Preclinical research

The effect of intra-aortic balloon counterpulsation on left ventricular functional recovery early after acute myocardial infarction: a randomized experimental magnetic resonance imaging study

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Aims: We sought to determine whether intra-aortic balloon pump (IABP) counterpulsation improves the recovery of left ventricular (LV) systolic function after reperfused acute myocardial infarction (AMI).

Methods and results: Fourteen dogs underwent 90-min coronary artery occlusion followed by reperfusion. Seven animals were randomized to IABP counterpulsation immediately after reperfusion. Tagged, cine, and contrast-enhanced magnetic resonance imaging were used for regional and global LV functional assessment and MI characterization, respectively. Image acquisition was performed at 1 h, 6 h, and 24 h after reperfusion, during which the IABP device was paused.

Animals randomized to IABP demonstrated an earlier improvement of LV ejection fraction when compared with controls (25 ± 3 vs. 25 ± 2% at 1 h, P = 0.91; 26 ± 3 vs. 26 ± 2% at 6 h, P = 0.015; and 38 ± 3 vs. 35 ± 1% at 24 h, P = 0.34). Regional functional analyses revealed the same behavior among non-infarcted risk regions, i.e., earlier circumferential systolic strain improvement in the IABP group than in controls. Importantly, however, the degree of LV functional recovery 24 h after reperfusion was similar whether IABP counterpulsation was used or not.

Conclusion: IABP counterpulsation accelerates but does not significantly improve the recovery of LV systolic function after reperfused AMI.

Keywords: Intra-aortic balloon pump; Magnetic resonance imaging; Myocardial infarction; Myocardial stunning

Introduction

The intra-aortic balloon pump (IABP) is currently the most widely used of all circulatory assist devices.1 Counterpulsation improves left ventricular (LV) performance by favourably influencing myocardial oxygen balance. It increases myocardial oxygen supply by diastolic augmentation of coronary perfusion2 and decreases myocardial oxygen requirements through a reduction in the afterload component of cardiac work.3

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Support for the use of IABP in patients with acute myocardial infarction (AMI) has been based on the above theoretical consideration. However, the relationship between the beneficial physiological effect of counterpulsation and post-AMI LV functional recovery remains largely undefined. In fact, several studies have investigated the immediate effect of IABP on LV performance and demonstrated that, during counterpulsation, there is a significant improvement in LV haemodynamics. However, an important difference exists between the improved haemodynamics provided by counterpulsation itself and the possible favourable effect IABP might have on post-AMI non-assisted LV contractility. In the present study we were interested in assessing this latter effect and, therefore, the IABP device was turned off during the entire scanning session.

It is well known that myocardial stunning is an important component of the reperfused AMI pathophysiology. Indeed, it has become evident that in the current era of widespread reperfusion therapy, the role of stunned myocardium on the functional, and ultimately, clinical recovery of patients with AMI becomes increasingly important. In addition, it has been previously reported that a large proportion of the mortality of patients undergoing reperfusion therapy occurs within the first 24 h of AMI. Patients dying early are more likely to present with pump failure and die of events related to LV dysfunction than those dying after the first 24 h. So far, however, the potential contribution of IABP counterpulsation to restore the contractile power of salvaged stunned myocardium has not been completely understood.

In this randomized experimental study, we have used cardiac magnetic resonance imaging (MRI) as a gold standard for the assessment of LV regional function, to determine whether the favourable effect of IABP counterpulsation translates into improved global and regional LV functional recovery early after reperfused AMI.

**Methods**

**Experimental model**

Fourteen adult mongrel dogs (25 to 30 kg) were anaesthetized, intubated, and mechanically ventilated with isoflurane anaesthesia. AMI was created in all animals by a 90-min closed-chest occlusion of either the proximal left anterior descending or the left circumflex coronary artery using an angioplasty balloon. After 90 min, the balloon was deflated to allow full reperfusion of the infarcted territory, and all animals were followed for 24 h thereafter. The study protocol was approved by the Johns Hopkins Institutional Animal Care and Use Committee and the animals in this study were handled according to the Guide for the Care and Use of Laboratory Animals (NIH Publication no.80-23, revised 1985).

**IABP protocol**

After angioplasty balloon inflation, but prior to reperfusion, each animal was randomized either to receive IABP counterpulsation, or to the control group. The animals randomized to the IABP group received a 40-ml intra-aortic balloon containing no ferromagnetic material, specially designed for this experiment (Datascope Corporation, Mahwah, NJ), inserted under X-ray fluoroscopy via a femoral sheath immediately before reperfusion. The tip of the intra-aortic balloon was placed distal to the left subclavian artery and counterpulsation (ECG-triggered, 1:1 assist ratio) was started immediately after reperfusion and maintained for 24 h. To avoid any interference from the physiological changes induced by counterpulsation, including altered loading conditions, the IABP device was paused during the entire scanning session (~90 min). Data acquisition for global and regional functional analyses was performed 43 ± 4 and 66 ± 5 min after pausing the counterpulsation device.

