Timing of initiation of intra-aortic balloon pump in patients with acute myocardial infarction complicated by cardiogenic shock: A meta-analysis

Kongyong Cui | Shuzheng Lyu | Hong Liu | Xiantao Song | Fei Yuan | Feng Xu | Min Zhang | Mingduo Zhang | Wei Wang | Dongfeng Zhang | Jinfan Tian | Yunfeng Yan | Kuo Zhou | Lingxiao Chen

Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China

Correspondence
Shuzheng Lyu, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart Lung and Blood Vessel Diseases, 2 Anzhen Road, Beijing 100029, China.
Email: shuzheng023@163.com

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Abstract

**Background:** For patients with acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) undergoing primary percutaneous coronary intervention (PCI), the optimal timing of the initiation of intra-aortic balloon pump (IABP) therapy remains unclear. Therefore, we performed the first meta-analysis to compare the outcomes of IABP insertion before vs after primary PCI in this population.

**Methods:** Electronic databases of PubMed, EMBASE, and Cochrane Library were comprehensively searched from inception to April 1, 2019, to identify the eligible studies. The main outcomes were short-term (in-hospital or 30 days) and long-term (≥ 6 months) mortality. In addition, pooled analysis of risk-adjusted data were also performed to control for confounding factors.

**Results:** Seven observational studies and two sub-analysis of randomized controlled trials involving 1348 patients were included. Compared to patients inserted IABP after PCI, patients who received IABP therapy before primary PCI had similar risks of short-term (odds ratio [OR] 0.88, 95% CI 0.49 to 1.59) and long-term (OR 0.99, 95% CI 0.58 to 1.68) all-cause mortality. Moreover, a pooled analysis of risk-adjusted data also found similar effects of the two therapies on short-term (OR 0.65, 95% CI 0.34 to 1.25) and long-term (OR 0.68, 95% CI 0.17 to 2.72) mortality. Besides, no significant difference was found between the two groups with respect to reinfarction, repeat revascularization, stroke, renal failure, and major bleeding.

**Conclusions:** The timing of the initiation of IABP therapy does not appear to impact short-term and long-term survival in patients with AMI complicated by CS undergoing primary PCI.

**KEYWORDS**
acute myocardial infarction, cardiogenic shock, intra-aortic balloon pump, survival, timing
1 | INTRODUCTION

In patients with acute myocardial infarction (AMI), 6%-9% can be affected by cardiogenic shock (CS) and the mortality rate is close to 50% during hospitalization. Despite adoption of early revascularization strategies, CS remains the leading cause of death in this population. Moreover, supportive drug treatments with inotropes and vasopressors bring no benefit to patients. Cardiologists hope that mechanical circulatory support will improve clinical outcomes in this population. The intra-aortic balloon pump (IABP) becomes the first mechanical circulatory support strategy of IABP insertion before vs after primary PCI; and (c) studies that assessed the endpoints of interest. The selection was conducted by scanning titles and/or abstracts, and full-text reviews were performed for further analysis. When several reports overlapped, we selected the largest and the latest one. The studies were reviewed by two independent investigators (Jinfan Tian and Yunfeng Yan) to determine whether they met the inclusion criteria. Any disagreements were resolved through discussion with a third investigator (Dongfeng Zhang).

2 | METHODS

This study was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE) statements.

2.1 | Search strategy

Two independent investigators (Lingxiao Chen and Kuo Zhou) searched the electronic databases of PubMed, EMBASE, and Cochrane Library from inception to April 1, 2019, to identify the pertinent English articles regarding the IABP inserted before vs after primary PCI for the treatment of AMI complicated by CS. The following medical subject headings and search terms were used: “acute myocardial infarction,” “cardiogenic shock,” “before primary percutaneous coronary intervention,” “after primary percutaneous coronary intervention,” and “timing.” In addition, the references of the identified articles and relevant reviews were examined to include other potentially eligible studies.

2.2 | Study selection

Studies satisfying the following criteria were eligible: (a) patients who were diagnosed with CS from AMI; (b) studies that compared the strategy of IABP insertion before vs after primary PCI; and (c) studies that assessed the endpoints of interest. The selection was conducted by scanning titles and/or abstracts, and full-text reviews were performed for further analysis. When several reports overlapped, we

2.3 | Data extraction and quality assessment

For each eligible study, three authors (Fei Yuan, Mingduo Zhang, and Wei Wang) independently extracted the following data through a standardized form: first author, year of publication, study design, quality indicators, baseline as well as procedural characteristics, and clinical outcomes. Discrepancies were resolved by consensus. The primary endpoint was short-term mortality (in-hospital or 30 days). Long-term mortality (≥ 6 months), reinfarction, stroke, repeat revascularization, acute renal failure, and major bleeding were the secondary outcomes. Deaths were classified as either cardiac or noncardiac, and classifications of other outcomes were in agreement with the included studies.

