Intra-aortic Balloon Counterpulsation in Cardiogenic Shock

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III

Introduction

What can we expect from the implementation of an intra-aortic balloon counterpulsation pump (IABP) in a patient with shock (Fig. 1)? The conventional indication for IABP is cardiogenic shock of ischemic etiology. With the IABP in place in the thoracic aorta, inflation of the balloon in diastole and active deflation in systole induces higher perfusion pressures in the brain and the coronary arteries in diastole and unloads the diseased heart by reducing left ventricular afterload in systole. Of special relevance is the volume shifting of about 40 ml per beat by the IABP, increasing left ventricular ejection fraction and thereby cardiac output in the range of at best 1 l/min.

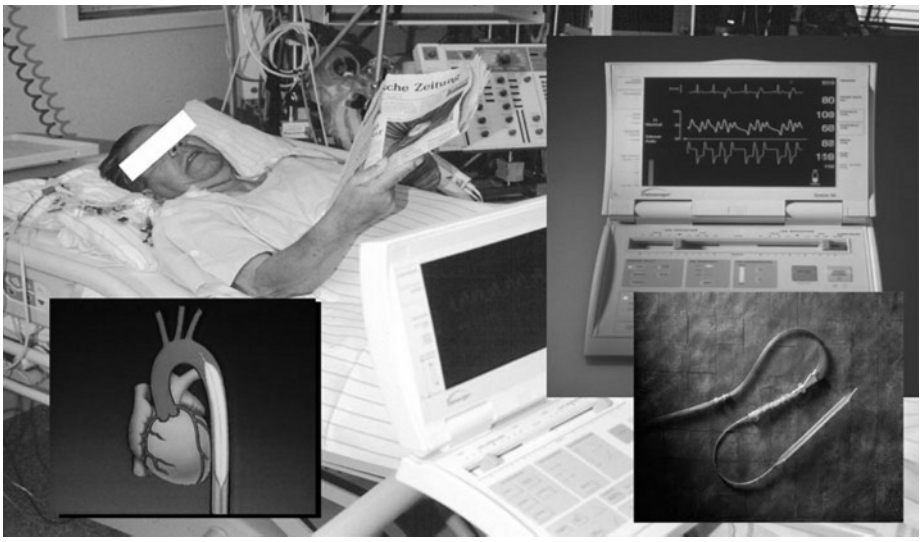

Fig. 1. Patient with myocardial infarction complicated by cardiogenic shock. After treatment with primary percutaneous coronary intervention the patient is still under adjunctive therapy with the intra-aortic balloon counterpulsation (IABP). Written permission obtained from the patient

What do the Guidelines tell Us and What about 'Real Life'?

The European STEMI (ST elevation myocardial infarction) guideline [1] states that IABP should be used in patients with myocardial infarction complicated by cardiogenic shock, with a recommendation level of grade I and an evidence level of grade C, for bridging till an interventional/surgical coronary intervention can take place. In patients with mechanical complications of myocardial infarction – ventricular septal defect and in most cases of acute mitral insufficiency – an IABP is also indicated to stabilize hemodynamic status.

The American STEMI guideline [2] recommends the use of IABP a) in STEMI patients with hypotension (systolic blood pressure less than 90 mmHg or 30 mmHg below baseline mean arterial pressure [MAP] who do not respond to other interventions (I/B); in STEMI patients with low output states (I/B); c) in STEMI patients as a stabilizing measure for angiography and prompt revascularization when cardiogenic shock is not quickly reversed with pharmacological therapy (I/B); d) in addition to medical therapy in STEMI patients with recurrent ischemic-type chest discomfort and signs of hemodynamic instability, poor left ventricular function, or a large area of myocardium at risk, as additional support to the urgently needed revascularization procedure (I/C); e) in STEMI patients with refractory polymorphic ventricular tachycardia to reduce myocardial ischemia (IIa/B); f) in STEMI patients with refractory pulmonary congestion (IIb/C); g) in STEMI patients with mechanical complications (acute mitral insufficiency due to papillary muscle rupture, ventricular septal rupture) for preoperative hemodynamic stabilization.