**MRI Protocol**

Image acquisition was performed at 1 h, 6 h, and 24 h after reperfusion using a 1.5-T Signa CV/i scanner (GE Medical Systems, Waukesha, WI). Tagged magnetic resonance images were acquired with an ECG-gated, segmented k-space, fast gradient recalled echo pulse sequence with spatial modulation of magnetization to generate a grid tag pattern. Eight contiguous short-axis slices were prescribed to cover the LV from base to apex. Imaging parameters were as follows: 6.5-mm tag separation, 280-m field of view, 8-mm slice thickness, matrix size 256 × 160, repetition time 5.5 ms, echo time 1.4 ms, flip angle α = 12°, and temporal resolution 22 ms.

For the assessment of global LV function, a non-tagged cine acquisition in the same short-axis locations as the tagged images was performed using a steady-state free precession pulse sequence. Imaging parameters were as follows: repetition time 4.4 ms, echo time 1.7 ms, flip angle α = 45°, 280-m field of view, 8-mm slice thickness, matrix size 256 × 160 and temporal resolution 18 ms.

After completion of the cine acquisition, an intravenous bolus injection of 0.1 mmol/kg gadolinium-DTPA (5 mL/s, Magnevist, Berlex) was administered for first-pass perfusion imaging. Details of the MRI perfusion pulse sequence are given elsewhere. After completion of the first-pass image acquisition, a second bolus of 0.1 mmol/kg gadolinium-DTPA was given. Delayed-enhancement images were acquired 15 min after second contrast injection using a previously described inversion recovery fast gradient-echo pulse sequence. Both first-pass and delayed-enhancement images were acquired in the same short-axis locations as the tagged images. After completion of the MRI study, the animals were humanely euthanized.

**Radioactive microspheres blood flow analysis**

Regional myocardial blood flow was measured at baseline and during coronary artery occlusion to determine the regions at risk. For each measurement, ~2 × 10⁶ radioactive microspheres (15–16 μm diameter) labeled with 113Sn, 46Sc, 57Co, or 114Ru (New England Nuclear) were injected into the left ventricle. Starting before microsphere injection and continuing for 2 min thereafter, arterial blood samples were withdrawn at a rate of 2.06 mL/min. Regional blood flow was then determined using standard techniques.

**Data analysis**

Cine (steady-state free precession), first-pass perfusion and delayed-enhancement MRI data were quantitatively analysed using a custom software tool (Cinetool, General Electric). Global LV functional assessment was based on Simpson’s Rule Method. Endocardial borders were manually contoured in cine short-axis slices at end-diastolic and end-systolic phases.
(Figure 1A and B). From delayed-enhancement images, infarct extent was semi-automatically determined by computer counting of all hyper-enhanced pixels within the myocardium, i.e., those with image intensity >2SD above mean signal intensity of a remote region in the same image (Figure 1C). Similarly, from first-pass perfusion images, microvascular obstruction areas were semi-automatically determined as the sum of all hypo-enhanced pixels within the infarcted myocardium, i.e., those with image intensity <2SD below mean signal intensity of remote myocardium (Figure 1D).

Images from all data sets were cross-registered using the point of insertion of the right ventricular wall in the LV anteroseptal intersection as an anatomic landmark. For each animal, only five short-axis slices from the tagged MRI dataset were used for regional functional analyses. From the original eight slices acquired, the most apical and most basal slice locations were always excluded. From the remaining six slices, based on DE images, the five consecutive short-axis locations that covered the largest volume of infarcted myocardium were selected for regional functional analyses. Each slice was divided into six segments (30 segments/animal).

Tagged images were analysed quantitatively using a custom software package (Diagnosoft HARP®, Diagnosoft Inc) based on the HARP method (Figure 1E, F, and G). For each cardiac phase, the Lagrangian circumferential shortening strain was computed at the mid-wall LV layer of each segment to generate strain curves. Peak systolic circumferential strain was determined and recorded for each segment (Figure 1H). Peak systolic strain could be calculated in 402 (96%), 399 (95%), and 389 (93%) of a total of 420 segments at 1 h, 6 h, and 24 h after reperfusion, respectively.

