maximum, and the hyperenhanced region was traced to determine infarct size. Endocardial and epicardial contours were delineated on delayed images. The extent of infarct size and no-reflow by MRI was calculated as the sum of region-of-interest for all slices divided by the sum of the LV cross-sectional areas for all slices. To minimize the influence of the infarct swelling at 24 h, the measurements were given as percentage of LV mass using the LV cross-sectional at the respective time-point (1 and 24 h).
Postmortem measurements. INfarct SIZE. After euthanization, the heart was excised, sectioned into short-axis slices (~1 cm thickness), and incubated in 2,3,5-triphenyltetrazolium chloride (TTC) for 20 min at 38°C to delineate viable myocardium. Each slice was photographed with a digital camera. Using a custom software package (cine, GE Medical Systems), TTC-negative areas and LV borders were manually traced for each slice. Infarct size was determined as a percentage of LV mass, given by measurements from the digital pictures.

MICROSPHERE BLOOD FLOW ANALYSIS. To determine regional MBF, short-axis slices were sectioned into 300- to 500-mg wedges and further subdivided into 3 transmural pieces (i.e., endocardial, midwall, and epicardial). Myocardial samples were weighed and counted in a gamma emission well spectrometer (PerkinElmer Inc.) along with reference blood samples. Blood flow was determined using standard techniques (12). Microsphere data from two animals (one from each group) were not included in the analysis, due to problems with microsphere sampling.

On the basis of TTC staining and MBF, we assigned the entire protocol, two animals in the IABC group and one in control group. Seventeen animals were randomized to either the IABC (n = 9) or control (n = 8) arms of the experimental study. Three animals did not complete the entire protocol, two animals in the IABC group and one in control group. Table 1 summarizes hemodynamic and blood flow parameters. Blood pressure decreased significantly with coronary occlusion (p < 0.001), and returned to baseline 24 h after reperfusion. Myocardial blood flow in the infarcted region was similar for both groups at baseline, occlusion, or reperfusion (ANOVA; p = NS). No differences in the size of the risk region were observed between the two groups (36.1 ± 3.8% IABC vs. 37.1 ± 2.5% controls; p = NS).

RESULTS

Hemodynamics and MBF. Seventeen animals were randomized to either the IABC (n = 9) or control (n = 8) arms of the experimental study. Three animals did not complete the entire protocol, two animals in the IABC group and one in control group. Table 1 summarizes hemodynamic and blood flow parameters. Blood pressure decreased significantly with coronary occlusion (p < 0.001), and returned to baseline 24 h after reperfusion. Myocardial blood flow in the infarcted region was similar for both groups at baseline, occlusion, or reperfusion (ANOVA; p = NS). No differences in the size of the risk region were observed between the two groups (36.1 ± 3.8% IABC vs. 37.1 ± 2.5% controls; p = NS).

Postmortem analysis. There was a high degree of agreement between the amount of MO measured by microspheres and by MRI at 1 and 24 h after reperfusion (Fig. 1). A high correspondence for infarct location was demonstrated from hyperenhanced areas observed on delayed contrast MRI and TTC-negative regions (Fig. 2). Infarct size by MRI (15.5 ± 2%) had a high agreement with infarct size measured by TTC (12 ± 2%) (Fig. 3).

Table 1. Hemodynamic Measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Occlusion</th>
<th>Reperfusion (1 h)</th>
<th>Reperfusion (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>93 ± 5</td>
<td>113 ± 10</td>
<td>94 ± 5</td>
<td>108 ± 11</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>121 ± 5</td>
<td>87 ± 4*</td>
<td>88 ± 7*</td>
<td>111 ± 10</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>100 ± 6</td>
<td>70 ± 5*</td>
<td>70 ± 6*</td>
<td>92 ± 7</td>
</tr>
<tr>
<td>MBF (ml/min/g)-IABC group</td>
<td>0.6 ± 0.1</td>
<td>0.26 ± 0.1*</td>
<td>0.69 ± 0.3</td>
<td>0.54 ± 0.1</td>
</tr>
<tr>
<td>MBF (ml/min/g)-control group</td>
<td>0.72 ± 0.1</td>
<td>0.26 ± 0.1*</td>
<td>0.96 ± 0.2</td>
<td>0.67 ± 0.1</td>
</tr>
<tr>
<td>MBF %</td>
<td>104 ± 11</td>
<td>8.7 ± 3</td>
<td>166 ± 28</td>
<td>92 ± 16</td>
</tr>
</tbody>
</table>

*p < 0.001 vs. baseline.

