What is the role of intra-aortic balloon counterpulsation in acute myocardial infarction presenting without shock?

Kalpa De Silva, Divaka Perera

Cardiovascular Division, St Thomas' Hospital Campus, Kings College London, UK

Percutaneous coronary intervention (PCI) in the presence of impaired left ventricular function is associated with significant mortality and morbidity, principally when the underlying coronary artery disease (CAD) subtends a large proportion of viable myocardium.[1] The consequences of the ischemic cascade are particularly marked in this subset of patients, whose diminished physiological reserve renders them less able to withstand the consequences of ischemia or arrhythmias occurring during a PCI procedure. This may result in a deleterious downward spiral of hemodynamic compromise, culminating in cardiogenic shock or death. Intra-aortic balloon counterpulsation simultaneously increases coronary blood flow, by augmentation of the diastolic aorto-coronary pressure gradient, and decreases myocardial oxygen demand, by reducing the end-diastolic pressure, and, therefore, the after-load. This makes it an attractive means of ameliorating ischemia and consequently enhancing cardiac output.

Contemporary registry evidence suggests that cardiogenic shock and high-risk PCI remain the commonest indications for intra-aortic balloon pump (IABP) use, with the American College of Cardiology/American Heart Association and European Society of Cardiology classifying the use of an IABP as a 1B and 1C recommendation, respectively.[2-4] However, at present, international guidelines do not offer formal recommendations for the use of IABP outside the setting of shock, but recommend counterpulsation *in patients at the extreme end of the spectrum of hemodynamic compromise*.

The use of IABP in the context of ST-elevation myocardial infarction (STEMI) has been postulated as a potential clinical scenario where the added hemodynamic support afforded by the device may improve outcomes, reducing infarct size, and, therefore, reducing morbidity and mortality, in both the short and long term. However, previous randomized control data by Stone *et al.* in PAMI-II[5] had shown a lack of discernible benefit from routine use of IABP, with major cardiovascular mortality and morbidity end points and left ventricular ejection fraction at 6-months in the IABP arm being no different to those treated conservatively. Furthermore, Sjauw *et al.*[6] reported a meta-analysis of the 1,009 patients studied across seven randomized trials of IABP use in STEMI. However, an important caveat for all of the trials included in this analysis was that IABP therapy was instituted after initial primary PCI; therefore, the question regarding whether *up-front* IABP therapy may provide additive benefit to PPCI had not been definitively answered. Contrary to these previous clinical trials, recent animal model data have suggested increased myocardial salvage with left ventricular unloading provided by early routine use of the IABP.[7-9]

The Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP AMI) trial was a multi-center randomized control trial assessing the role of routine use of IABP in patients presenting with myocardial infarction, in the absence of cardiogenic shock.[10,11] Three hundred and thirty-seven patients with anterior MI were randomized to mandated placement of IABP before PCI, compared to standard of care (SOC) PCI, without IABP support (161 to IABP+PCI and 176 to PCI alone). The primary end point was infarct size, using well-validated late-gadolinium enhancement cardiac MRI (CMR) techniques,[12,13] to determine the overall myocardial infarction volume, as a proportion of the entire left ventricular mass, performed at Days 3-5 of the index event. The enrolled population had clinical features consistent with large anterior STEMIs (60% had more than 6 mm of ST segment elevation on ECG and 63% had culprit lesions in the proximal LAD) but were hemodynamically stable at outset. The mean infarct size in the SOC group was 37.5% of LV mass, confirming that the study had sufficient power to address the primary hypothesis. However, pre-procedure IABP insertion failed to reduce infarct size; mean infarct size in the IABP group was 42.1%, a difference of 4.6% (95% CI, −0.2% to 9.4%], P=0.06. This finding was mirrored in the pre-specified subgroup analysis involving only those patients with proximal LAD occlusion. The results suggest that routine elective use of IABP in this setting does not reduce infarct size.

There are several reasons why the theoretically protective hemodynamic effects of the IABP device failed to show a clear difference in the outcomes measured. Firstly, IABP insertion itself may have delayed reperfusion time, offsetting any potential gain from using the device. Whilst Door-to-Balloon times were significantly longer in the IABP group (77 min IABP arm *vs* 68 min in PCI-only arm, P=0.04), this did not translate into a significant difference in relation to pain-to-balloon time (203 *vs* 183 min, respectively, P=0.85), which is considered a more important determinant of infarct size. Therefore, any delay in reperfusion was unlikely to be contributory. A more plausible explanation for the lack of effect may relate to the duration of IABP use prior to revascularization, as this may have been too short an interval to allow any hemodynamic benefit to ameliorate coronary flow and unload the left ventricle, and therefore aid myocardial recovery. Though this remains a possible explanation, given that *time is muscle*, this consideration is not applicable or relevant in clinical practice.

