Direct Comparison of Percutaneous Circulatory Support Systems in Specific Hemodynamic Conditions in a Porcine Model

Running title: Ostadal et al.; Comparison of circulatory support systems

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Abstract:

**Background** - Several percutaneous circulatory support systems have been recently introduced into clinical practice for the treatment of cardiogenic shock or refractory non-tolerated ventricular tachycardia, in support of high-risk catheter interventions and occasionally, cardiopulmonary resuscitation. To date, however, a direct comparison of the available systems has not been performed.

**Methods and Results** - Adult female pigs (weight 50 kg to 60 kg) were used throughout the experiment. Under deep anesthesia and mechanical ventilation, three percutaneous circulatory support systems were compared: (i) right atrium – aorta (RA-Ao), extracorporeal membrane oxygenation (N=4); (ii) left atrium – aorta (LA-Ao), TandemHeart system (N=4); (iii) left ventricle – aorta (LV-Ao), Impella 2.5 system (N=4), and (iv) LV-Ao + norepinephrine (NE) 0.1 μg/kg/min (N=4). Hemodynamic efficacy (mean arterial pressure [MAP]) was measured at three specific conditions: ventricular pacing (VP) 200 beats/min and 300 beats/min, and ventricular fibrillation. While no or only non-significant differences were found among the systems at VP 200 beats/min and VP 300 beats/min, under ventricular fibrillation, the RA-Ao system was significantly the most efficacious, followed by the LA-Ao system, and the LV-Ao system (P<0.001). However, the LV-Ao system with NE still maintained MAP comparable with the LA-Ao system.

**Conclusions** - Differences were seen in the hemodynamic efficacy of available percutaneous circulatory support systems – particularly under the most severe hemodynamic condition, ventricular fibrillation.

**Key words:** percutaneous circulatory support system; heart-assist device; cardiogenic shock; ventricular tachycardia; ventricular fibrillation
Introduction

Over the past few years, several percutaneous systems have been introduced into clinical practice for circulatory support in hemodynamic conditions with markedly decreased cardiac output. Currently, three different systems are widely available in adult human intensive cardiac care: the Impella 2.5 system (Abiomed, Germany), a catheter-based, impeller-driven, axial flow pump that pumps blood directly from the left ventricle across the aortic valve to the ascending aorta; the TandemHeart system (Cardiac Assist, USA), a left atrial-to-femoral arterial circulatory support system, driven by a continuous flow pump; and extracorporeal membrane oxygenation (ECMO), which in the heart and lung support setting is a right atrial-to-femoral arterial assist device, driven by a continuous flow pump with a membrane oxygenator included in the circuit. These three systems represent a powerful alternative to the currently widely used intra-aortic balloon pump (IABP). They offer a bridge to recovery, a bridge to heart transplantation, a bridge to implantation of long-term cardiac-assist devices or a bridge to decision (in patients with acute and rapidly deteriorating HF where full evaluation for indication to long-term cardiac-assist devices or heart transplant has not been possible and in whom death will occur without urgent mechanical cardiac support). Their higher hemodynamic effectiveness is, however, counterbalanced by the increased size of catheters and cannulas, which are associated with a higher risk of device-related complications.

Successful applications of these systems have been recently reported, not only in cases of cardiogenic shock but also as a life-saving procedure during cardiopulmonary resuscitation or for hemodynamic support in high-risk coronary or electrophysiological interventions\textsuperscript{1-5}, particularly in patients with severe left ventricle dysfunction undergoing electrophysiological mapping and tachycardia ablation\textsuperscript{6-9}. To date, only small randomized trials comparing the safety and efficacy
of these systems with IABP have been published\textsuperscript{10-12}; neither clinical nor experimental data on the direct comparison of these circulatory support systems are available. An estimation of the power of each support system is, however, essential for the selection of the most appropriate system for individual patients. The objective of our study was, therefore, to perform a head-to-head comparison of the efficacy of these systems under specific hemodynamic conditions in a porcine model.

Methods

Animal preparation

Sixteen female pigs (Sus scrofa domestica; 50 kg to 60 kg) were used. The investigations were performed in accordance with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). The animals were premedicated with azaperone (2 mg/kg) and ketamine (20 mg/kg i.m.). Fifteen minutes after premedication, the pigs were provided with 100% oxygen via a facial mask, a venous cannula was inserted into the ear vein, and anaesthesia was induced by the injection of propofol (2 mg/kg). After intubation, the animals were connected to a volume-controlled ventilation system (Siemens Elema 900D, Germany). Anaesthesia was maintained with propofol at a rate of 8 mg/kg/h to 12 mg/kg/h; the dose was adjusted based on physiological variables, reflexes (palpebral and corneal), lacrimation and spontaneous movements. Electrocardiogram, invasive blood pressures (femoral artery and jugular vein), pulse oximetry, capnometry, and invasive central venous oxygen saturation were continuously monitored in all animals (Monitor Life Scope TR, Nihon Kohden, Japan and Vigilance II, Edwards Lifesciences, USA). A pacing catheter was introduced into the right ventricle apex via the femoral or jugular vein. Other venous and arterial catheters and cannulas were inserted individually according to the circulatory
support system used. The arterial pH, pO2, pCO2 and levels of sodium and potassium were followed throughout the study. Ventilation support as well as oxygenator gases flow were regularly adjusted to reach the target values (pH 7.4, pO2 12.0 kPa, and pCO2 5.0 kPa). Of note, the metabolic factors were quite well preserved after ten minute periods of both VP 200 beats/min and 300 beats/min in healthy animals and only mild adjustment of ventilation/oxygenation was necessary in most animals; the levels of sodium and potassium remained stable.