BP = blood pressure; IABC = intra-aortic balloon counterpulsation; MBF = myocardial blood flow in the infarcted area; MBF (%) = percentage of myocardial blood flow in the infarcted area relative to remote.

Statistical analysis. Analyses were performed using STATA software (College Station, Texas). All values are expressed as mean ± SEM. Hemodynamic and MBF parameters were analyzed by multiple measures analysis of variance (ANOVA). Risk region sizes were compared between groups using an unpaired t test. Linear regression analysis (Stata Corporation, College Station, Texas) was used to compare MRI measurements (no-reflow zone and infarct size) across time and between groups. We also used robust regression technique to suppress distortions introduced by outlying observations in the data set. Robust regression, as previous described in details elsewhere (14,15), adjusts the weights applied to observations in an iterative fashion based upon the residuals from a prior estimation step—the larger the residual the smaller the weight. When no substantial changes to the weights can be found, the iterative procedure stops, and a different weighting scheme is used. The entire procedure stops after the two weighting strategies are exhausted. A level of p < 0.05 was considered statistically significant.
MO size from 4.9 ± 2.2% to 3.6 ± 1.5% between 1 and 24 h (p < 0.001) (Fig. 5A). In a 24-h period of study, there was an overall increase of 60 ± 22% in MO extent on the control group, whereas a decrease of 10 ± 10% was seen with intra-aortic balloon augmentation (from 9.1 ± 1.5% to 13.5 ± 3.1%; p < 0.05). The same pattern was noted when analyzed inside the risk region and the infarcted myocardium. In the risk region, the amount of myocardial tissue involved by MO showed a significant decrease with intra-aortic balloon augmentation (from 13.3 ± 5.9% to 9.3 ± 3.9%), whereas an important increase was observed in the control group (from 9.1 ± 1.5% to 13.5 ± 3.1%; p < 0.05). The same pattern was noted when analyzed inside the infarcted myocardium, with the MO extent decrease in the IABC group (from 25.9 ± 9% to 19.1 ± 7.6%), and an increase in controls (from 27.1 ± 4.6 to 29.4 ± 4.2%; p = NS).

The above findings were confirmed by microsphere measurements. The MO extent assessed as TTC-negative areas with MBF <50% of the remote evolved differently between the groups. In the control group, an important increase in MO extension was noted (from 8.8 ± 1.7% to 43.2 ± 11.1% of infarcted myocardium; p < 0.05) (Fig. 5C). In contrast, the IABC group did not exhibit significant changes (from 21.3 ± 7.1% to 25.8 ± 14.7%; p < 0.05 vs. control at 24 h). These findings support the importance of balloon augmentation during the early phase of reperfusion.

**Infarct size.** Magnetic resonance imaging hyperenhanced area increased over 24 h in both groups (from 13.2 ± 1.8% to 15.5 ± 2.1%, 1 and 24 h after reperfusion, p < 0.05) (Fig. 6). However, hyperenhanced region increase was significantly less in the IABC group than in control animals (13 ± 2
2.9% to 14.9% in the IABC group vs. 13.5% in controls, at 1 and 24 h, respectively; \( p < 0.05 \) (Fig. 6). Also, relative to the risk region, the hyperenhanced region increased for the entire group from 1 to 24 h (36.9 ± 5.5% to 45 ± 5.8%; \( p < 0.01 \)). In the IABC group, hyperenhanced area increase was less (36.2 ± 8.6% to 40.8 ± 9.3%) than in the control group (37.9 ± 6.6% to 47 ± 6.4%; \( p = \text{NS} \)).

