Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: The prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome*

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Objective: Patients undergoing percutaneous coronary intervention (PCI) for acute myocardial infarction with cardiogenic shock (CS) are often treated with intra-aortic balloon pump counterpulsation (IABP), even though the evidence to support this is limited. We determined whether IABP as an addition to PCI-centered therapy ameliorates multiorgan dysfunction syndrome (MODS) in patients with acute myocardial infarction complicated by CS.

Design: A prospective, randomized, controlled, open-label clinical trial recruiting patients between March 2003 and June 2004 (ClinicalTrials.gov ID NCT00469248).

Setting: Tertiary care university hospital.

Patients and Interventions: Forty-five consecutive patients with AMI and CS undergoing PCI were randomized to treatment with or without IABP.

Measurements and Main Results: Acute Physiology and Chronic Health Evaluation (APACHE) II scores (primary outcome measure), hemodynamic values, inflammatory markers, and plasma brain natriuretic peptide (BNP) levels (secondary outcomes) were collected over 4 days from randomization. The prospective hypothesis was that adding IABP therapy to “standard care” would improve CS-triggered MODS. The addition of IABP to standard therapy did not result in a significant improvement in MODS (measured by serial APACHE II scoring over 4 days). IABP use had no significant effect on cardiac index or systemic inflammatory activation, although BNP levels were significantly lower in IABP-treated patients. Initial and serial APACHE II scoring correlated with mortality better than cardiac index, systemic inflammatory state, and BNP levels in this group of patients. Nonsurvivors had significantly higher initial APACHE II scores (29.9 ± 2.88) than survivors (18.1 ± 1.66, p < 0.05). Nevertheless, discrepancies among patients within the groups cannot be ruled out and might interfere with our results.

Conclusions: In this randomized trial addressing addition of IABP in CS patients, mechanical support was associated only with modest effects on reduction of APACHE II score as a marker of severity of disease, improvement of cardiac index, reduction of inflammatory state, or reduction of BNP biomarker status compared with medical therapy alone. However, the limitations of our present trial preclude any definitive conclusion, but request for a larger prospective, randomized, multicentered trial with mortality as primary end point. (Crit Care Med 2010; 38:000–000)

Key Words: intra-aortic balloon pump; angioplasty; transluminal; percutaneous coronary; myocardial infarction; shock; cardiogenic; Acute Physiology and Chronic Health Evaluation; systemic inflammatory response syndrome

Acute myocardial infarction (AMI) is complicated by cardiogenic shock (CS) in 7–10% of cases, and mortality in these patients is as high as 80% (1). Early revascularization by percutaneous coronary intervention (PCI) and intensive support, including the use of positive inotropic agents, vasopressors, and circulatory assistance devices, are routinely used to improve cardiac output and to prevent progression to multiorgan failure. Nowadays, IABP is the most commonly used mechanical assistance device for patients with CS. Its use is encouraged by a class I recommendation in the AHA/ACC guidelines for the management of AMI patients with cardiogenic shock (2). The level B evidence behind this recommendation can largely be attributed to pathophysiological considerations and benefits observed in registries in which predominantly patients treated with thrombolytic therapy had been enrolled in the pre-PCI era (3, 4). However, data from large prospective registries suggest that IABP placement has little benefit in CS patients treated with primary PCI. One trial even reported higher mortality rates associ-
ated with IABP use in this group of patients (5). Despite intensive, multifaceted therapy, patients with CS often develop a systemic inflammatory response syndrome (SIRS) that progresses to multiple organ dysfunction syndrome (MODS) and subsequent death caused by multiple organ failure. It is clinically important to identify these patients from among the spectrum of AMI patients with CS. Previous studies in patients with MODS of septic origin have shown the utility of serial Acute Physiology and Chronic Health Evaluation (APACHE) II scoring (from admission for 4 days) as a predictor of prognosis. Nonsurvivors show persistently elevated APACHE II scores during this period, whereas a significantly decreasing (by 4 points in 4 days) APACHE II is observed in survivors (6, 7). Given that a similar clinical pattern of systemic inflammation and MODS precedes death in AMI patients with CS, the APACHE II scoring system may help predict prognosis and guide therapeutic intervention in these patients too.

We hypothesized that serial APACHE II scoring reliably reflects systemic disease severity and outcome in AMI and CS (and may thus guide therapeutic intervention). Furthermore, we hypothesized that the addition of IABP to “standard” PCI-centered therapy for patients with AMI and CS would improve hemodynamic, inflammatory, and biochemical markers as well as attenuate the development of prognostically significant MODS as assessed by APACHE II scoring.