An IABP benchmark registry [3] presents the 'real life' of IABP applications and complications and includes a total of 5,495 patients with acute myocardial infarction. In 250 institutions worldwide, IABP implementations were documented between June 1996 and August 2001. In patients with myocardial infarction, cardiogenic shock was the most frequent indication (27.3 %), followed by hemodynamic support (27.2 %) during percutaneous coronary interventions (PCI), and support before high risk cardiac surgery (11.2 %), the latter indication – as shown recently [4] – shifting high-risk patients undergoing coronary bypass grafting into a lower-risk category. In 11.7 % of cases, mechanical complications following myocardial infarction were the indication, and in 10 %, refractory unstable post-infarction angina. Total mortality in patients with myocardial infarction was 20 %, and in patients with myocardial infarction complicated by cardiogenic shock it was 30.7 %. Severe complications of IABP insertion were seen in 2.7 % of cases, during a mean duration of IABP application of 3 days. Premature temination of IABP treatment was necessary in only 2.1 % of the patients.

Does Hemodynamic Improvement Improve Prognosis in Infarction-triggered Cardiogenic Shock?

In 5 – 10 % of all patients with myocardial infarction, cardiogenic shock develops in the acute phase, with a high mortality of at least 50 %, predominantly (80 %) as a result of left heart failure [5]. There is no doubt that cardiac pump failure due to coronary occlusion plays the dominant role in the early phase of shock. However, in prolonged shock states, development of multiple organ failure (MOF) due to impaired organ perfusion and due to the systemic inflammatory response syndrome (SIRS) determines the unfavorable prognosis. The relative importance of each of these components – cardiac impairment and failure, MOF and SIRS – becomes evi-

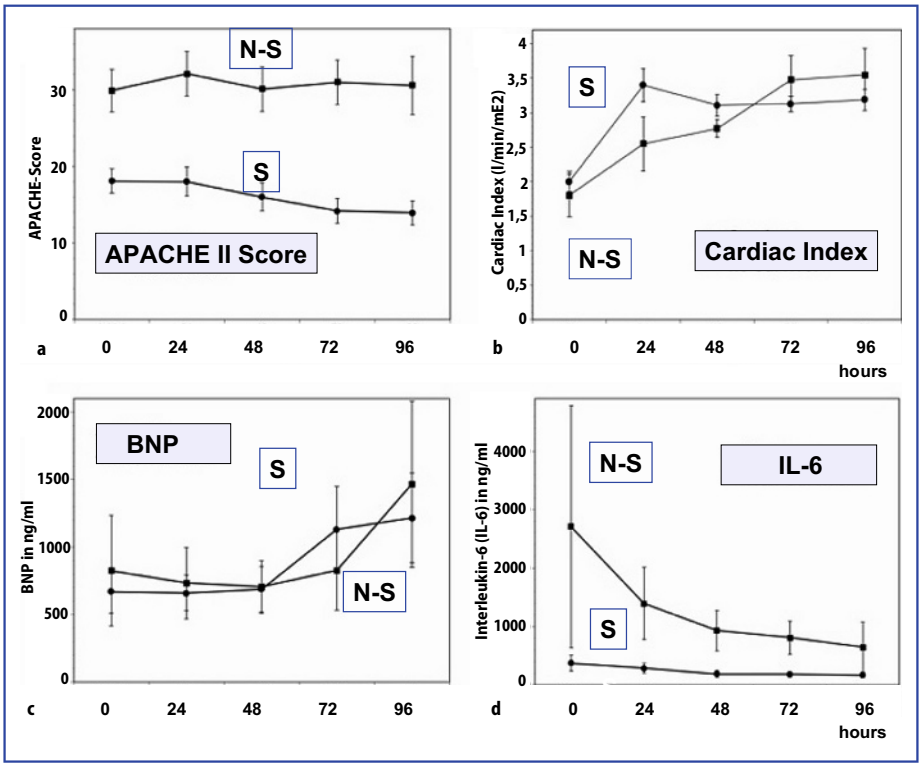

Fig. 2. The "IABP Shock" Trial [6]: What determines prognosis? Forty patients with myocardial infarction complicated by cardiogenic shock and treated with percutaneous coronary intervention (PCI) were prospectively randomized to receive or not additional hemodynamic support with IABP. In this figure, serial biomarker monitoring is presented for the 27 survivors (S) and for the 13 non-survivors (N-S) during the first 96 hours after having started treatment. APACHE II score represents severity of disease, cardiac index represents heart function, plasma B-type natriuretic peptide (BNP) represents pump failure, and serum interleukin (IL)-6 represents systemic inflammation. The values for APACHE II and for IL-6 were significantly different at all time points ($p < 0.05$) and cardiac index differed significantly at 24 hours ($p < 0.05$). BNP levels, however, were not different between the groups. Modified from [6] with permission.