Circulatory support systems

Right atrium-to-descending aorta support (RA-Ao). An inlet 21F cannula was inserted via the femoral vein into the right atrium, and an outlet 15F cannula was inserted into the femoral artery. Cannulas were connected to the circuit with a blood pump (Levitronix Centrimag, Levitronix, USA) and oxygenator (Quadrox, Maquet, Germany), constituting an ECMO system (Figure 1A).

Left atrium-to-descending aorta support (LA-Ao). An inlet 21F cannula was inserted via the femoral vein and trans-septal puncture (guided by fluoroscopy and intracardial echocardiography) into the left atrium, and an outlet 15F cannula was inserted into the femoral artery. Cannulas were connected to the circuit with a blood pump (TandemHeart, Cardiac Assist, USA) (Figure 1B).

Left ventricle-to-ascending aorta support (LV-Ao). A 13F catheter-based, impeller-driven, axial flow pump (Impella 2.5, Abiomed, USA) was inserted via the femoral artery and across the aortic valve with the inlet area placed into the left ventricle and the outlet area placed into the ascending aorta (guided by fluoroscopy and intracardial echocardiography) (Figure 1C).

Study design

Three study groups were originally created according to the support system used: RA-Ao group,
LA-Ao group and LV-Ao group (four animals per group). After hemodynamic data analysis, the fourth group was added (LV-Ao+NE), in which norepinephrine was administered together with LV-Ao support (N=4). Figure 2 shows a schematic illustration of the study design. After a 10 min stabilization period, ventricular tachycardia (VT) at 200 beats/min was simulated by right ventricular apical pacing (VP) 200 beats/min for 10 min, followed by a 5 min stabilization period, then VT 300 beats/min was simulated by VP 300 beats/min for 10 min, followed again by a 5 min stabilization period, and finally ventricular fibrillation (VFib) was induced and maintained for 10 min. During the experiment, a target mean arterial pressure (MAP) of 70 mmHg to 80 mmHg was maintained only by adjustment of the pump speed (rpm); no pharmacological interventions were allowed. Norepinephrine was administered only in the LV-Ao+NE group, simultaneously with the induction of VFib, at a dose of 0.1 μg/kg/min (with the exception of norepinephrine administration during VF; the animals in LV-Ao+NE group underwent the same protocol as other groups). MAP was selected as the primary end point.

Statistical analysis

The results are expressed as means ± S.E.M. A two-way ANOVA repeated measures test with subsequent Bonferroni test was used for comparison of differences between groups. Differences were considered to be statistically significant at P<0.05.

Results

No difference in MAP was found among the systems at VP 200 beats/min (Figure 3A). At VP 300 beats/min, the differences did not achieve statistical significance but the target MAP was reached only in the RA-Ao group (Figure 3B). Statistically significant differences were found during VFib: the highest MAP was maintained in the RA-Ao group, followed by the LA-Ao group, and the lowest efficacy was observed in the LV-Ao group, P<0.001 (Figure 4A, Table 1).
Administration of norepinephrine to the LV-Ao support (LV-Ao+NE group) increased the MAP to levels comparable with the LA-Ao group (Figure 4B, Table 1).

Discussion

The major finding of the present study was the significant difference in the hemodynamic efficacy of the currently available percutaneous circulatory support systems, favouring the RA-Ao system (ECMO), followed by the LA-Ao system (TandemHeart). The least efficacious appeared to be LV-Ao system (Impella 2.5). However, even the LV-Ao system allowed short-time blood pressure support during VFib when norepinephrine at 0.1 ug/kg/min was added.

A substantial number of articles describing the use of different circulatory support systems in patients with cardiogenic shock and high-risk coronary intervention have been published. Three randomized trials and their meta-analysis compared the Impella or TandemHeart support with IABP in the treatment of cardiogenic shock, showing increased cardiac index at the cost of higher incidence of bleeding; there was no difference in mortality. There are, however, clinical conditions in which IABP is clearly insufficient for life support, such as recurrent non-tolerated VT, electrical storm, serious mechanical complications of acute myocardial infarction, or cardiac arrest, that does not respond to conventional resuscitation approaches. Similarly, electrophysiological activation and entrainment mapping and catheter ablation of non-tolerated VT, particularly in patients with severe left ventricular dysfunction, is often not feasible without hemodynamic support. Several papers have been already published with case reports or small series of patients undergoing electrophysiological mapping and catheter ablation on circulatory support – the successful use of the Impella system was described by Fishberger et al. and Abuissa et al., support with the TandemHeart system was reported by Friedman et al., and the efficacy of ECMO was shown by Carbucicchio et al. and Thomas et
The largest series during VT ablation has been with the use of the Impella 2.5 system (used with intravenous vasoactive agent support). There is also an increasing number of reports describing the favorable effect of ECMO on survival with good neurological outcome in patients who underwent resuscitation, particularly for in-hospital cardiac arrest. Accordingly, our study was driven by the urgent clinical need for comparative data on the hemodynamic efficacy of available percutaneous circulatory support systems, which can be useful in the decision-making process for the selection of the most appropriate support for each patient.