The methodological quality of the observational studies was assessed using the Newcastle Ottawa Scale. Studies with a Newcastle-Ottawa score ≥ 6 (maximum, 9) were considered high quality. In addition, the quality of randomized controlled trials (RCTs) were assessed using the Cochrane risk of bias tool.

2.4 | Statistical analysis

The present study used Review Manager 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stats/SE12.0 (StataCorp, College Station, Texas) for data analysis. All results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). Potential heterogeneity was evaluated with the I² statistic, and a value >50% was defined as statistical heterogeneity. For all comparisons, the DerSimonian and Lair random-effects model was used to account for the wide range of methodological variability across the studies.

Pooled analysis of risk-adjusted data were performed to control for confounding factors, and to test the sensitivity of the short-term and long-term mortality. The adjusted variables are listed in Table S1. In addition, sensitivity analysis was conducted by reanalyzing the results of studies that enrolled patients presented with ST-segment elevation myocardial infarction (STEMI) or published in full text. In case of significant heterogeneity, sensitivity analysis was also conducted by omitting one study in each turn to test the influence of single trial. Meta-regression analysis was carried out to assess patient characteristics with the primary endpoint, that is, male, current smoker, diabetes mellitus, hypertension, and culprit vessel of left anterior descending coronary artery. The risk of potential publication bias was assessed by the Begg’s and Egger’s tests. When there was an indication of publication bias from the statistical tests, we used the trim and fill method to evaluate the influence of potentially unpublished studies on the summary estimates. All statistical tests were two-sided and were considered to be statistically significant at P < .05.
3 | RESULTS

3.1 | Eligible studies

The comprehensive search yielded 1093 potentially relevant articles; after exclusion of duplicates and assessment of titles and/or abstracts, 29 articles were chosen for complete review. Finally, nine studies including 1348 patients met our inclusion criteria, published between 2005 and 2017\(^\text{20-28}\) (Figure S1).

The main characteristics of the included studies are presented in Table 1 and quality assessment results are described in Tables S2 and S3. Seven studies were observational studies,\(^\text{21-27}\) and the remaining two were sub-analysis of randomized controlled trials.\(^\text{20,28}\) Five of the

| Study           | No. patients | Period          | Region       | Design/center | Inclusion criteria | Exclusion criteria                                                                 | Adjusted method | Follow-up duration |
|-----------------|--------------|-----------------|--------------|---------------|-------------------|-----------------------------------------------------------------------------------|-----------------|-------------------|
| Thiele 2005     | 9/11         | 2000-2003       | Germany      | Sub-analysis of RCT, single | AMI with CS       | Age > 75 y, mechanical complication, shock >12 h, right heart failure, sepsis, significant aortic regurgitation, severe cerebral damage, resuscitation >30 min, severe peripheral vascular disease | NA              | 30 d              |
| Abdel-Wahab 2010| 26/22        | 2005-2008       | Germany      | Retrospective registry, single | AMI with CS due to left ventricular failure | Mechanical complication, isolated right ventricular infarction, shock due to other causes, > 24 h after primary PCI | Multivariable adjusted | In-hospital |
| Sjauw 2012      | 59/140       | 1997-2005       | Netherlands  | Prospective registry, single | STEMI with CS     | NA                                                                                | Propensity-score adjusted | 30 d              |
| Cheng 2013      | 87/86        | 2000-2009       | Netherlands  | Retrospective registry, single | STEMI with CS     | CS developed during primary PCI or hospitalization                                  | Multivariable adjusted | 5 y               |
| Bergh 2014      | 72/67        | 2004-2008       | Sweden       | Prospective registry, single | STEMI with CS     | NA                                                                                | Propensity-score adjusted | 30 d              |
| Negi 2014       | 76/98        | NA              | United States| Retrospective study, single | STEMI with CS     | NA                                                                                | NA              | 1 y               |
| Schwarz 2016    | 49/53        | 2005-2010       | Germany      | Retrospective registry, single | AMI with CS due to left ventricular failure | No spontaneous circulation, mechanical complication, isolated right ventricular infarction, shock due to other causes, > 24 h after primary PCI | Multivariable adjusted | In-hospital |
| Yuan 2016       | 106/112      | 2008-2014       | China        | Prospective study, single   | STEMI with CS     | Incomplete data                                                                    | Multivariable adjusted | 1 y               |
| Fuernau 2017    | 33/242       | 2009-2012       | Germany      | Sub-analysis of RCT, multi  | AMI with CS       | Resuscitation >30 min, no spontaneous circulation, coma, mechanical complication, shock >12 h, massive pulmonary embolism, severe peripheral arterial disease or aortic regurgitation, age > 90 years, shock due to other causes | Multivariable adjusted | 1 y               |