dent when we look for the respective biomarkers in surviving versus non-surviving patients with myocardial infarction complicated by cardiogenic shock (**Fig. 2**; [6]). Surprisingly, cardiac index was higher in survivors only at 24 hours, and brain natriuretic peptide (BNP) levels did not differ at all. In contrast, serum interleukin (IL)-6 levels were significantly higher in survivors during the total period (96 hours). The most impressive difference between survivors and non-survivors was seen with the APACHE II score: Non-survivors had much higher initial values (29.9 ± 2.9), and the values even increased by 0.7 points to 30.6 ± 3.6 over the next 96 hours; in contrast, survivors had lower initial score values (18.1 ± 1.7), which further fell by 4.2 points to 13.9 ± 1.6. The fall in APACHE II score of > 4 points/96 hours in survivors reflects a considerable improvement in severity of MOF, with, as consequence, an improved prognosis. These findings are similar to those shown in a prospective manner in the Score-Based Immunoglobulin Therapy of Sepsis (SBITS) trial for patients with

severe sepsis and septic shock (APACHE II change from day 0 to day 4 in survivors (n = 385) was – 5.9 and in non-survivors (n = 238) was + 0.4 [7]).

Receiver operating characteristic (ROC) curves calculated for the initial biomarker values demonstrate the relative accuracy of these variables: APACHE II score 0.850; cardiac index 0.771; IL-6 0.769; BNP 0.502. Therefore, prognosis in patients with myocardial infarction complicated by cardiogenic shock is determined not only by hemodynamic impairment but also by systemic inflammation and even more by the severity of disease and development of MOF.

Effects of IABP on Hemodynamics, Systemic Inflammation and MOF in Infarction-triggered Cardiogenic Shock

As shown in **Fig. 2**, and discussed earlier, the prognosis of infarction-triggered cardiogenic shock is not only dependent on impaired hemodynamics, but also on