Mortality at six months was numerically lower in the group treated with IABP during the index PPCI procedure but this difference did not reach statistical significance, likely being a consequence of the relatively small number of events [1.9% (n=3) IABP+PCI *vs* 5.2% (n=9) SOC, P=0.12]. Whilst these results

Correspondence: Divaka Perera, Cardiovascular Division, Rayne Institute, St. Thomas' Hospital, London SE1 7EH, UK.
E-mail: divaka.perera@kcl.ac.uk

Key words: high risk PCI, IABP, myocardial infarction.

Received for publication: 24 November 2011.
Accepted for publication: 21 December 2011.

Heart International 2012; 7:e1
doi:10.4081/hi.2012.e1

do not support a strategy of routine insertion of IABP in all patients undergoing PCI in the setting of an anterior MI, without evidence of cardiogenic shock, there remains an important caveat: one in 12 of those initially randomized to a PCI-only strategy crossed-over and required bail out IABP therapy due to hemodynamic deterioration prior to or following the intended PCI. This cross-over population consisted of 15 patients, 12 of whom had had sustained hypotension or developed cardiogenic shock. The MACE rate in this cross-over group, requiring emergent IABP therapy, was disproportionately increased. This is in keeping with previous findings,[1,14] suggesting that whilst bail-out IABP therapy is frequently life saving, the need to acutely require increased hemodynamic support indicates an adverse prognostic marker. The importance of the cross-over cohort was borne out in the exploratory composite end point of time to death, shock, or new or worsening heart failure, which consisted of 8 events (5.0%) *vs* 21 events (12.0%) (P=0.03) in the IABP+PCI compared to the PCI alone arm, respectively. This was primarily driven by the presence of an increased rate of cardiogenic shock in the PCI alone group, compared to the absence of cardiogenic shock events in the IABP+PCI arm. Though not confirmatory, there is an important indication that those requiring bail-out may be patients at the extreme end of the hemodynamic spectrum, Therefore, whilst bail-out IABP therapy remains an important tool in the management armoury, the ideal scenario would allow pre-procedural prediction of the patient's characteristics that may lead to potential adverse hemodynamic sequelae. However, the trial was not sufficiently powered for subgroup analysis and, therefore, could not attempt to generate a model to predict this risk.

Albeit addressing IABP use in distinct clinical scenarios, there are several interesting similarities between the CRISP AMI findings and those of the balloon-pump assisted coronary intervention study (BCIS-1). BCIS-1 compared the safety and efficacy of elective IABP therapy during PCI with routine (unsupported) PCI in 301 patients with severe impairment of left ventricular function (mean EF 23.6%) and extensive coronary disease (mean jeopardy score 10.4; maximum possible score 12) who were hemodynamically stable at outset.[15] Sixteen percent of those who underwent unsupported PCI suffered major adverse cardiac or cerebrovascular complications at hospital discharge, and it was not possible to reduce the incidence of these complications by elective IABP insertion (15.2%). However, as with the recent CRISP-AMI findings, a trend to reduced 6-month mortality was noted in the elective IABP arm. Owing to the relatively small number of events at six months, it was not possible to distinguish a treatment effect related to IABP use from a statistical quirk, but this question is likely to be addressed by the BCIS-1 follow-up study which is currently underway. Furthermore, 12% of those initially randomized to receive unsupported PCI suffered hemodynamic compromise during the procedure, sufficient to warrant rescue IABP insertion in BCIS-1; a similar proportion to those needing bail-out IABP in CRISP-AMI. Importantly, these patients were more likely to suffer periprocedural infarction than those who did not need IABP insertion, and required a longer duration of IABP support than those who received an IABP before PCI. As such, it is important to acknowledge that a proportion of patients presenting with large myocardial infarctions and in high-risk stable CAD cases, may require bail-out IABP insertion during PCI. Therefore a *stand-by* approach should be adopted when undertaking these types of cases. The standby strategy itself is likely to vary between centers; however, early priming of the catheter laboratory staff for the potential need for IABP insertion will allow timely response if a balloon catheter is required.