The differential efficacy of ECMO, TandemHeart, and Impella 2.5 during VFib in our experiment could be explained by different capacity of the systems to generate blood flow. Whereas the lowest blood flow during VFib was observed with Impella 2.5, the highest blood flow was seen with ECMO, where the target MAP was reached with sub-maximal pump rate. But it should also be noted that the decision as to which mechanical support device to use must take into account factors beyond their efficacy in maintaining blood pressure and blood flow. That is, the ease of use of a particular device must also be taken into consideration. For example, while the Impella 2.5 device provided the least level of support, given the fact that it is quicker and easier to place and use, it may be appropriate for many patients with reasonable ventricular function. On the other hand, for the patient with a mechanical aortic valve or severe systolic dysfunction and recurrent polymorphic VT/VF, the TandemHeart device may be preferable. Or for the patient with concomitant lung dysfunction or cyanotic congenital heart disease, the peripheral ECHO device may be better suited for use. The choice of device should be tailored to the individual patient and clinical requirement.

**Limitations:** A limitation of this study was the selection of MAP as the primary end point for the evaluation of hemodynamic efficacy. The comparison of systems with different principles of
support, however, makes it impossible to use the conventional techniques for cardiac index measurement based on standard flow in pulmonary artery or aorta, ie, the RA-Ao system decreases flow in the pulmonary artery, and both the RA-Ao and LA-Ao systems change the direction of flow in the aorta. An alternative to the measurement of MAP as a hemodynamic efficacy end point could be the assessment of flow rate in the major aortic arch branches (e.g., the carotid artery) which is, however, associated with other measurement errors. Nevertheless, MAP in our experiment was not affected by any vasopressor therapy (with exclusion of norepinephrine during the VFib study in LV-Ao+NE group). Other monitoring options that were not assessed in this study include: a) central venous oxygen saturation, and b) evaluating end-organ perfusion using cerebral oximetry; these should be considered in future studies.\textsuperscript{15} Our results may be also influenced by the limited number of animals used (four per group). Only norepinephrine at 0.1\,\mu g/kg/min was employed in this study; however, it is likely that other vasoactive agents would provide similar benefits. Future studies should also evaluate these devices in animal models of pathological disease states such as in post-MI or heart failure models.

In conclusion, the present study has clearly shown highly significant differences in hemodynamic efficacy among the currently available percutaneous circulatory support systems. These data should be considered when selecting the most appropriate circulatory support for specific medical conditions in individual patients.

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**Conflict of Interest Disclosures:** V.Y. Reddy has received clinical research grant support and consulting fees from Abiomed, Inc.
References:


Table 1. Comparison of the effect of circulatory support systems on the mean arterial pressure (MAP) at ventricular fibrillation (Vfib) - Bonferoni post-test. The mean differences are expressed in mmHg. The P-values represent the actual values and the levels of significance corrected for six comparisons are shown as * < 0.05, ** < 0.01, *** < 0.001. RA-Ao, ECMO; LA-Ao, TandemHeart; LV-Ao, Impella 2.5; NE, norepinephrin.

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**Figure 1.** Schematic illustration of percutaneous circulatory support systems. Panel A: RA-Ao (extracorporeal membrane oxygenation) system; Panel B: LA-Ao (TandemHeart) system; Panel C: LV-Ao (Impella 2.5) system. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; Ao, aorta.

**Figure 2.** Hemodynamic protocol.

**Figure 3.** Comparison of the effect of circulatory support systems on the mean arterial pressure (MAP). Panel A: ventricular pacing 200 beats/min; Panel B: ventricular pacing 300 beats/min. Data are expressed as means ± SEM.

**Figure 4.** Panel A: Comparison of the effect of circulatory support systems on the mean arterial pressure (MAP) at ventricular fibrillation (VFib). Panel B: Comparison of the effect of circulatory support systems on the MAP at VFib, including the LV-Ao+NE group (with norepinephrine administered at the induction of VFib). Data are expressed as means ± SEM.
Circulatory support system introduction

- **200 bpm 10 min**
- **300 bpm 10 min**
- **V fib 10 min**

- **Stabilization 10 min**
- **Stabilization 5 min**
- **Stabilization 5 min**
A

200 BPM

MAP (mmHg)

RA-Ao
LA-Ao
LV-Ao

P = 0.34

Min

B

300 BPM

MAP (mmHg)

RA-Ao
LA-Ao
LV-Ao

P = 0.16

Min
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