Usefulness of Intra-aortic Balloon Pump Counterpulsation

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Intra-aortic balloon pump (IABP) counterpulsation is the most widely used mechanical circulatory support device because of its ease of use, low complication rate, and fast manner of insertion. Its benefit is still subject of debate, and a considerable gap exists between guidelines and clinical practice. Retrospective nonrandomized studies and animal experiments show benefits of IABP therapy. However, recent large randomized trials do not show benefit of IABP therapy, which has led to a downgrading in the guidelines. In our view, this dichotomy between trials and practice might be the result of insufficient understanding of the prerequisites needed for effective IABP therapy, that is, exhausted autoregulation, and of not including the right patient population in trials. The population included in recent large randomized trials has been heterogeneous, also including patients in whom benefit of IABP could not be expected. The clinical condition in which most benefit is expected, that is, persistent ischemia in acute ST-elevation myocardial infarction, is discussed in this review. In conclusion, this review aims to explain the physiological principles needed for effective IABP therapy, to reflect critically on the large randomized trials, and to solve some of the controversies in this field. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;117:469—476)

Appropriate use of intra-aortic balloon pump (IABP) counterpulsation has been subject to heavy debate over the past years.\textsuperscript{1—4} Use of IABP is generally confined to 3 groups of patients, that is, high-risk percutaneous coronary intervention (PCI), acute myocardial infarction, and cardiogenic shock. There have been large randomized trials for all 3 indications, which will be discussed in the following sections. However, before analyzing these trials in detail, it is mandatory to better understand the presumed physiological principles of IABP counterpulsation and the prerequisites needed for adequate effect (or absence of effect) of IABP.

Physiological Principles and the Role of Coronary Autoregulation

The IABP, positioned in the descending thoracic aorta through the femoral artery, inflates and deflates in synchrony with the cardiac cycle. By inflating in the diastolic phase of the cardiac cycle, the diastolic aortic pressure is augmented, resulting in higher coronary perfusion pressure (Figure 1). This could theoretically lead to improved coronary blood flow and thereby increase of myocardial oxygen supply.\textsuperscript{5,6}

Early in systole, the balloon rapidly deflates, reducing the afterload of the left ventricle (Figure 1). In turn, this is believed to decrease myocardial workload and oxygen demand.\textsuperscript{5} However, the supposed direct mechanical effect of counterpulsation on coronary blood flow can be easily undone by the reactive vasoconstriction of the coronary and myocardial bed, known as coronary autoregulation. Under normal physiological circumstances, sphincters at the entrance of coronary arterioles constrict or dilate in response to coronary perfusion pressure, thereby guaranteeing constant myocardial blood flow over a wide range of aortic pressures (60 to 140 mm Hg).\textsuperscript{9} Therefore, in physiologic conditions with intact coronary autoregulation, myocardial blood flow is not dependent on perfusion pressure, and it is illusionary to expect increased coronary blood flow because of higher perfusion pressure by IABP counterpulsation. Thus, improved coronary blood flow by IABP can only be expected in situations with exhausted autoregulation.

Recently, De Silva et al\textsuperscript{10} performed intracoronary flow and pressure measurements during IABP counterpulsation with “switched on” and “switched off” coronary autoregulation using intravenous adenosine infusion for minimizing coronary vascular resistance. The investigators showed that the effect of IABP on coronary flow is directly dependent on coronary autoregulation. With intact autoregulation, balloon pump augmentation did lead to an increase in coronary pressure and also to a reactive increase in microvascular resistance, and as a result unchanged coronary blood flow. In contrast, with “switched off” autoregulation, the balloon pump augmentation led to an increase in distal coronary pressure and coronary blood flow, whereas the microvascular resistance remained unchanged.

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Also in recent studies performed in the isolated beating pig heart, it was documented that with exhausted autoregulation, a linear relation between diastolic aortic pressure and coronary blood flow is present and that IABP increases coronary blood flow by up to 50% in the presence of pump failure because of ongoing myocardial ischemia.\textsuperscript{11,12}

In short, only when autoregulation is exhausted, coronary blood flow is directly dependent on perfusion pressure, and effects of IABP on coronary blood flow can be expected. This is the case in the following clinical situations: (1) in the perfusion territory of a critical, subtotal stenosis; (2) in ischemic myocardium, including “stunning” after myocardial infarction or during weaning from extracorporeal circulation; and (3) in patients with low mean aortic pressures outside the autoregulatory range (<60 mm Hg).

The importance of autoregulation when assessing the effect of IABP was neither fully understood nor investigated until recently and is not reflected in the inclusion criteria in the large randomized clinical trials, including acute myocardial infarction and cardiogenic shock.