In contrast, balloon counterpulsation is often considered an integral therapy when managing cardiogenic shock, which continues to be associated with mortality rates in excess of 50%,[16] despite advances in PCI techniques and management algorithms aimed at rapid revascularization. However, to date, there are no robust randomized trial data on IABP therapy in cardiogenic shock. Consequently, current practice and recommendations are based upon relatively small registries. Sjauw and colleagues recently reported a meta-analysis of 9 such registries, including over 10,000 shock patients.[6] This analysis showed an impressive synergistic effect of IABP therapy and thrombolysis on survival, but interestingly no clear benefit of IABP therapy was found in the primary PCI registries. Interpretation of this data is hampered by the selection bias that is inherent in registries, as exemplified by higher revascularization rates in patients receiving thrombolysis as well as IABP, compared to those who were treated conservatively. Notwithstanding the difficulties of studying this group of patients, there is a clear need for a randomized trial of IABP therapy in cardiogenic shock and the on-going IABP SHOCK-2 trial[17] seeks to fulfill this requirement, hoping to randomize 600 STEMI patients in cardiogenic shock to receive primary PCI with or without elective IABP support.

Intra-aortic balloon pumps remain an important adjunct to PCI in patients who have an increased risk of death or major cardiac complications. The findings of CRISP-AMI and BCIS-1 have clarified the role of elective IABP during two different settings of high-risk PCI . While these studies demonstrate that routine IABP placement is not mandatory, a standby approach is recommended, as an important minority may require bail-out IABP insertion in the event of hemodynamic compromise. Ongoing RCTs are expected to strengthen the evidence base relating to IABP therapy, but there is considerable heterogeneity within each of these groups, and translation of guidelines to individual care will continue to be based on estimation of risk and benefit in each case.

References

1. Perera D, Stables R, Thomas M, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. JAMA 2010;304:867-74.
2. Ferguson JJ 3rd, Cohen M, Freedman RJ Jr, et al. The current practice of intra-aortic balloon counterpulsation: results from the Benchmark Registry. J Am Coll Cardiol 2001;38:1456-62.
3. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004; 110:e82-292.
4. Van de Werf F, Ardissino D, Betriu A, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2003;24:28-66.
5. Stone GW, Marsalese D, Brodie BR, et al. A prospective, randomized evaluation of prophylactic intraaortic balloon counterpulsation in high risk patients with acute myocardial infarction treated with primary angioplasty. Second Primary Angioplasty in Myocardial Infarction (PAMI-II) Trial Investigators. J Am Coll Cardiol 1997;29: 1459-67.
6. Sjauw KD, Engstrom AE, Vis MM, et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? Eur Heart J 2009; 30:459-68.
7. Achour H, Boccalandro F, Felli P, et al. Mechanical left ventricular unloading prior to reperfusion reduces infarct size in a canine infarction model. Catheter Cardiovasc Interv 2005;64:182-92.
8. LeDoux JF, Tamareille S, Felli PR, et al. Left ventricular unloading with intra-aor-

tic counter pulsation prior to reperfusion reduces myocardial release of endothelin-1 and decreases infarction size in a porcine ischemia-reperfusion model. Catheter Cardiovasc Interv 2008;72:513-21.
9. Azevedo CF, Amado LC, Kraitchman DL, et al. The effect of intra-aortic balloon counterpulsation on left ventricular functional recovery early after acute myocardial infarction: a randomized experimental magnetic resonance imaging study. Eur Heart J 2005;26:1235-41.
10. Patel MR, Smalling RW, Thiele H, et al. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. JAMA 2011; 306:1329-37.
11. Patel MR, Thiele H, Smalling RW, et al. A multicenter, randomized, controlled study of mechanical left ventricular unloading with counterpulsation to reduce infarct size prepercutaneous coronary intervention for acute myocardial infarction: rationale and design of the Counterpulsation Reduces Infarct Size Acute Myocardial Infarction trial. Am Heart J 2011;162:47-55 e41.
12. Kim RJ, Wu E, Rafael A, Chen EL, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445-53.
13. Kwong RY, Schussheim AE, Rekhraj S, et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. Circulation 2003;107:531-7.
14. Mishra S, Chu WW, Torguson R, et al. Role of prophylactic intra-aortic balloon pump in high-risk patients undergoing percutaneous coronary intervention. Am J Cardiol 2006;98:608-12.
15. Perera D, Stables R, Booth J, et al. The balloon pump-assisted coronary intervention study (BCIS-1): rationale and design. Am Heart J 2009;158:910-6 e912.
16. Babaev A, Frederick PD, Pasta DJ, Every N, Sichrovsky T, Hochman JS. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA 2005;294:448-54.
17. Intra-aortic Balloon Pump in Cardiogenic Shock 2 (IABP SHOCK 2), 2010. Available from: http://www.clinicaltrials.gov