Thus, patients undergoing PCI for CS as a complication of AMI were randomized to receive “standard therapy” with or without IABP. We performed initial and serial APACHE II scoring from enrollment (the day shock developed) up to day 4. We postulated that favorable initial and serial Acute Physiology and Chronic Health Evaluation (APACHE) II scores may indicate improved morbidity and might translate to a higher probability of survival and that IABP use may reduce the development of MODS as assessed by serial APACHE scoring.

MATERIALS AND METHODS

Study Design and Randomization

The study was designed to test the hypothesis that adding IABP support to the management of patients with AMI and CS reduces morbidity (assessed by APACHE II scoring) within 4 days. The trial was a prospective, controlled trial with 45 consecutive patients randomized to one of two study groups. Patients were enrolled in the study immediately after admission to the hospital and were randomized just before coronary angiography and PCI. Following assessment of suitability for inclusion by the attending cardiologist, each patient was randomized upon opening an envelope (prepared in advance by the study group) with treatment allocation group details. Patients assigned to group 1 (“standard” treatment group or “no IABP” group) were treated with PCI, received pharmacologic hemodynamic support (inotropic and vasopressor agents), and, as required, ventilatory support. Patients assigned to group 2 (i.e., “IABP group”) received identical standard treatment with the addition of IABP support. The study was not blinded. The term “standard care” describes the guideline-compliant care (2) currently given to patients with AMI and CS presenting at our institution.

Appropriate to the critical care setting, patients underwent regular clinical assessment, complete invasive monitoring, and frequent blood sampling to determine laboratory markers. However, datasets for APACHE II scores and secondary end point parameters were prospectively gathered for study inclusion at the following time points: 1) initial, i.e., shortly after admission to our hospital and study randomization, but before PCI (except in the case of cardiac index which was measured immediately after PCI to avoid delaying reperfusion), and 2) every subsequent day (i.e., days 1 to 4) with datasets gathered at 10 AM. Thus, days 1, 2, 3, and 4 represented comparable 24-hr observation periods for all patients.

Verbal and written informed consent was obtained from all patients or their relatives. Patients were randomized between March 2003 and June 2004. The trial was approved by the Martin Luther University research ethics committee and registered with ClinicalTrials.gov (ID NCT00469248).

Inclusion and Exclusion Criteria

Patients treated with primary PCI for CS secondary to AMI who required inotropic and/or vasopressor support despite appropriate volume filling were included.

The diagnosis of acute myocardial infarction (AMI) required that symptoms of AMI be present for 30 mins within the preceding 48 hrs and one of the following: electrocardiogram ST-segment elevation in two or more contiguous leads (requiring ≥2 mm in the precordial leads or ≥1 mm in limb leads), new left bundle branch block (LBBB), new pathologic Q waves, nonspecific electrocardiogram changes, but an acute coronary syndrome associated with a serum creatinine kinase activity increase to ≥2.85 μmol/l*s and/or elevation in troponin I to >1.5 ng/mL, or, finally, radiographic evidence of acute coronary artery occlusion on coronary angiography.

The following criteria were required for a diagnosis of CS: symptoms and signs of organ hypoperfusion (e.g., cool peripheries, oliguria) plus one of the following: systolic blood pressure ≤90 mm Hg for at least 30 mins or hypotension requiring inotropic/vasopressor therapy at a heart rate ≥60/min or a cardiac index ≥2.2 l/min/m² on invasive monitoring.

Exclusion criteria included absent lower limb pulses (precluding IABP placement) or any mechanical complications of AMI such as acute, severe mitral valve insufficiency, an ischemic ventricular septal defect, or hemodynamically relevant aortic valve insufficiency.

Primary and Secondary Efficacy End Points

The primary efficacy end point was a change in APACHE II scores over 4 days from enrollment. We tested whether the addition of IABP to standard therapy leads to an improvement in the severity of illness (characterized by a fall in APACHE II score) in patients with AMI complicated by CS. APACHE II scores (8) were collected at enrollment and then daily for the first complete 4 days after randomization. A significant APACHE II score reduction between the initial time point and day 4 would indicate a favorable therapeutic effect of the additional IABP therapy (6, 7).

Secondary end points were cardiac index (CI), plasma brain natriuretic peptide (BNP), and serum levels of interleukin-6 (IL-6).

Coronary Angiography and Percutaneous Coronary Intervention

Coronary angiography and PCI were performed using standard techniques as soon as possible after admission. At the commencement of PCI, all patients were given aspirin (250 mg IV), glycoprotein-IIb/-IIIa-receptor blocker (weight-adjusted IV abciximab or tirofiban) for 12–24 hrs, and heparin, 5000 to 10,000 U IV bolus followed by continuous infusion to maintain an activated partial thromboplastin time of between 2 and 3 times normal. Treatment protocols were identical in the two groups.