For each animal, the 30 myocardial segments were divided into four categories according to the degree of ischaemic injury sustained during coronary occlusion and reperfusion. Transmural infarction segments were defined as those with delayed-enhancement involving ≥50% of their areas, sub-endocardial infarction segments as those with involvement of <50% of their areas by delayed-enhancement, and risk region segments as those without any involvement by delayed-enhancement, but with regional blood flow measured by radioactive microspheres <50% of remote during coronary artery occlusion. All other regions were considered remote segments. Moreover, based on first-pass perfusion images, all MI segments were further sub-divided into those with and without microvascular obstruction (‘no-reflow’).

**Statistical analysis**

All continuous values are reported as mean ± SEM. Simple linear regression analysis was used to compare continuous variables between the groups at different time points. The observations derived from segmental analyses were regarded as independent across dogs, but not within dogs (STATA 7.0, College Station, TX, USA). The Huber/White/sandwich estimator of variance was used in order to take into account the correlation within dogs. All tests were two-tailed and a value of P < 0.05 was considered indicative of statistical significance.

**Results**

Fourteen animals were randomized to either the IABP (n = 7) or control (n = 7) groups. AMI was identified by the delayed-enhancement technique in all 14 animals and involved 163 segments (81 transmural infarction and 82 sub-endocardial infarction segments). Based on regional myocardial blood flow measured by radioactive microspheres, 90 segments without any involvement by delayed-enhancement were considered to be risk region segments. The remaining 167 segments were considered as remote. In addition, based on first-pass perfusion images, a total of 78 AMI segments (65 transmural infarction and 13 sub-endocardial infarction segments) were found to contain areas of microvascular obstruction, i.e. they were affected by the no-reflow phenomenon.

The characteristics of IABP and control groups in terms of myocardial damage sustained during coronary occlusion were compared using a simple linear regression model. The results are presented in Table 1. The difference in infarct size between the IABP and control groups was significant (P < 0.05).
occlusion and reperfusion are summarized in Table 1. In addition, haemodynamic parameters from both groups at different time points are summarized in Table 2.

Global LV function

Both the IABP and control groups exhibited severe global LV dysfunction 1 h after reperfusion (Figure 2). Left ventricular ejection fraction (LVEF) was significantly reduced in both groups, with no significant difference between them at 1 h (25 ± 2% IABP group vs. 25 ± 2% controls, \( P = 0.91 \)). At 6 h after reperfusion, however, the IABP group demonstrated significantly higher LVEF than controls (36 ± 3 vs. 26 ± 2%, \( P = 0.015 \)). In fact, between 1 h and 6 h after reperfusion, the magnitude of LVEF improvement was higher in the IABP group than in controls (improvement of 11 ± 3% in IABPs vs. 0 ± 1% in controls, \( P = 0.003 \)). On the other hand, between 6 h and 24 h, the magnitude of LVEF improvement was higher in controls (improvement of 2 ± 1% in IABPs vs. 10 ± 2% in controls, \( P = 0.012 \)). Global LV systolic function was similar in both groups 24 h after reperfusion (38 ± 3% IABP vs. 35 ± 1% controls, \( P = 0.34 \)) (Figure 2).

Regional LV function

Transmural infarction

Both groups displayed significant regional systolic dysfunction among segments with transmural AMI. In addition, peak systolic strain was not significantly different between the groups at all time points (0.7 ± 0.5 vs. 0.5 ± 0.5% at 1 h, \( P = 0.78 \); −0.2 ± 0.7 vs. 0.5 ± 0.4% at 6 h, \( P = 0.40 \) and −0.1 ± 0.5 vs. −0.3 ± 0.4% at 24 h, \( P = 0.74 \); for IABPs vs. controls, respectively) (Figure 3).

Subendocardial infarction

Both groups also exhibited marked functional impairment within segments with non-transmural, sub-endocardial infarction. Initially, systolic strain did not differ between groups at 1 h and 6 h after reperfusion (−2.2 ± 0.5 vs. −2.9 ± 0.6% at 1 h, \( P = 0.39 \) and −2.4 ± 0.4 vs. −2.8 ± 0.4% at 6 h, \( P = 0.43 \); IABPs vs. controls, respectively). However, at 24 h after reperfusion, sub-endocardial AMI segments from animals randomized to IABP demonstrated significantly better regional systolic contractility compared with those from the control group (systolic strain = −7.2 ± 1.2% in IABPs vs. −4.4 ± 0.3% in controls, \( P < 0.001 \)) (Figure 3).