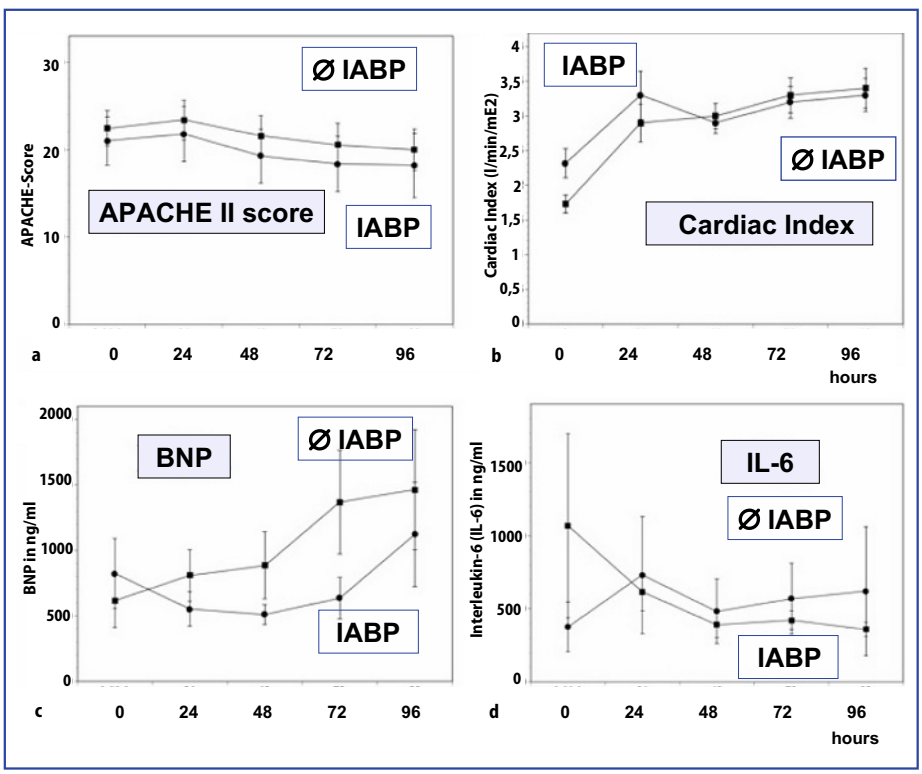

Fig. 3. The "IABP Shock" Trial [6]: Effects of adjunctive IABP therapy. Patients with myocardial infarction complicated by cardiogenic shock and treated by primary PCI were randomly assigned to receive (IABP, n = 19) or not (∅ IABP, n= 21) adjunctive support with IABP. In this figure, serial biomarker monitoring is presented during the first 96 hours after having started treatment. APACHE II score represents severity of disease, cardiac index represents heart function, plasma B-type natriuretic peptide (BNP) represents pump failure, and serum interleukin (IL)-6 represents systemic inflammation. Of all biomarker measurements, only BNP plasma levels at 48 and at 72 hours were significantly different between the groups ($p < 0.05$). Modified from [6] with permission.

shock-triggered systemic inflammation and the development of MOF. The question is whether IABP implementation can improve not only hemodynamics, but also this systemic inflammatory process finally resulting in MOF. This question was assessed by the prospective, randomized, monocenter, unblinded IABP Shock Trial [6], where we looked for the effects of early IABP therapy in 45 patients with infarction-triggered cardiogenic shock, all treated initially with primary PCI. The primary endpoint of the study was the effect of IABP on severity of disease (MOF) within the initial 96 hours, as measured by serial APACHE II scoring; secondary endpoints were the effects of IABP on cardiac output, BNP and IL-6 (**Fig. 3**). Complete data were available for 19 patients treated with IABP (IABP group) and for 21 patients without IABP (non-IABP group). Thirty-day mortality was 36.8 % in the IABP group and 28.6 % in the non-IABP group (p=n.s). The severity of disease (APACHE II score) was not improved in the IABP- compared to the non-IABP-group within the initial 96 hours, neither was cardiac index nor systemic inflammation (serum IL-6 levels). Only plasma BNP levels, at 48 and 72 hours, were significantly ($p < 0.05$) lower in the IABP patients.

What do these results tell us? In this randomized prospective trial – representative of a one-year population of patients with infarction-triggered cardiogenic shock treated in a medical intensive care unit (ICU) – we were unable to demonstrate a relevant beneficial effect of the adjunctive use of IABP. Although this trial was small, we can nevertheless conclude that the numbers needed to treat must be high concerning a possible benefit of IABP in these well-defined patients with infarction-triggered cardiogenic shock treated by primary PCI.

What Does a Meta-Analysis Tell Us?

In contrast to the numerous data from registries and non-controlled trials concerning the effects of IABP in infarction-triggered cardiogenic shock, the number of controlled trials with mortality as an endpoint are rare. A recently published meta-analysis [8] has summarized the available data:

In two separate meta-analyses, the authors looked for the effects of IABP on mortality in high-risk patients with STEMI (meta-analysis I) and in patients with STEMI complicated by cardiogenic shock (meta-analysis II). In meta-analysis I (**Fig. 4**) seven randomized trials (1,009 STEMI patients) were analyzed. Use of IABP in these patients did not reduce 30-day mortality or improve left ventricular ejection fraction; however patients treated with IABP had significantly higher complication rates, including strokes (+ 2 %) and bleeding (+ 6 %) (**Fig. 4**). Meta-analysis II (**Fig. 5**) included 9 cohorts of STEMI patients with cardiogenic shock (N = 10,529). In those patients treated with systemic thrombolysis, IABP was associated with an 18 % (95 % confidence interval 16 – 20 %; $p < 0.001$) decrease in 30-day mortality, albeit with significantly higher revascularization rates compared to patients without support. Contrariwise, in patients treated with primary PCI, IABP was associated with a 6 % increase (95 % confidence interval 3 – 10 %; $p < 0.0008$) in 30-day mortality.