Intra-Aortic Balloon Counterpulsation

A 40 mL balloon IABP (IABP System 97, Datapace; Fairfield, NJ) was inserted (in those randomized to the IABP group) via the femoral artery using an 8-French sheath immediately after PCI. Aortic counterpulsation was continued for a minimum of 48 hrs.
Measurement of Cardiac Index

Standard care included complete invasive monitoring and was undertaken in all patients. Cardiac output data were obtained using the thermodilution method (Thermodilution Paceport Catheter, Edwards Lifesciences LLC, Irvine, CA) and was indexed to body surface area using standard formulas. The initial datapoint for CI was taken immediately after cath/PCI when the thermodilution catheter was placed.

Blood Sampling for Plasma Brain Natriuretic Peptide and Interleukin-6 Levels

Blood samples drawn by venesection were immediately placed on ice, centrifuged within 30 mins, and stored at −70°C until analysis. Plasma BNP and serum IL-6 levels were measured by commercially available enzyme-linked immunosorbent assays (ELISA, Medgenix, Ratingen, Germany).

Statistical Analysis

Statistical analysis was performed for the primary end point by examining the change in Apache II scores over 4 days (from day 0 to day 4) based on a planned sample size of 2x20 patients using the two-sided two-groups Student’s t test. The required sample size was calculated prospectively based on a type I error of 5%, a power of 86%, a mean difference between IABP and standard treatment groups of 4 points after 4 days together with a SD of 4 points. Further APACHE analysis was conducted with and without the dropouts. Secondary end points were cardiac index (CI), plasma brain natriuretic peptide (BNP), and serum levels of interleukin-6 (IL-6). All secondary analyses are declared supportive.

All efficacy analyses were conducted on an intention-to-treat (ITT) basis. Statistical calculations for the primary end point were assessed by an additional conservative analysis using the last observation carried forward method. All data are expressed as mean ± se; p values <0.05 were considered significant.

RESULTS

Patient Flow

All patients who were randomized to a treatment group and who successfully commenced that therapy (irrespective of its duration or the duration of data collection in that patient) were included in a ITT analysis. We randomized five additional patients to compensate five observed dropouts. Thus, of 23 randomized to receive IABP, four were excluded (two patients did not fulfill the shock criteria; in one patient, the time from MI to shock >48 hrs; and for one patient, no postrandomization data were available for technical reasons).

Among the 22 patients randomized to the NO IABP arm, one patient did not commence this therapy (because of crossover to the IABP arm), but these data were analyzed in the no IABP arm. One patient was excluded because he did not fulfill the criteria for CS.

Of the patients commencing the assigned therapy, three in the IABP arm did not complete the preassigned 4-day data collection period (because of one death and two transfers) and two patients from the NO IABP arm did not complete the data collection period (because of one death and one transfer). These patients who were lost to follow-up were dealt with on a last observation carried forward (LOCF) basis. A chart summarizing the patient flow is shown in Figure 1. The resulting number of patients in each study group is shown in Table 1. No patients developed complications (i.e., bleeding, infection, arrhythmias, regurgitation, etc) that could be attributed to intra-aortic balloon pump counterpulsation use.

Baseline Characteristics

A summary of the baseline characteristics for the 40 patients from whom data were gathered is given in Table 2. Nineteen patients were randomized to therapy with IABP and 21 without. Mechanical ventilation was required in 7 of 19 (37%) in the IABP group and 14 of 21 (67%) in the nonIABP group. Four patients (two in each group) required dialysis in the early stages of their hospital stay for acute renal failure.

Of the study patients, 26 had STEMI and 14 had a NSTEMI, 22 had an anterior wall MI, and 16 had an inferior wall MI (in two patients no clear localization was possible). There were no significant differences in any of the patient or disease characteristics between the two groups.
Table 2. Patient characteristics, procedures, and success