**High-Risk PCI**

IABP is often used as circulatory support system to prevent major complications during high-risk PCI.\textsuperscript{13} Patients with severe left ventricular dysfunction undergoing PCI are at higher risk of morbidity and mortality.\textsuperscript{14,15} This risk increases when the target lesion is supplying a substantial proportion of the myocardium. By inducing ischemia during PCI, left ventricular function will further deteriorate, and patients are at risk of entering a downward spiral of myocardial ischemia, hemodynamic compromise, cardiogenic shock, and ultimately death. Especially if a subtotal stenosis is present in a large contralateral coronary artery, secondary ischemia of the contralateral myocardial territory due to compensatory hyperkinesia might induce a downward spiral with deleterious outcome.

Until 2010, evidence supporting use of IABP in such patients consisted of several retrospective observational and small randomized studies.\textsuperscript{16–19} The Balloon Pump—Assisted Coronary Intervention Study (BCIS-1) randomized 301 patients scheduled to undergo high-risk single-vessel or multivessel PCI to either IABP insertion before PCI or no planned IABP insertion.\textsuperscript{20} On the basis of the predicted and actual event rates, the study was adequately powered. Outcome at hospital discharge was similar between the 2 groups, without significant differences in myocardial infarction, death, cerebrovascular accident, or further revascularization. In the control group, 12% of the patients needed rescue IABP insertion because of intra-procedural complications, mainly hypotension. Six-month mortality was 4.6% in the IABP group and 7.4% in the control group (p = 0.32). Although not statistically significant at first, this relative risk reduction of 38% remained constant over time, resulting in a significant benefit in favor of IABP over long-term follow-up, with a hazard ratio of 0.66 (95% confidence interval 0.44 to 0.98; p = 0.039).\textsuperscript{21} This consistent relative risk reduction by 1/3 is of huge impact in a patient population in which 1 out of every 3 patients died within the long-term follow-up period (Figure 2). The constant hazard ratio during follow-up implies that this is attributable to an early treatment effect, that is, IABP insertion before PCI. There were no other detectable procedural differences between the 2 groups in terms of number of vessels treated, success rate, and proportion of left main or proximal left anterior descending coronary arteries stented.

Explanation of this difference in outcome could be the reduction of ischemia by IABP during high-risk PCI and the prevention of intraprocedural complications. Effects of IABP on coronary blood flow is not undone by coronary autoregulation in these patients because autoregulation is completely exhausted in the coronary tree distal to a significant stenosis and in the presence of ischemic myocardium during and shortly after balloon inflation. Even small periprocedural myocardial infarctions, only measured by elevated troponin levels, have shown to affect outcome in cardiac patients.\textsuperscript{22} In patients with severe ischemic cardiomyopathy as included in BCIS-1, this effect might be more pronounced, causing this significant difference in long-term outcome. It is well conceivable that better protection of the myocardium during the procedure itself will result in a decrease in mortality in the long term, explaining the late results of BCIS-1.

**Acute Myocardial Infarction**

Primary PCI in patients presenting with ST-segment elevation myocardial infarction (STEMI) has resulted in an impressive improvement in outcome.\textsuperscript{23} During the last decade, however, despite optimizing time intervals, outcome has not further improved. This may be ascribed to “reperfusion injury,” “no-reflow,” or “persistent ischemia,” which occurs in up to 30% of the patients and is caused by a variety of factors including microembolization of atherothrombotic debris, vasospasm, and external compression of the capillaries due to intramyocardial edema, hemorrhage, and other factors, suppressing adequate myocardial perfusion after successful epicardial stenting.\textsuperscript{24} In such patients, this “ongoing” or “persistent” ischemia leads to reduced salvage of myocardium, even if the occluded epicardial

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Figure 1. Hemodynamic effects of intra-aortic balloon pump counterpulsation. Waveform of an unassisted and assisted heartbeat. After the aortic valve closes, the IABP inflates, increasing the diastolic pressure. Before systole, the balloon deflates, resulting in lower end-diastolic pressure, reflecting afterload for the left ventricle. Reproduced from Myat et al with permission from the publisher.
coronary artery has been opened successfully by primary PCI.

Animal experiments have shown that IABP is effective in reducing no-reflow, improves myocardial salvage, and decreases infarct size. A clinical registry in nearly 1,500 consecutive patients showed prophylactic insertion of IABP to be associated with fewer events in all high-risk patients presenting with acute myocardial infarction.

The Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP AMI) trial sought to determine if routine IABP therapy before primary PCI in patients with anterior STEMI without shock reduces infarct size as assessed on cardiac magnetic resonance imaging (CMR) and randomized 337 patients. The study was designed and powered to detect a 25% reduction in infarct size as assessed by CMR after 3 to 5 days showed no difference and a trend toward larger infarctions in the IABP group (42.1% vs 37.5%, p = 0.06). All-cause mortality at 6 months occurred less frequent in the IABP group, although not statistically significant (2% vs 5%, p = 0.12). The exploratory composite end point of death, shock, or new or worsening heart failure did reach statistical significance in favor of the IABP group (5% vs 12%, p = 0.03). So, in CRISP AMI, the primary end point was not achieved, and some confusion originated with respect to other end points.

However, 40% of the population in CRISP AMI had summed ST-elevation <6 mm, representing a cohort of patients with relatively small infarctions with a good prognosis anyway, whether treated with IABP or any other additional therapy. It is unlikely that in these patients, any of the pre-defined end points like death or congestive heart failure would be reached anyway, irrespective if and how they were treated. This is corroborated by the systolic and diastolic blood pressure and heart rate of the study population, not suggesting a very sick trial population. Inclusion of these patients most likely diluted a possible effect of IABP insertion by under-powering the study. A recent substudy of CRISP AMI in patients with large myocardial infarction (summed ST-deviation ≥15 mm) and persistent ischemia (ST-resolution after PCI <50%) showed a significant reduction in mortality despite a much smaller patient population (Figure 3).

Furthermore, in CRISP AMI, there was a considerable and asymmetrical crossover from control group to IABP group (8%), because of sustained hypotension or cardiogenic shock, failed PCI, or continued chest pain. The impact of this asymmetrical crossover will be discussed later in this report.

Finally, the primary end point was infarct size as assessed at 3 to 5 days using CMR. Using CMR in a patient population with the highest event rate in the first days will automatically create bias because patients (mainly without IABP) who died in the first days or were too unstable to undergo CMR are not included in this analysis of infarct size.

More in general, it is questionable if CMR 3 to 5 days after acute myocardial infarction is a reliable method to predict the ultimate infarct size and ejection fraction. Considerable further recovery is reported by consecutive CMR examinations at later follow-up.

Overall, use of IABP is not indicated routinely in acute myocardial infarction. Especially in patients with relatively small infarctions or fast successful reperfusion, reflected by complete ST-resolution, there is no effect to be expected by IABP counterpulsation. However, in patients with large myocardial infarction complicated by persistent ischemia (ongoing pain or insufficient ST-resolution), a significant decrease of mortality was observed, which fits with the pathophysiological considerations mentioned previously. This decrease of outcome was observed in a substudy, with all its limitations. Therefore, a prospective randomized controlled trial in such patients has been started recently to investigate this standpoint (SEMPER FI study: Survival in patients with Extensive Myocardial infarction complicated by PErSistent ischemia Following IABP insertion; NCT02125526).

Cardiogenic Shock

Treatment of cardiogenic shock complicating acute myocardial infarction remains a challenge with persisting high mortality rates. Pharmacological therapy often fails
to stabilize the patient in cardiogenic shock and carries the additional risk of increasing myocardial ischemia because of increased myocardial oxygen demand. This is the reason why physicians attempted to improve treatment of these patients by the use of mechanical circulatory support devices, one of them being the IABP.

Most trials with favorable results regarding IABP use in acute myocardial infarction complicated by cardiogenic shock were performed in the thrombolytic era. Registries and retrospective studies in the era of primary PCI showed no difference in outcome by the use of IABP. The Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial prospectively randomized 600 patients with acute myocardial infarction (with or without ST-segment elevation) complicated by cardiogenic shock to primary PCI with adjunctive IABP support or PCI alone. This landmark study showed no reduction in short-term and long-term mortality (30-day mortality 39.7% vs 41.3%; 1-year mortality 52% vs 51%, respectively; Figure 4). Strengths and limitations of this landmark trial have been discussed extensively. It is the largest randomized trial performed in patients with cardiogenic shock, including 600 patients in 32 months, and with a very high percentage of follow-up (1-year follow-up completed in 99.2%). Apart from that the study was underpowered because of a lower event rate in the control group than anticipated, several other important limitations were present in this study, questioning its conclusions.

First, there was a large asymmetrical crossover from control group to the IABP group and an increase in the use of left ventricular assist devices in the control group of together 17.4% of the patients not randomized to IABP. The impact of this high and asymmetrical crossover on statistical analysis and conclusions of the study will be discussed further on.

Second, almost half the patients randomized were resuscitated before PCI, and almost 40% received induced hypothermia after PCI. Outcome in these patients is poor irrespective of the use of IABP and primarily dependent on neurologic recovery rather than myocardial salvage by IABP.