This meta-analysis [8] yielded unexpected results. Consequently, we should rethink our concept of adjunctive IABP therapy in patients with myocardial infarction complicated by cardiogenic shock. First, we have to accept that in STEMI patients in general the use of IABP neither reduces 30-day mortality nor improves left ventricular ejection fraction, but increases the risk of stroke and of bleeding. Therefore, IABP cannot be recommended in general for high risk STEMI patients

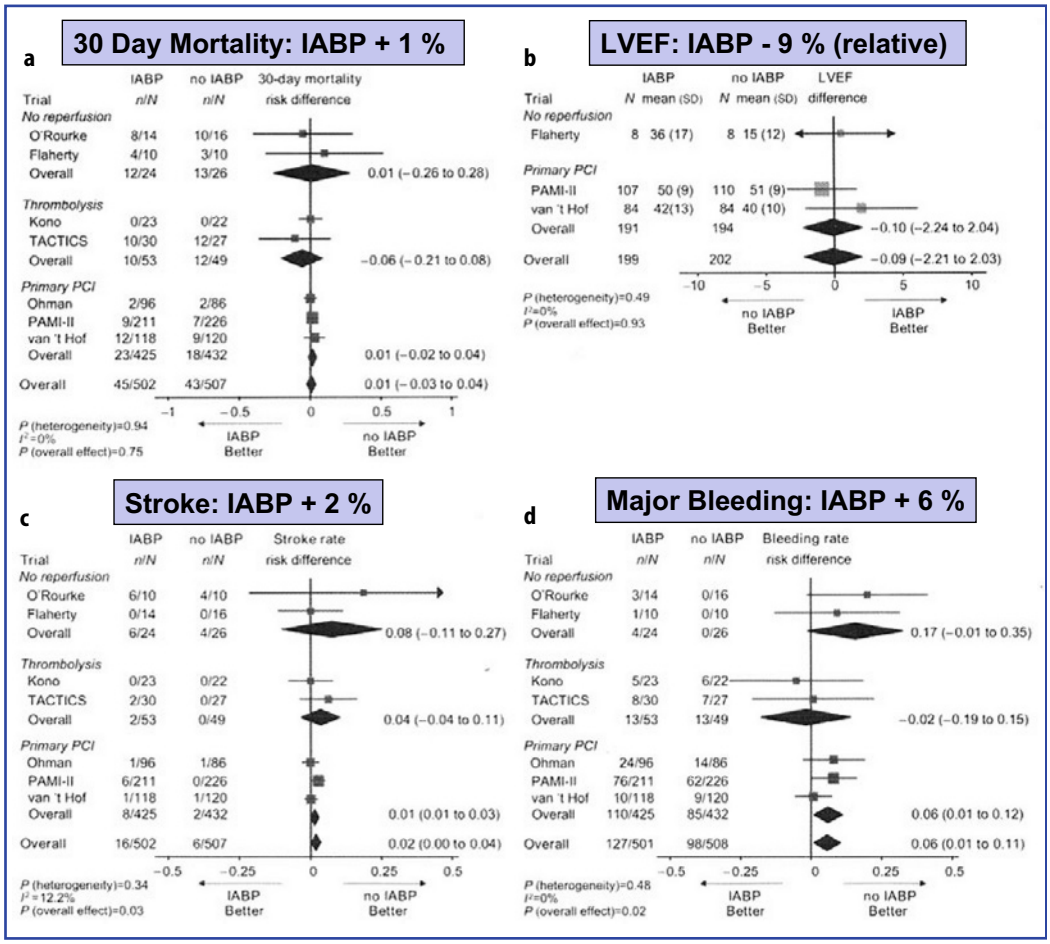

Fig. 4. Meta-analysis of randomized clinical trials of intraaortic balloon counterpulsation (IABP) therapy in patients with ST elevation myocardial infarction (STEMI). All meta-analyses show effect estimates for the individual trials, for each type of reperfusion therapy, and for the overall analysis. The size of each square is proportional to the weight of the individual trial. In panel **a**, the risk difference in 30-day mortality is shown; in panel **b**, the mean difference in left ventricular ejection fraction (LVEF); in panel **c** the risk difference in stroke; and in panel **d**, the risk difference in rate of major bleeding. PCI: percutaneous coronary intervention. Modified from [8] with permission.

without cardiogenic shock. Second, in patients with cardiogenic shock complicating STEMI, analysis is hampered by bias and confounding. What can be said is that the available observational data support IABP therapy adjunctive to thrombolysis. In contrast, observational data do not support IABP therapy adjunctive to primary PCI. To resolve these issues, we urgently need a multicenter, prospective, randomized IABP trial with mortality as an endpoint. Organization of such a study has been initiated in Germany and hopefully it will start in 2010.