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 40)</th>
<th>IABP Group (n = 19)</th>
<th>No IABP Group (n = 21)</th>
<th>Significance Among Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male; female</td>
<td>31, 78%; 9, 22%</td>
<td>14, 74%; 5, 26%</td>
<td>17, 81%; 4, 19%</td>
<td>0.583</td>
</tr>
<tr>
<td>Age in years, mean; range</td>
<td>64.2; 38–82</td>
<td>62.1; 38–82</td>
<td>66.1; 49–82</td>
<td>0.303</td>
</tr>
<tr>
<td>BMI, mean; range Kg/m²</td>
<td>27.8; 20.1–31.5</td>
<td>20.6; 20.1–31.9</td>
<td>27.7; 28.7–31.5</td>
<td>0.842</td>
</tr>
<tr>
<td>Smoker, n, %</td>
<td>15, 37.5%</td>
<td>8, 42.1%</td>
<td>7, 33.3%</td>
<td>0.567</td>
</tr>
<tr>
<td>Hypertension, n, %</td>
<td>18, 45.0%</td>
<td>8, 41.2%</td>
<td>10, 47.6%</td>
<td>0.726</td>
</tr>
<tr>
<td>Dyslipidemia, n, %</td>
<td>3, 7.5%</td>
<td>2, 10.5%</td>
<td>1, 4.8%</td>
<td>0.596</td>
</tr>
<tr>
<td>Diabetes mellitus, n, %</td>
<td>20, 50.0%</td>
<td>10, 52.6%</td>
<td>10, 47.6%</td>
<td>0.752</td>
</tr>
<tr>
<td>Previous acute myocardial</td>
<td>9, 22.5%</td>
<td>4, 21.1%</td>
<td>5, 23.8%</td>
<td>0.635</td>
</tr>
<tr>
<td>infarction, n, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known heart failure, n, %</td>
<td>8, 20.0%</td>
<td>5, 26.3%</td>
<td>3, 14.3%</td>
<td>0.342</td>
</tr>
<tr>
<td>Cardiac risk factors, n, %</td>
<td>37, 92.5%</td>
<td>17, 89.5%</td>
<td>20, 92.5%</td>
<td>0.596</td>
</tr>
<tr>
<td>Time: symptoms to cardiogenic</td>
<td>9.92 ± 2.05</td>
<td>13.37 ± 3.50</td>
<td>6.97 ± 2.22</td>
<td>0.131</td>
</tr>
<tr>
<td>shock in hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time: symptoms to PCI in hours</td>
<td>11.26 ± 1.98</td>
<td>13.91 ± 3.06</td>
<td>8.75 ± 2.49</td>
<td>0.080</td>
</tr>
<tr>
<td>STEMI n, %</td>
<td>26, 65%</td>
<td>10, 52.6%</td>
<td>16, 76.2%</td>
<td>0.119</td>
</tr>
<tr>
<td>Anterior/inferior ML n, %</td>
<td>22, 55%/16, 40%</td>
<td>10, 52.6%/8, 41.2%</td>
<td>12, 57%/8, 38.1%</td>
<td>0.555</td>
</tr>
<tr>
<td>Infarction size: CFinmax/Tmax</td>
<td>68.75 ± 18.56/123.13 ± 34.47</td>
<td>94.1 ± 37.6/71.5 ± 25.8</td>
<td>45.7 ± 8.4/63.8 ± 57.2</td>
<td>0.839/0.093</td>
</tr>
<tr>
<td>1/2/3-Vessel CAD, n, %</td>
<td>5, 12%/5, 22%/6, 65%</td>
<td>3, 16%/6, 32%/10, 53%</td>
<td>2, 10%/3, 14%/16, 76%</td>
<td>0.288</td>
</tr>
<tr>
<td>IABP before, during, and after PCI</td>
<td>5, 12.5%, 6, 15%, 9, 22.5%</td>
<td>4, 21.1%, 6, 31.6%, 9, 47.4%</td>
<td>1, 4.8%, 0, 0%, 0, 0%</td>
<td>1.48%</td>
</tr>
<tr>
<td>0/1/2/3-Vessel PCI n, n, %</td>
<td>2, 5%/9%, 76%/5, 13%/2, 5%</td>
<td>0, 0%/14, 78%/3, 17%/1, 6%</td>
<td>2, 10%/15, 75%/2, 10%/1, 5%</td>
<td>0.545</td>
</tr>
<tr>
<td>PTCA/stent, n, %</td>
<td>36, 90%/34, 85%</td>
<td>18, 45%/76, 64.2%</td>
<td>18, 85%/18, 85.7%</td>
<td>0.697/0.894</td>
</tr>
<tr>
<td>GPIIb/IIIa, n, %</td>
<td>13, 32.5%</td>
<td>6, 31.8%</td>
<td>7, 33.3%</td>
<td>0.906</td>
</tr>
<tr>
<td>TIMI flow before 0/1/2/3 in IRA</td>
<td>1.35 ± 0.20</td>
<td>1.47 ± 0.28</td>
<td>1.24 ± 0.29</td>
<td>0.152</td>
</tr>
<tr>
<td>TIMI flow after PCI 0/1/2/3 in IRA</td>
<td>2.52 ± 0.16</td>
<td>2.58 ± 0.23</td>
<td>2.48 ± 0.23</td>
<td>0.357</td>
</tr>
<tr>
<td>EF after PCI in %</td>
<td>37.6 ± 1.6</td>
<td>37.3 ± 2.4</td>
<td>37.8 ± 2.1</td>
<td>0.873</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.0 ± 0.1</td>
<td>2.3 ± 0.2</td>
<td>1.7 ± 0.1</td>
<td>0.072</td>
</tr>
<tr>
<td>PCWP in mm Hg (mean value, day – 1)</td>
<td>17.6 ± 1.0</td>
<td>20.1 ± 1.2</td>
<td>14.8 ± 1.3</td>
<td>0.012</td>
</tr>
<tr>
<td>PAP in mm Hg</td>
<td>27.1 ± 1.2</td>
<td>28.6 ± 1.5</td>
<td>25.6 ± 1.1</td>
<td>0.114</td>
</tr>
<tr>
<td>Ventilation, n, %</td>
<td>21, 52.5%</td>
<td>7, 36.8%</td>
<td>14, 66.7%</td>
<td>0.059</td>
</tr>
<tr>
<td>Dobutamine dosing, mean daily cumulative</td>
<td>26, 11</td>
<td>27, 81</td>
<td>24, 75</td>
<td>0.838</td>
</tr>
<tr>
<td>Noradrenaline dosing, mean daily cumulative</td>
<td>1,69[1]</td>
<td>0, 32</td>
<td>1, 71</td>
<td>0.571</td>
</tr>
</tbody>
</table>