To establish whether or not the above findings were due to edema or necrosis, further microsphere ratio analysis was performed. In the control group, baseline microsphere ratio analysis demonstrated microsphere dilution and consequent infarct expansion (infarct/remote spheres ratio \( 1.0 ; 0.9 \pm 0.05 \)). However, in the IABC group no infarct expansion was noted (infarct/remote spheres ratio equal to 1.0 ± 0.06).

**DISCUSSION**

This is the first study to demonstrate a reduction in the postinfarction progression of microvascular obstruction due to IABC. Moreover, our results also demonstrate a reduction in postreperfusion infarct size expansion, which may be related to microvessel patency. Furthermore, our study confirms previous observations (3) with respect to the magnitude of both MO and infarct size increase after reperfusion in control animals.

**MO (no-reflow).** Microvascular obstruction is a common byproduct of reperfused acute MI (7,16–18). Recent studies estimate that 25% to 30% of acute MI patients treated with direct or rescue angioplasty develop significant microvessel occlusion with deleterious effects on prognosis in terms of greater LV remodeling (18,19), greater propensity for malignant arrhythmias (20), and adverse clinical outcomes (18,21). The degree of postreperfusion MO is directly related to the duration of coronary artery occlusion (17,22). Similarly, the magnitude of MO is directly related to the amount of ischemic tissue during coronary occlusion (2).

Significantly, the process of microvascular damage is clearly progressive after epicardial artery ref low (3,16). While several previous studies have attributed the beneficial effects of diverse interventions to a reduction in MO, this is the first experimental demonstration of a direct effect on the progression of no-reflow after infarction.

The mechanisms by which MO influences postinfarct prognosis remain poorly understood. Several previous studies established a link between MO and greater LV remod-
The quality of life of patients who suffer acute MI (3,5) and control (n = 8) animals increased over 24 h of reperfusion in both groups (p < 0.03). Infarct expansion was decreased in IABC relative to controls (p < 0.04). p < 0.04 vs. control. LV = left ventricular.

Figure 6. Infarct expansion measured by delayed magnetic resonance imaging (MRI) in intra-aortic balloon counterpulsation (IABC) (n = 9) and control (n = 8) animals increased over 24 h of reperfusion in both groups (p < 0.03). Infarct expansion was decreased in IABC relative to controls (p < 0.04). p < 0.04 vs. control. LV = left ventricular.

The many other factors involved in the clinical utilization of any therapeutic modality may confound and even negate the beneficial effects of IABC on no-reflow and infarct size increase demonstrated in our study. In addition, the mechanisms underlying the inhibitory effect of IABC on MO remain unknown. The possibility that enhanced microvessel flow prevents intracapillary cell adhesion and consequent transmigration of inflammatory cells into the interstitial space is a potential explanation for the differences in the rate of microvessel occlusion observed in the two groups of animals. This potential mechanism is also invoked to explain the beneficial effects of adenosine and other tissue vasodilators shown to improve outcomes in coronary interventions (25). Other possibilities relate to the potential effects of IABC on reperfusion injury, ventricular load, or inflammation by yet unknown mechanisms. The previously demonstrated beneficial effect of IABC on patients with postinfarct cardiogenic shock could be, in part, due to IABC’s effect on reducing MO, given that patients in shock frequently have large territories of injured myocardial tissue caused by prolonged epicardial coronary occlusion.

**Infarct size.** Previous research has demonstrated an increase in infarct size over time, described as a progressive wavefront of necrosis away from the infarct core (16). However, the differentiation between true necrosis and expansion due to edema and the inflammatory process still poses a significant challenge to clinical practice.