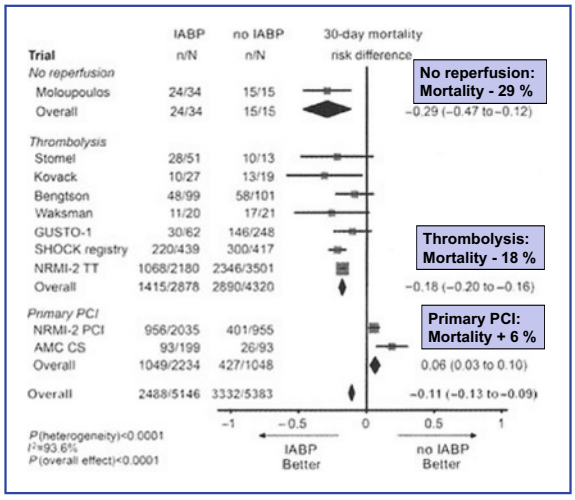

Fig. 5. Meta-analysis of cohort studies of intraaortic balloon counterpulsation (IABP) therapy in patients with ST elevation myocardial infarction (STEMI) complicated by cardiogenic shock. The risk differences in 30-day mortality for the individual studies, for each type of reperfusion therapy and for the overall analysis are given. The size of each square is proportional to the weight of the individual study. PCI: percutaneous coronary intervention. Modified from [8] with permission.

Beyond IABP: Do We Have Better Alternatives for the Treatment of Cardiogenic Shock?

A large number of surgically and percutaneously implantable left ventricular assist devices (LVAD) are available, providing better hemodynamic support for the patient than does IABP [9]. But improving hemodynamics is not everything! Coupling improvement in hemodynamics to a better prognosis is what is needed. So, the question arises as to whether this goal can be met by any of the short-term cardiovascular assist devices:

Impella® Pump

In a prospective randomized trial, 26 STEMI patients with cardiogenic shock and PCI intervention were treated adjunctively either with an Impella pump or with IABP [10]. Although cardiac index (primary endpoint) rose significantly more in the Impella group than in the IABP group (0.49 ± 0.46 vs. 0.11 ± 0.31 l/min/m^2, $p = 0.02$), 30-day mortality (one of the secondary endpoints) was identical in the two groups (46 %).

Extracorporeal Membrane Oxygenation (ECMO)

Eighty-one patients with refractory cardiogenic shock were treated adjunctively with pump-driven ECMO [11]. Hospital mortality was 42 %. At least one serious ECMO-related complication occurred in 57 % of patients. Independent predictors of ICU-mortality were: Device insertion under cardiac massage (odds ratio [OR] 22.68); 24 h urine output < 500 ml (OR 6.52); prothrombin activity < 50 % (OR 3.93), and female sex (OR 3.89). Quality of life one year after shock was less than that of matched healthy controls, but higher than that reported for patients on chronic hemodialysis, with advanced heart failure or after recovery from acute respiratory distress syndrome (ARDS). One third (16/44) of the patients had suffered from infarction-triggered cardiogenic shock; their 1-year-mortality was 31 %. A relatively simple, easy-to-apply pumpless ECMO device is the iLA Novalung [12].

Tandem Heart®

This device can pump up to 4 l/min. In 42 patients with infarction-triggered cardiogenic shock and primary PCI a Tandem Heart® or an IABP were used adjunctively in a randomized manner [13]. Hemodynamic improvement was much better in the Tandem Heart group than in the IABP group – e.g., cardiac output increase by 1.0 l/min from 3.5 to 4.5 vs increase by 0.3 l/min from 3.0 to 3.3 – but the 30-day-mortality was not significantly different (43 vs 45 %; p = 0.86). However, complications were considerably higher in the Tandem Heart® group (severe bleedings: n = 19 vs n = 8, p = 0.002; limb ischemia n = 7 vs n = 0, p = 0.09).

Assisted Extracorporeal Life-support in Adults with In-hospital Cardiac Arrest

Extracorporeal life-support as an adjunct to cardiac resuscitation has been associated with encouraging outcomes in patients with cardiac arrest. An important trial is that by Chen et al [14], which compared conventional cardiopulmonary resuscitation (CPR) and assisted extracorporeal life-support in adults with in-hospital cardiac arrest. From 975 resuscitated patients, 113 were enrolled in the conventional CPR group and 59 in the assisted extracorporeal CPR group. Patients in the assisted extracorporeal group had a significantly better outcome than those in the conventional CPR group in terms of hospital-survival (RR 0.51; 95 % confidence interval 0.35 – 0.74; p< 0.0001), 30-day mortality (RR 0.47; 0.28 – 0.77; p = 0.003), and one-year survival (RR 0.53; 0.33 – 0.83; p = 0.006).