IABP, intra-aortic balloon pump counterpulsation; PCI, percutaneous coronary intervention.

treatment groups (Table 2). Percutaneous coronary intervention (PCI, i.e., PTCA or Stents) was performed in all patients and did not differ between treatment groups (Table 2). All patients randomized to the IABP group received an IABP, and one of the patients randomized to the standard treatment group received IABP therapy. Echocardiography at enrollment revealed a mean left ventricular ejection fraction (LVEF) of 27.1 ± 2.1%, with no significant differences between groups. Hemodynamic parameters were similar in the patients and no significant differences were observed except for without PCWP (Table 2). Interestingly, dosing of epinephrine and dobutamine was also similar in the two groups (Table 2). No patient presented with hemodynamically significant valvular disease or any mechanical complications of AMI listed as exclusion criteria. Nevertheless, disparities within the groups cannot be ruled out because of the small patient number in this trial.

Effect of Intra-Aortic Balloon Pump Counterpulsation on Acute Physiology and Chronic Health Evaluation II Score in Patients with Cardiogenic Shock

For a global assessment of morbidity secondary to AMI-related CS, the changes in APACHE II score from the initial time point to day 4 were measured (Fig. 24). In the group without IABP therapy, the initial APACHE II score was 22.4 ± 2.8, falling marginally (by 2.4 points) to 20.0 ± 2.4 over the 4-day observation period. In the IABP-treated group, the initial APACHE II score was similar (21.0 ± 2.8; p = ns), and by day 4, the score was 18.2 ± 3.7. This modest fall of 2.8 points was not significantly different to that seen in the standard therapy group. Mortality in the two groups was statistically similar at 36.8% (7 of 19) in the IABP group and 28.6% (6 of 21) in the standard treatment group. A similar APACHE II score analysis with and without dropouts did not produce any statistically significant differences. Further, we performed our analysis with and without adjusting for the imbalances between the treatment groups in time from symptoms to PCI and CS and infarct size (maximum CK and Trop I) at baseline. Again, these results were not significantly different.

Effect of Intra-Aortic Balloon Pump Counterpulsation on Cardiac Index in Patients With Cardiogenic Shock

Cardiac index increased substantially from 1.7 ± 0.1 to 3.4 ± 0.3 L/min/m² with standard therapy (i.e., therapy including dobutamine and noradrenaline) throughout the study period (Fig. 2B). Use of IABP resulted in a similar increase in CI from 2.3 ± 0.2 to 3.3 ± 0.2 L/min/m² over the 4-day treatment period. The changes in CI were not significantly different between the two treatment groups.
Figure 2. Comparison of Acute Physiology and Chronic Health Evaluation II score (A), cardiac index (B), plasma brain natriuretic peptide (C), and serum interleukin-6 levels (D) over 4 days between patients treated with intra-aortic balloon pump counterpulsation and patients not treated by intra-aortic balloon pump counterpulsation with cardiogenic shock as a complication of acute myocardial infarction. Plasma brain natriuretic peptide levels measured on days 2 and 3 were the only significant differences between treatment groups ($p < 0.05$). For confidence intervals, see Table 3.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IABP Group (n = 19)</th>
<th>No IABP Group (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II, initial</td>
<td>21.0 (14.2, 27.8)</td>
<td>22.4 (17.6, 27.3)</td>
</tr>
<tr>
<td>APACHE II, day 4</td>
<td>18.2 (9.0, 27.4)</td>
<td>20.2 (14.2, 25.8)</td>
</tr>
<tr>
<td>Cardiac index, initial</td>
<td>2.3 (1.7, 3.0)</td>
<td>1.7 (1.4, 2.1)</td>
</tr>
<tr>
<td>Cardiac index, day 4</td>
<td>3.3 (2.6, 4.0)</td>
<td>3.4 (2.6, 4.2)</td>
</tr>
<tr>
<td>BNP, initial</td>
<td>822 (168, 1476)</td>
<td>615 (111, 1120)</td>
</tr>
<tr>
<td>BNP, day 4</td>
<td>1122 (52, 2193)</td>
<td>1462 (287, 2637)</td>
</tr>
<tr>
<td>Interleukin-6, initial</td>
<td>375 (0.793$^a$)</td>
<td>1157 (0.4460$^a$)</td>
</tr>
<tr>
<td>Interleukin-6, day 4</td>
<td>619 (0, 1802)$^a$</td>
<td>186 (67, 304)$^a$</td>
</tr>
</tbody>
</table>