Finally, the time windows in these patients were very wide; patients could be included up to 12 hours after onset of cardiogenic shock. If a patient with acute myocardial infarction complicated by cardiogenic shock presents too late (i.e., there is no persisting ischemia, neither viable myocardium in the infarcted area anymore), no salvage of myocardium leading to a better prognosis can be expected anyway. In such patients, in the best case, IABP therapy will lead to temporary relief and stabilization of hemodynamics. Volume pumps are more effective to increase output in such patients, but these effects are temporary as well and will disappear as soon as the device is removed.

Cardiogenic shock should not be seen as a yes-or-no phenomenon such as cardiac arrest but rather as a very heterogeneous condition which requires a tailored treatment. By solely including the patients presenting with STEMI complicated by cardiogenic shock with still viable myocardium and persistent ischemia as reflected by ongoing chest pain and persisting ST-deviation, and by excluding resuscitated patients, IABP therapy could be expected to be more effective based on pathophysiological grounds, as discussed here previously.
A recent study in the isolated beating pig heart simulated large myocardial infarction whether complicated by cardiogenic shock, and tested the effects of IABP counterpulsation in healthy state, preshock state, and shock state, with and without superimposed myocardial ischemia. These experiments showed a strong increase by IABP of coronary flow (up to 50%), cardiac output (up to 20%), and myocardial oxygen utilization (up to 25%) in large myocardial infarction, cardiogenic shock, and ongoing ischemia (Figures 5 and 6).

Statistical Limitations of Prospective Randomized IABP Trials

In both the CRISP AMI and IABP-SHOCK II trials, there was a large percentage of crossover from control group to IABP group. One can wonder why the treating physician in such open trials decides for crossover from the control group to the IABP group, and in which patients this happens. It is likely that the patients in whom crossover occurred were those in the worst condition, that is, at highest risk for events. This crossover also occurs in other large randomized open studies in critically ill patients in intensive care units (such as the use of steroids in septic shock) and is almost inevitable in patients randomized to the control group (“back-against-the-wall” situations), but it hampers correct interpretation of data.

It is impossible to fully comprehend the effect of such a high asymmetrical crossover on trial results, but it should be clearly recognized that this high asymmetrical crossover in an open trial is prohibitive for an intention-to-treat analysis. Any possible positive effect of a study drug or device will automatically be masked when the worst patients in the control group are subject to crossover and receive the device, in this case IABP.

In an attempt to avoid such bias, the investigators of the IABP-SHOCK II trial also performed a per-protocol analysis and as-treated analysis. However, in a per-protocol analysis, the crossover patients (i.e., those at highest risk) are excluded for analysis and the control group is most likely in a more healthy baseline condition in comparison with the IABP group. In addition, when using an as-treated analysis, all crossover patients are included in the IABP group, thereby creating a less-healthy IABP group at baseline. Absence of a difference in such analyses, in 2 groups with different characteristics, cannot exclude effectiveness of the study device.

Thus, conclusions from such open randomized trials in critically ill patients with a high and asymmetrical crossover rate remain controversial.

Recent Guidelines, Recommendations, and Conclusions

The IABP is a therapeutic device advocated to be used in critically ill patients with cardiogenic shock or myocardial infarction. After 40 years, despite clear improvement in individual patients, there are still extensive discussions about its potential benefits. Most likely, it is too good to simply abandon but not good enough to recommend without restrictions in patients with cardiogenic shock or myocardial infarction in general.

A key issue in this respect is the better understanding of the underlying physiological principles and more specifically the role of coronary autoregulation, which was insufficiently recognized and investigated until recently.

Recent guidelines by the European Society of Cardiology downgraded routine use of IABP in patients with cardiogenic shock (Class of Recommendation III, Level of Evidence A).40

Undoubtedly, routine use of IABP in cardiogenic shock without ischemia is not indicated. In such patients, hemodynamic support using flow-driven support devices such as Impella or LVAD is more effective.41 Similarly, IABP is not indicated as a routine device in STEMI, as learned from the CRISP AMI trial. However, in subgroup analysis of this trial based on recent pathophysiological insights from experimental and human studies, a decrease of mortality by IABP and improved outcome was observed. Especially, in case of patients with persistent ischemia and large myocardial infarction (whether complicated by cardiogenic shock),
there are arguments for the effectiveness of IABP to reduce ischemia, leading to salvage of myocardium, decreased mortality, and improved long-term outcome.

The key message of this discussion is that in selecting patients who might benefit from IABP therapy, a more tailored and patient-specific approach is paramount. Presence of ischemia, whether in high-risk PCI, acute myocardial infarction, or cardiogenic shock, seems to be the key factor in selecting patients who might benefit from IABP therapy. The rationale for effective IABP therapy is the trinity of exhausted autoregulation, persistent ischemia, and still viable myocardium. We should be careful not to throw out the baby with the bathwater.

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