These results [14] are very impressive, although the logistics and technology necessary are ambitious! A portable miniature version of extracorporeal life support is the Lifebridge® system [15] which can be brought to the patient for resuscitation. However, no randomized trial data are yet available for this specific system.

IABP versus Percutaneous LVAD in Cardiogenic Shock: A Meta-analysis

In comparing IABP and percutaneous LVAD in cardiogenic shock, effects on hemodynamic status and prognosis need to be evaluated, as has been done in a recent meta-analysis [16]. Three controlled trials compared the effects of IABP with LVAD systems (two trials using Impella® and one using the Tandem Heart®) in a total of 53 LVAD patients and of 47 IABP patients. The increase in cardiac index was greater in the LVAD patients than in the IABP group (+ 0.35 l/min/m^2); MAP increased to a greater extent (+ 12.8 mmHg) and pulmonary artery occlusion pressure (PAOP) decreased more (- 5.3 mmHg). However, 30-day-mortality in the LVAD group was not significantly different from 30-day mortality in the IABP group (RR 1.06). Concerning side effects, the incidence of limb ischemia was not significantly different; however, bleeding occurred 2.35-fold more often in the LVAD group.

We Should Change the Guidelines for IABP Use in Infarction-triggered Cardiogenic Shock!

In view of the data from the described meta-analysis [8], we believe we really do not have enough evidence to give a class I recommendation for the adjunctive use of IABP in all STEMI patients with cardiogenic shock, as has been made by the European [1] and the American [2] Cardiological Societies (see above). A German-Aus-

trian expert team are developing a guideline for infarction-triggered cardiogenic shock (Werdan et al., unpublished data] and took this meta-analysis into account to make the following recommendations:

- Adjunctive IABP therapy is indicated in cases of primary systemic thrombolysis in patients with infarction-triggered cardiogenic shock.
- Adjunctive IABP use can be considered in cases of primary PCI in patients with infarction-triggered cardiogenic shock; whether this will be helpful, is unclear.
- If an emergency PCI is not possible and the patient with infarction-triggered cardiogenic shock is treated with systemic thrombolysis, then an IABP should be inserted for hemodynamic stabilization and the patient should be transported to a PCI center.
- When a mechanical complication of myocardial infarction occurs – ventricular septal defect and acute severe mitral insufficiency – then IABP should be inserted for hemodynamic stablilization before the patient is transferred to cardiac surgery.
- Percutaneous LVAD can undoubtedly improve hemodynamics more than IABP. However, it has not yet been shown that this hemodynamic improvement results in a better prognosis. Therefore, no general recommendation for LVAD in refractory cardiogenic shock should be given (although this is the case in the European STEMI guidelines [1]); the decision to use a percutaneous LVAD should be made on an individual basis.
- In-hospital cardiac arrest has a very unfavorable prognosis. Assisted extracorporeal life-support may represent a real progress in resuscitating these patients, although the logistics and the technology are ambitious!

Intra-aortic Balloon Counterpulsation in Septic Shock?

In severe sepsis and septic shock, every second death is due to refractory cardiovascular shock [17]. Most intensivists would attribute this cardiovascular shock primarily to refractory vascular shock and not to myocardial depression: Septic shock typically presents as a hyperynamic, high cardiac output, low systemic vascular resistance (SVR) state. However, one quarter of adult patients and even more children with fluid refractory septic shock have a hypodynamic cardiovascular profile [18]. Furthermore, one would assume that the dramatic reduction in afterload seen in septic shock may trigger an even higher cardiac output than that seen under normal afterload conditions. With this in mind, it becomes obvious that 'septic cardiomyopathy' contributes more to the septic shock state than is often suggested: 40 % of patients have a cardiac output corresponding to only 60 – 80 % of the expected value, and in a further 40 % of the patients, cardiac output is even worse [19, 20]. Consequently, supporting the heart not only by inotropes but also by mechanical assist devices, like IABP, could be helpful to rapidly improve the deleterious shock state.