$^a$IABP, intra-aortic balloon pump counterpulsation; APACHE, Acute Physiology and Chronic Health Evaluation; BNP, brain natriuretic peptide.

| Corrections of the upper limit of 95% confidence interval with the smallest possible value.

Effect of Intra-Aortic Balloon Pump Counterpulsation on Plasma Brain Natriuretic Peptide Levels in Patients With Cardiogenic Shock

BNP levels were measured initially and then every 24 hrs for the 4-day study period; the results are shown in Figure 2C. In patients treated without IABP, BNP levels were 615.3 ± 206.4 ng/mL initially and increased throughout the observation period to 1462.2 ± 458.9 ng/mL. The addition of IABP to standard therapy resulted in a significant fall in BNP levels from initial values of 822.0 ± 267.6 ng/mL to 551.0 ± 131.6 at day 1 and 510.7 ± 73.9 ng/mL at day 2 ($p < 0.05$). BNP levels subsequently increased (at 4 days) to 1122.6 ± 398.7 ng/mL. Thus, in the IABP treatment group, the drop in BNP levels at days 2 and 3 was significantly greater than in the standard therapy group ($p < 0.05$), suggesting an element of left ventricular unloading. Interestingly, the changes in BNP were temporally related to IABP placement and were greatest up to 48 hrs (when an IABP device was still in situ in the IABP group) and least by day 4 (by which time the IABP had been removed in most patients).

Effect of Intra-Aortic Balloon Pump Counterpulsation on Interleukin-6 Levels in Patients With Cardiogenic Shock

IL-6 levels were elevated in both groups of patients, reinforcing the concept of systemic inflammatory activation in CS patients as compared to the control population. These values remained increased and did not differ significantly over time or between the two treatment groups (Fig. 2D).

Confidence intervals for patients with and without IABP are shown in Table 3.

Acute Physiology and Chronic Health Evaluation II Score, Cardiac Index, Interleukin-6, Plasma Brain Natriuretic Peptide, and Survival

Data for initial and serial APACHE II scores are shown in Figure 3A. Among survivors, the initial APACHE II score was 18.1 ± 1.7, falling to 13.9 ± 1.6 over the 4-day observation period, i.e., a fall of 4.2 points ($\Delta = -4.2$). The initial APACHE II score was significantly higher in nonsurvivors (29.9 ± 2.9) and rose still further to 30.6 ± 3.9 at day 4, i.e., an increase of 0.7 points ($\Delta = +0.7$). The fall in APACHE II score of >4 points reflects a considerable improvement in MODS severity in survivors.

Cardiac index (CI) and IL-6 levels were also found to differ between survivors and nonsurvivors (Figs. 3B–D). CI on day 1 was significantly different among these groups, while IL-6 levels were significantly lower at the initial time point, day 1, and day 3 in survivors than in nonsurvivors. BNP levels showed a poor relationship to survival. Confidence intervals for survivors and nonsurvivors are shown in Table 4.

Receiver operating characteristic (ROC) curves calculated for the initial values and shown in Figure 4 demonstrate the relative accuracy of each of these variables in predicting survival in this group of patients. Table 5 shows accuracy data derived from area under the curve analysis of the ROC curves and confirms the greater accuracy of APACHE II scoring over the other identified parameters in predicting mortality. Of the other parameters, cardiac index gives the greatest accuracy and BNP the least.
DISCUSSION

Urgent reperfusion of the infarct-related artery (IRA) is essential in the management of patients with AMI (1, 9). Unfortunately, despite reperfusion, CS can develop and this is associated with a high mortality, with over half of the deaths occurring within 48 hrs of admission. A vicious cycle develops with low cardiac output, poor coronary perfusion, and worsening cardiac contractility (10). It is increasingly substantiated in the literature that this initiates a systemic inflammatory process characterized by SIRS and subsequently MODS, with the possibility that some of the inflammatory mediators (such as TNF and IL-6) contribute to depressed myocardial contractility (11). The inflammatory stimulation of the vasculature generates inducible nitric oxide synthase and, hence, nitric oxide (12), which also depresses cardiac function (13).