Risk regions

Among non-infarcted, risk region segments, both groups displayed significant regional systolic dysfunction at 1 h (−5.4 ± 0.4 vs. −5.3 ± 0.5%, IABPs vs. controls, respectively; \( P = 0.86 \)). At 6 h after reperfusion, however, the group randomized to IABP counterpulsation recovered normal contractility, while controls still displayed significant regional systolic dysfunction (−12.1 ± 1.0 vs. −6.0 ± 0.4%, \( P < 0.001 \)). Both exhibited normal contractility by 24 h (−13.9 ± 1.1 vs. −12.8 ± 0.6%, IABPs vs. controls, respectively; \( P = 0.40 \)). Therefore, among non-infarcted risk region segments, both groups showed a significant systolic strain improvement over time, but the improvement occurred earlier in the IABP group (Figure 3).

Remote myocardium

Both groups displayed normal systolic strain values in remote segments at all times (−12.9 ± 0.7 vs. −11.9 ± 0.8% at 1 h, \( P = 0.32 \); −13.5 ± 0.6 vs. −12.9 ± 0.5% at 6 h, \( P = 0.39 \), and −13.3 ± 0.7 vs. −13.2 ± 0.5% at 24 h, \( P = 0.92 \); IABPs vs. controls, respectively).

Microvascular obstruction

Among AMI segments affected by microvascular obstruction, both groups displayed the same degree of regional dysfunction at 1 h after reperfusion (0.6 ± 0.3% in IABPs vs. 0.8 ± 0.6% in controls, \( P = 0.75 \)). However, at both 6 h and 24 h after reperfusion, LV systolic contractility was slightly but significantly better in the group that received IABP counterpulsation compared to controls (−1.2 ± 0.4 vs. 0.6 ± 0.4% at 6 h, \( P = 0.011 \) and −1.9 ± 0.5 vs. −0.1 ± 0.3% at 24 h, \( P = 0.007 \)).

Discussion

In this randomized experimental study, we have demonstrated that IABP counterpulsation improves the time course of recovery of LV systolic function after reperfused AMI. More specifically, using both tagged and contrast-enhanced magnetic resonance imaging, we have demonstrated that this beneficial effect is mainly due to an acceleration of the functional recovery of non-infarcted, stunned myocardial regions. However, despite the accelerated functional recovery, IABP counterpulsation did not result in a significant improvement of LV systolic function 24 h after reperfusion. Indeed, global and regional LV systolic function showed similar levels of recovery whether

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<th>Table 1 The characteristics of IABP and control groups in terms of myocardial damage sustained during coronary occlusion and reperfusion</th>
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<td><strong>AMI segments affected by no-reflow, n</strong></td>
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LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery.
IABP counterpulsation was used or not. Our results can be summarized as follows:

(i) When started immediately after reperfusion, IABP counterpulsation accelerated the recovery of regional systolic contractility among reversibly injured risk region segments.

(ii) IABP counterpulsation also significantly improved regional systolic contractility in segments with sub-endocardial infarction 24 h after reperfusion.

(iii) Although animals randomized to receive IABP counterpulsation demonstrated earlier recovery of LV global systolic function, both groups displayed similar levels of functional recovery 24 h after reperfusion.

(iv) Finally, among infarcted segments presenting with microvascular obstruction, IABP counterpulsation resulted in a discrete but significant systolic strain improvement over time.

Currently, the main indications for IABP placement in patients with AMI include cardiogenic shock, haemodynamic support during catheterization and/or angioplasty or prior to high-risk surgery, mechanical complications of AMI, and refractory post-AMI unstable angina. In essence, the use of IABP in these patients has been supported based on its ability to concomitantly increase myocardial oxygen supply by diastolic augmentation of coronary perfusion and decrease myocardial oxygen requirements through a reduction in the impedance to LV ejection. However, despite the widespread use of IABP in patients with complicated AMI, particularly in those with severe LV dysfunction, the influence of counterpulsation on LV functional recovery after reperfused AMI remained poorly understood.

In a large multi-centre randomized study, Stone et al. 18 found that post-AMI patients randomized to IABP, as well as those treated conservatively, demonstrated a significant improvement in LVEF between acute and pre-discharge left ventriculograms. However, they were unable to detect any treatment-related difference in the degree of LVEF improvement. Our results are in partial agreement with these findings in that, as early as 24 h after reperfusion, no LVEF difference could be detected between animals randomized to IABP and controls. However, since we followed the recovery of LV systolic function more closely (at 1 h, 6 h, and 24 h after reperfusion), we were able to demonstrate that the improvement in LVEF occurred earlier in the IABP group than in controls. Moreover, while Stone et al. evaluated LV regional function and defined the infarct zones based on left ventriculography, we used tagged MRI for regional functional assessment and delayed-enhancement MRI for infarct characterization. Therefore, we were able to demonstrate that this superior LVEF improvement is, in fact, related to the accelerated regional functional recovery of reversibly injured myocardium in the risk region and sub-endocardial AMI segments.