Abbreviations: AMI, acute myocardial infarction; CS, cardiogenic shock; IABP, intra-aortic balloon pump; NA, not applicable; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction.

aData are expressed as IABP before primary PCI/ IABP after primary PCI.
eligible studies only enrolled patients who presented with STEMI,22-25,27 and the remaining four included patients with non-STEMI.20,21,26,28 Two studies were abstract slides from conference proceedings. Overall, eight studies reported short-term mortality (in-hospital and 30-days),20-26,28 while four studies reported long-term mortality (≥6 months).23,25,27,28 In addition, five21-24,26 and three23,27,28 studies reported multivariable-adjusted data of short-term and long-term mortality, respectively.

As presented in Table 2, baseline characteristics of the patients were similar between the two treatment strategies, except that dyslipidemia was more common in patients who received IABP insertion before primary PCI than the control group (48.3% vs 38.7%).

### 3.2 | Primary endpoint

In summary, short-term death occurred in 149 patients (36.3%) in the IABP inserted before primary PCI group compared with 264 patients (36.7%) in the IABP inserted after primary PCI group. As shown in Figure 1A, short-term mortality was comparable between the two treatment strategies (OR 0.88, 95% CI 0.49 to 1.59, \( P = 0.67 \), with significant heterogeneity across studies (I² = 76%, \( P = 0.0002 \)). Sensitivity analysis indicated that no significant difference was found between the two groups when studies that enrolled patients with STEMI (OR 1.34, 95% CI 0.79 to 2.29, I² = 60%) (Figure S2) or published in full text (OR 0.90, 95% CI 0.40 to 2.00, I² = 81%) (Figure S3) were analyzed. In addition, sensitivity analysis by the removal of any single trial showed that it did not essentially affect the overall pooled estimate of short-term mortality, whereas the heterogeneity existed consistently across the studies (I² > 50%). Moreover, a pooled analysis of risk-adjusted data also demonstrated similar effects of the two therapies on short-term mortality (OR 0.65, 95% CI 0.34 to 1.25, \( P = 0.19 \), I² = 47%) (Figure 1B). After removing the study by Schwarz et al., the statistical heterogeneity of adjusted short-term mortality no longer existed (OR 0.86, 95% CI 0.49 to 1.51, I² = 47%).

### 3.3 | Secondary endpoints

In the pooled estimate, the initiation of IABP therapy before primary PCI had similar risk of long-term mortality compared to that of inserted after primary PCI based on both unadjusted data (OR 0.99, 95% CI 0.58 to 1.68, \( P = 0.96 \), I² = 57%) (Figure 2A) and risk-adjusted data (OR 0.68, 95% CI 0.17 to 2.72, \( P = 0.59 \), I² = 94%) (Figure 2B). After removing the study by Negi et al., the heterogeneity of long-term mortality no longer existed (OR 1.19, 95% CI 0.81 to 1.75, I² = 0%). Besides, the heterogeneity of adjusted long-term mortality disappeared after excluding the study by Yuan et al. (OR 1.32, 95% CI 0.85 to 2.03, I² = 0%).

No significant difference was found between the two groups in terms of reinfarction (OR 1.14, 95% CI 0.60 to 2.15, \( P = 0.69 \), I² = 0%), repeat revascularization (OR 0.40, 95% CI 0.09 to 1.88, \( P = 0.25 \), I² = 41%), stroke (OR 0.88, 95% CI 0.35 to 2.21, \( P = 0.78 \), I² = 0%), acute renal failure (OR 0.85, 95% CI 0.44 to 1.61, \( P = 0.61 \), I² = 57%), and major bleeding (OR 1.02, 95% CI 0.62 to 1.68, \( P = 0.93 \), I² = 2%) (Figure 3). The heterogeneity of acute renal failure no longer existed.
when the study by Abdel-Wahab et al., (OR 1.07, 95% CI 0.62 to 1.84, $I^2 = 36\%$) or by Negi et al., (OR 0.66, 95% CI 0.36 to 1.20, $I^2 = 23\%$) was removed.

3.4 | Meta-regression analysis and publication bias

Meta-regression analysis showed significant association between patient characteristics of diabetes mellitus (regression coefficient $-0.07$, 95% CI $-0.21$ to $-0.02$, $P = .02$) or hypertension (regression coefficient $-0.05$, 95% CI $-0.09$ to $-0.01$, $P = .04$) and the short-term mortality. No interaction was found between male ($P = .51$), current smoker ($P = .42$), or culprit vessel of left anterior descending coronary artery ($P = .79$) and the primary endpoint of short-term mortality.