To arrest a deleterious spiral of pathophysiological events at an early stage, the application of the “golden hour” concept originally developed in trauma care has been advocated for the initial management of infarct-related CS (14). Current guidelines recommend the early insertion of an IABP to initially stabilize patients with CS who do not respond to medical therapy alone (15). However, evidence from large registries and small randomized trials suggests that the survival benefit associated with IABP placement might be restricted to CS patients treated with thrombolysis, as investigated in the TACTICS trial (16). Patients with CS undergoing primary PCI may derive less benefit from IABP therapy in terms of survival. The large National Registry of Myocardial Infarction (NRMI 2) that comprised 23,180 patients reported an increased mortality in CS patients with IABP placement (17, 18). However, in this registry the timing of IABP implantation is not determined. In a prospective trial on high-risk hemodynamically stable patients undergoing PCI for acute MI, a prophylactic IABP strategy did not improve clinical outcome (19). Likewise, in the GUSTO-1 trial, patients with CS showed no benefit of additional IABP therapy in the invasive strategy group treated with primary PCI (20).

The differing effects of IABP therapy between patients receiving thrombolysis and those undergoing primary PCI may be caused by augmenting diastolic coronary perfusion pressure that is greater in thrombolysed patients (who have a residual stenotic lesion, among other differing characteristics) than in post-PCI patients (21).

In the light of mixed data regarding the use of IABP as an adjunct to PCI in patients with AMI and CS, we conducted a randomized trial of IABP use in this group of patients. We believe mortality from AMI-related CS results from the
progression from initial hemodynamic instability followed by SIRS, MODS, and, finally, death caused by multiple organ failure. We hypothesized that IABP use may ameliorate the hemodynamic instability and reduce progression to MODS. Previous work with septic and high-risk CABG patients demonstrated that a 4-point reduction in the APACHE II score was related to improved survival (7); therefore, we used the same marker of morbidity as a primary end point to assess the impact of IABP treatment.

Addition of Intra-Aortic Balloon Pump Counterpulsation to Standard Therapy

The principle finding of this small, monocentric, randomized study was that the addition of IABP (for a minimum of 48 hrs) to standard therapy for AMI-related CS did not produce any significant reduction in APACHE II scores over 4 days. By using these criteria, we could not identify any reduction in disease severity (principally, the development of CS-related SIRS and MODS) associated with IABP use. The mortality for the two treatment groups was similar (although the study was not powered to identify mortality differences related to IABP use).

Previous studies describing important hemodynamic benefits of IABP (22, 23) have been tempered by more recent work showing only little impact of IABP on cardiac index (CI) in a group of patients similar to those of the present study (24). In keeping with this latter study, our data suggest that no significant improvement in CI and PCWP (data not shown) was associated with the addition of IABP to standard therapy in PCI-treated AMI patients.

An increase in ventricular wall tension caused by an increased end-systolic or end-diastolic volume may produce a greater ventricular wall stress that is sufficient for BNP release (25). Thus, elevated BNP levels may result from infarct-related ventricular impairment, similarly to many other causes of acute decompensation in ventricular function. Our results demonstrate a significant reduction in BNP levels with the addition of IABP to standard therapy. This difference was apparent between days 2 and 3, and appeared to lessen at the latest time point of day 4. “Ventricular unloading” may have been the principle contributor to this finding, with the greatest reduction in BNP being observed during or shortly after IABP use, and the effect waning after IABP removal. Grabowski et al (26) and Gheorghiade et al (27) found a weak correlation between BNP levels and mortality in patients with acute heart failure or STEMI.

Systemic inflammation with inappropriate vasodilatation in the setting of a reduced cardiac output is observed in many patients with acute heart failure and may contribute to excess mortality (28–31). Accordingly, it has recently been postulated that expression of inflammatory mediators may have a crucial role in the pathogenesis and prognostic of CS (12, 32). This has been supported by a recent study showing that patients with CS (especially in the setting of MODS) exhibit high concentrations of interleukin IL-6 (33), and it is well established that high IL-6 levels are associated with an adverse outcome in patients with septic shock (34, 35) and CS (36). We confirmed that IL-6 levels were elevated in AMI-related CS patients, and to some extent the degree of IL-6 elevation was found to be a predictor of mortality, although the addition of IABP to standard care did not significantly affect IL-6 levels over the 4-day observation period.