IABP counterpulsation and myocardial stunning

It is well known that acute myocardial ischaemia causes almost immediate regional wall-motion abnormalities. Moreover, it has been demonstrated that such episodes of transient ischaemic insult can result in prolonged mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite return of normal perfusion: the so called myocardial stunning phenomenon. Further, it has been shown that the rate of functional recovery of stunned myocardium is, in general, inversely proportional to the duration of coronary artery occlusion. In our experimental model we performed a 90-min coronary artery occlusion followed by full reperfusion of the ischaemic territory. Therefore, our study fits the experimental model of stunning after a partly reversible (no necrosis) plus partly irreversible (some areas of necrosis) episode of regional ischaemia in vivo (e.g. a coronary occlusion ≥ 20 min but < 3 h in the dog) as described by Kloner et al. 7

In our model, risk region and sub-endocardial AMI segments were totally or predominantly composed of

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<th>Table 2  Summary of the haemodynamic parameters from each group at different time points</th>
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![Figure 2] Bar graph comparing LVEF between groups at different time points (i.e. at 1 h, 6 h, and 24 h after reperfusion). Ejection fraction improves in the IABP earlier than in the control group.
non-infarcted myocardium that was subjected to reversible ischaemic injury. Therefore, our results indicate that, when started immediately after reperfusion, counterpulsation has a favourable effect on the functional recovery of post-AMI stunned myocardium. In contrast, among regions with little or no stunned myocardium, such as transmural AMI and remote segments, no improvement by IABP counterpulsation was detected. The phenomenon of myocardial stunning is likely to be a multifactorial process that results from the interaction of multiple pathogenic mechanisms. Current conceptual theory regarding the mechanisms of myocardial stunning suggests that it consists of two components: one that develops during ischaemia (ischaemic injury), and one that develops after reperfusion. Since, in our experimental model, IABP counterpulsation was started immediately after reperfusion and not during coronary artery occlusion, we believe that the observed favourable functional recovery effect must be related to the latter component. The two most important hypotheses regarding the myocardial stunning pathogenesis are the disturbance of calcium homeostasis and the oxidative stress secondary to the generation of reactive oxygen species during myocardial ischaemia and reperfusion. The exact mechanism by which the physiological changes induced by IABP counterpulsation favourably interfere with either or both these pathogenic processes remains to be elucidated. Yet, it seems reasonable to hypothesize that the combination of enhanced coronary blood flow with decreased myocardial oxygen requirements could contribute to the normalization of calcium homeostasis (including recovery of myofilament sensitivity to calcium) and the elimination and/or neutralization of reactive oxygen species.

IABP counterpulsation and microvascular obstruction

In a recent study, our group demonstrated that, when started immediately after reperfusion, IABP counterpulsation results in a reduction of the extent of the no-reflow phenomenon after reperfused AMI. In addition, it has previously been shown that the presence of microvascular obstruction is associated with worse regional systolic function and impaired LV functional recovery. Our finding that IABP counterpulsation was associated with improved functional recovery among AMI segments affected by microvascular obstruction is in accordance with these previous reports. Even though the degree of functional improvement among these segments was small and might not have had a significant influence on global LV functional recovery, we believe it could, hypothetically, have a favourable effect in terms of...
preventing LV remodelling. However, in the present study we followed the animals for only 24 h after coronary artery occlusion and reperfusion and, therefore, were not able to evaluate the relationship between IABP counterpulsation and long-term outcomes, such as LV remodelling.

Conclusion

In the current era of widespread reperfusion therapy, the role of the non-infarcted reversibly injured myocardium on the functional, and ultimately, clinical recovery of patients with AMI becomes ever more important. The use of intra-aortic balloon counterpulsation in the early post-AMI period has been advocated in many of these patients in an attempt to provide temporary mechanical support to the failing left ventricle. Therefore, IABP counterpulsation not only supports the heart through the early recovery stages, but also seems to have a favourable influence on the recovery process itself. Particularly in patients with large MIs presenting with cardiogenic shock, this may be especially important within the first 24 h of reperfusion, during which mortality is significant and frequently due to LV pump failure.

It is important to highlight, however, that at 24 h after reperfusion, the degree of functional recovery was similar whether IABP counterpulsation was used or not. Therefore, even though IABP counterpulsation might have an important role in supporting and improving the clinical status of patients in the early phases of reperfused AMI, it does not seem to have a significant beneficial effect in terms of long-term LV functional improvement.

Acknowledgements

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