In an experimental model of septic shock, use of IABP as an adjunctive measure was studied thoroughly [18]. In this hypodynamic, mechanically ventilated canine sepsis model triggered by intrabronchial *Staphylococcus aureus* challenge, IABP therapy showed some beneficial effects: In the animals receiving the highest bacterial dose, IABP improved survival time by 23 hours – but not survival – and lowered SVR index as well as norepinephrine requirements. On the negative side was the increase in blood urea nitrogen and creatinine. The authors [18] claim that because

of their findings in this animal model, a randomized controlled trial of IABP therapy may be indicated in carefully selected patients with low cardiac output septic shock and a high risk of death. As cardiac function is similarly depressed in patients with Gram-positive and Gram-negative septic shock [21], this finding could apply to a broad spectrum of septic patients.

But what can we really expect from the use of an IABP in a patient with hypodynamic septic shock [22]? We have the results of Solomon and colleagues [18] on Gram-positive septic shock in dogs that showed some beneficial effects. In newborn lambs infected with group B streptococci, septic shock was improved by IABP as indicated by an increase in cardiac output and a decrease in pulmonary resistance [23]. On the other hand, in a porcine model of endotoxemic shock, IABP was of no benefit [24]. Clinical data are anecdotal and were published more than a quarter of a century ago [25–27], showing beneficial effects in patients with cold extremities and low cardiac output, but not in those with warm extremities and high cardiac output. Finally, an interesting patient group for the IABP approach may be patients with cardiogenic shock complicating myocardial infarction, superimposed by sepsis, amounting to 18 % of the total population [28, 29]. In nearly all of these patients, IABP has been applied, with a higher median duration of IABP in septic than in non-septic cardiogenic shock patients, but not with a greater number of complications [28].

How, at best, could IABP help us in treating our patients with septic shock? We should not expect a lowering of mortality by use of the IABP itself; this has not been shown yet, even for the best validated IABP indications. But what we could expect is a lowering of the dosages of potentially detrimental vasopressors and a prolongation of survival time [18]. This prolongation of survival time could be used to enable causal anti-sepsis therapy time to work. Knowing that prognosis depends on 'early goal directed therapy', we should start very early in the process, because IABP needs more than three and up to 24 hours to be fully effective [30]. We also need to watch carefully whether worsening of renal function under IABP may override any beneficial IABP effects. Although complications of IABP are rare, they may be higher in septic shock owing to coagulation problems due to septic disseminated intravascular coagulation.

However, the most important consideration when thinking about IABP therapy in septic shock is how to precisely define the patient with 'hypodynamic septic shock'. What we need is a quantitative description of the extent of myocardial depression and a quantitative description of the sepsis-induced reduction in afterload, as measured by the SVR. Only when we correlate cardiac output with the SVR, can we clearly estimate the 'real' extent of cardiac output reduction [19, 20]. The 'ideal' patient for IABP would be the septic patient with a highly depressed myocardial function and an SVR that is not severely reduced. We could control the success of IABP treatment by following the cardiac power index/output, which is of prognostic relevance in patients with cardiogenic shock [31]. Finally, if we are thinking about mechanical hemodynamic support in patients with septic shock, perhaps we should move beyond the narrow limits of IABP to percutaneous LVADs, like the Impella® pump, which are able to provide more efficient hemodynamic support than IABP. This approach seems reasonable in view of ongoing attempts in patients with cardiogenic shock (see earlier). Nevertheless, improved survival and not hemodynamic improvement is the final goal.

Conclusion

The use of IABP in the adjunctive treatment of cardiogenic shock is accepted even at the guideline level. However, the promise of IABP use as an evidence-based standard procedure is by no means fulfilled. This is especially the case when we consider IABP use in the large group of patients with myocardial infarction complicated by cardiogenic shock: Available low quality study evidence may favor IABP use when patients are treated with systemic thrombolyis, but in patients treated with primary PCI, IABP use may even be detrimental. Unfortunately, percutaneous LVADs – although hemodynamically more efficient than IABP – have not shown superiority over IABP with respect to prognosis. The recent STEMI guidelines concerning the use of IABP in patients with infarction-triggered cardiogenic shock need to be revised, and, furthermore, we need a randomized controlled IABP trial for these patients, with mortality as the primary endpoint.

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