Nevertheless, since this was a small trial, these results might be attributed to some imbalances between the groups. However, among the patients and treatment criteria, a statistically significant differences was only shown for PCWP (20.1 ± 1.2 vs. 14.8 ± 1.3, IABP vs. no IABP, 0.002).

Acute Physiology and Chronic Health Evaluation II Scoring in Cardiogenic Shock

We found that survivors of AMI-related CS had significantly lower initial APACHE II scores that then fell (by 4 points over 4 days). In contrast, nonsurvivors had significantly higher initial scores and a slight increase in scores over time. The substantial differences between both initial values and dynamic trends in APACHE II score between survivors and nonsurvivors demonstrate the utility of the scoring system in gauging prognosis and assessing the impact of interventions such as IABP on morbidity and, hence, prognosis.

Thus, by using the APACHE II system, physicians can predict mortality from the initial score and from the progress over 4 days in response to treatment among the patients presenting with AMI and CS. The data are similar to that of Pilz and Werdan (6), who also found a 4-point reduction in APACHE II score that was closely related to mortality in septic patients. The AMI with CS population appears to be more heterogeneous and includes a wider range of morbidity at presentation (and hence initial APACHE II scores), and this range can be used to predict mortality even at the time of admission to hospital. In the simplest terms, our data suggest that an initial APACHE II score threshold of 25 and patients above threshold indicate a substantially higher risk of death than those below that threshold. This heterogeneity of organ dysfunction in patients with CS is also reflected in the various subgroups identified in the SHOCK trial registry (37, 38). By using the APACHE II score, various subtle stages of organ dysfunction can be identified, and the method appears to be useful for distinguishing survivors from nonsurvivors. Although the present study also found a predictive value of cardiac index and IL-6 for identifying survivors, ROC analysis shows each of these isolated parameters to be significantly less accurate than APACHE II scoring.

Conclusions drawn from this small pilot randomized IABP study are limited because of small patient numbers and mono-center design. However, trends of lack of effectiveness of the IABP in CS patients is claimed by a recently pub-

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**Table 5. Receiver operating characteristic curve analysis**

<table>
<thead>
<tr>
<th>Variable, Initial Time Point</th>
<th>Area Under Curve</th>
<th>Standard Error</th>
<th>Asymptotic Significance</th>
<th>Lower Limita</th>
<th>Upper Limita</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score</td>
<td>0.850</td>
<td>0.074</td>
<td>&lt;0.001</td>
<td>0.705</td>
<td>0.995</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.771</td>
<td>0.088</td>
<td>0.008</td>
<td>0.598</td>
<td>0.944</td>
</tr>
<tr>
<td>BNP</td>
<td>0.502</td>
<td>0.111</td>
<td>0.987</td>
<td>0.284</td>
<td>0.719</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>0.769</td>
<td>0.092</td>
<td>0.011</td>
<td>0.589</td>
<td>0.950</td>
</tr>
</tbody>
</table>

APACHE, acute physiology and chronic health evaluation; BNP, brain natriuretic peptide. aOf 95% asymptotic confidence interval.
lished study entitled “A systematic review and meta-analysis of intra aortic balloon pump therapy in ST-elevation myocardial infarction: Should we change the guidelines?” by Krishan D. Sjawu et al (39). These researchers come to the conclusion that there is insufficient evidence endorsing the current guideline recommendation for the use of IABP therapy in the setting of STEMI complicated by cardiogenic shock.

CONCLUSIONS

The present study suggests that APACHE II scoring has a role in assessing morbidity and prognosis in patients with acute myocardial infarction complicated by cardiogenic shock. In this randomized, mono-centric study, we were not able to demonstrate the anticipated benefit of adding IABP to optimal medical therapy in reducing short-term morbidity in this group of critically ill patients. Surprisingly, unloading the left ventricle with IABP appears to be less prognostically beneficial than expected. These effects of BNP reduction can be taken as proof that the IABP does what it is expected to do: it produced a significant reduction in afterload. However, this desirable effect could not be translated into a decrease in morbidity or mortality. Here, we might argue that, once triggered, SIRS cannot be modulated or decreased by beneficial hemodynamic measures. The data shown in Figures 2D and 3D support the following considerations:

First, IABP does not reduce elevated IL-6 levels (2D), and indeed IL-6 is a strong predictor of adverse outcome. Although the IABP shows the expected beneficial hemodynamic effects, systemic inflammation, which is prognostically much more important and is reflected by IL-6 levels, is not influenced by IABP support. In our opinion these findings are conclusive and support the results of the IABP shock trial.

Second, although the use of the IABP was achieved without measurable complications in the study population, we conclude that the paucity of evidence for adding IABP to standard, PCI-centered therapy in AMI patients with CS mandates a prospective, randomized, multi-centered trial with mortality as the primary end point.

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