Using MRI, our group has documented this pattern of increase delayed hyperenhancement areas, along with microvascular obstruction in a canine model (3). In the present study, infarct size was measured by MRI, and necrosis expansion was confirmed with infarct/remote spheres ratio given by microsphere analysis (13). There was a significant increase in the hyperenhanced region in the control animals compared with the IABC group. In spite of this, the infarct/remote spheres analysis did not confirm the presence of necrosis (infarct extension). The control group demonstrated infarct expansion (infarct/remote spheres ratio < 1.0; 0.9 ± 0.05), and, in the IABC group, no infarct expansion was noted (infarct/remote spheres ratio = 1.0 ± 0.06). This absence of infarct expansion, in 24 h of study, was associated with a decrease in MO progression. The presence of infarct expansion in the control group does not allow us to draw any conclusions regarding differences in necrosis extension between groups. However, these results suggest a cause/effect relationship between MO and cellular edema development. Future studies are necessary to clarify this cause/effect relationship.

Large clinical trials testing the effect of IABC on clinical outcomes have provided contradictory results (6,26). While IABC is clearly beneficial in patients with large MIs accompanied by cardiogenic shock (6), another trial that enrolled a large variety of postinfarction patients failed to demonstrate a clear-cut benefit of IABC over conventional therapy (26). None of the previous trials measured the effect of balloon augmentation directly in the infarcted area, and, thus, it is difficult to make a direct comparison with the present study. The discrepant results from different trials could be due to the possibility that patients with large infarcts benefit more from IABC therapy than patients with smaller infarcts. The results from our study suggest that clinical trials in patients with large infarcts should be reconsidered, given the potential for reducing ultimate infarct expansion, possible due to an improvement in myocardial stiffness after acute MI.

The mechanisms of protection relative to infarct expansion that are associated with IABC therapy also remain unclear. The idea that the MO could further expend the infarcted region is not new and has been intensely debated over the last three decades. Areas of MO are commonly
concentrated at the infarct core where ischemia was greatest at the time of coronary occlusion and cell death is widespread (3,16,22). In addition, widespread microvessel damage could impair the delivery of nutrients and removal of toxins to and from the infarct penumbra, promoting inflammatory process with consequent infarct expansion and a worse prognosis. However, our study documents the association between both phenomena in an experimentally controlled trial of IABC.

Methodological considerations. The most positive methodologic feature of this study is its randomized design. Randomization was performed after the infarct-related artery was occluded but before it was reopened by balloon deflation. Second, the two main determinants of myocardial injury (occlusion time and risk region size) were controlled rigorously in this experimental design. Third, infarct size and extent of no-reflow were quantified by objective criteria and blindly, relative to group assignment.

The measurement of microvascular obstruction extent depends on the criteria chosen to define microvessel occlusion by different methods (27). We chose a threshold of 50% or less relative to remote myocardial flow to allow for comparability with previously published data. At present, there is no definitive data to identify the ideal delay time after contrast injection for measurement of MO extent by MRI. Due to the dynamics of the contrast agent, MO decreases over time after contrast. Problems with measurements would be anticipated if images in the control group were acquired at slightly different postcontrast times, compared with the IABC group. In this study, measurements were performed using definitive criteria. Microvascular obstruction extent was defined as the largest hypoenhanced area at the first minute after contrast injection, as agreed by two observers blinded to the randomization. We found a very good correlation between no-reflow defined by microspheres and MRI, as previously documented in our earlier work (5,28). Also, much has been written about infarct size measurements made by MRI (3,5,22,28). This noninvasive, in vivo method is undoubtedly reliable and consistently produces overestimation when compared with TTC ex vivo, primarily because of partial volume effects (28). To control the influence of a possible partial volume effect and to permit a clear interpretation of our results, further analyses-based microsphere ratio analysis was performed.

Conclusions. In conclusion, this study documents a reduction in the process of microvascular obstruction produced by IABC in experimental acute MI. In addition, the study demonstrates a concomitant reduction in infarcted area expansion caused by IABC. Finally, the study confirms the findings of previous studies, which show that both microvascular obstruction and infarcted area expansion progress significantly after reperfusion following acute MI. These findings have important implications to our understanding of the pathophysiology of acute MI, and may impact the design of future strategies to further limit left ventricular damage beyond reperfusion in patients with this condition.

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