In addition, the assessment of the funnel plot was performed, and no publication bias was found for the outcomes except for major
bleeding (Egger’s test, \( P = .03 \); Begg’s test, \( P = .09 \)). One study was added with the trim and fill method, and the risk of major bleeding remained similar between the two treatment strategies (OR 1.00, 95% CI 0.53 to 1.88) (Figure S4).

**4 | Discussion**

This is the first meta-analysis comparing the two treatment strategies of IABP inserted before and after primary PCI in patients with AMI complicated by CS. Our data suggest that the timing of initiation of IABP therapy does not have an effect on short-term and long-term survival in this population. Besides, the risks of reinfarction, repeat revascularization, stroke, acute renal failure, and major bleeding were similar between the two groups.

Since 1968, the IABP has been used for mechanical cardiac assistance in patients with CS.29 In theory, the deflation during systole reduces ventricular afterload and helps the ventricle push blood into the aorta, while the inflation during diastole enhances coronary artery perfusion and promotes blood flow to systemic organs.3 Based on pathophysiological considerations and benefits observed in non-randomized studies in the pre-PCI era, previous American Heart
Association/American College of Cardiology and European Society of Cardiology guidelines gave the use of IABP a class I recommendation for the management of AMI patients with CS. Nevertheless, the results of recent meta-analyses and the landmark intraaortic balloon pump in cardiogenic shock II (IABP-SHOCK II) trial have cast doubt on the efficacy of IABP because IABP support does not reduce short-term and long-term mortality in patients with AMI complicated by CS. Although the beneficial effect of IABP therapy on hemodynamic parameters has not translated to a beneficial effect on mortality in these studies, this result may be affected by multiple other factors. For example, 10%-30% patients with CS in the non-IABP group received emergency IABP insertion, and the frequent crossover in the randomized controlled trials definitely had an impact on the results according to the intention-to-treat principle. In addition, only 13.4% patients in the IABP group inserted the balloon pump before revascularization in the IABP-SHOCK II trial, and the timing of initiation of IABP therapy might be also of great importance in this setting.

Over the last decade, the debate about the timing of IABP insertion has never stopped, and clinical trials have produced conflicting results. Previous experimental study with animal models of ischemia-reperfusion demonstrated that unloading the left ventricle with IABP prior to revascularization might provide an additional infarct size reduction. Thereafter, a small population study with 48 patients reported that patients who underwent primary PCI assisted by IABP had a more favorable in-hospital survival rate than those who received IABP therapy after primary PCI. Contrarywise, Cheng et al. (n = 173) found that IABP insertion before PCI was associated with a larger infarct size, and no difference was found between the two strategies regarding short-term and long-term mortality. Considering the small sample size of the studies and the controversial results, pooled analysis of the individual data may be informative.

The principal finding of this study is that the timing of IABP insertion that is, before or after primary PCI does not have an effect on the short-term and long-term mortality in patients with AMI complicated by CS. It is believed that the early initiation of IABP therapy improves myocardial perfusion and results in significant myocardial salvage than reperfusion alone. More importantly, hemodynamic stabilization in the setting of cardiogenic shock can prevent the relevant multi-organ dysfunction or failure. One possible explanation is that the advantages of early initiation of IABP support are offset by the delay in revascularization associated with the time needed for IABP insertion. In patients with AMI treated with primary PCI, the timing of initiation of IABP therapy does not appear to impact short-term and long-term outcomes. However, this result should be interpreted as hypothesis-generating only, and could not be overstated. The random-effect model was used to account for the heterogeneity. Although sensitivity analysis with multivariable-adjusted data was performed, the potential bias cannot be completely eliminated. Furthermore, meta-regression analysis found that short-term mortality might be interfered by baseline characteristics of diabetes mellitus and hypertension. Second, patients with STEMI and non-STEMI were both enrolled in our meta-analysis. In this case, sensitivity analysis was conducted by analyzing the results of studies that enrolled patients with STEMI exclusively, and the results were in line with the overall population. Third, data about the time needed for IABP insertion or door-to-balloon time were not available in most of the studies. Finally, most of the eligible studies reported in-hospital or 30-day mortality, and long-term data with more than 6 months were limited.

### 5 | CONCLUSIONS

In patients with AMI complicated by CS undergoing primary PCI, the timing of initiation of IABP therapy does not appear to impact short-term and long-term clinical outcomes. However, this result should be interpreted with caution based on observational data. Appropriately, powered randomized trials are warranted to investigate the relative benefit of the two strategies, that is, IABP inserted before or after primary PCI in the future.

### CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

### ORCID

Shuzheng Lyu https://orcid.org/0000-0002-4243-2341
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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