Risk of Thrombus Formation in Patients on Mechanical Circulatory Support with POLVAD-MEV

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Congestive heart failure is a challenging problem due to increasing prevalence in developed countries. Patients admitted due to decompensated congestive heart failure symptoms who do not respond to medical treatment require mechanical circulatory support. Patients with biventricular failure are at particularly high mortality risk.

Material/Methods: We analyzed the function of 49 pumps (POLVAD-MEV, FRK Intra-cordis, Poland) implanted to rescue INTERMACS 1 and 2 profile patients referred to our department due to severe congestive heart failure. All patients were waiting for heart transplantation and were readmitted due to acute decompensations of congestive biventricular heart failure with resistance to medical therapy.

Results: During the observational period, there were no technical problems in pump function. The mean duration of pump therapy was 30.6±8.3 (5-49) days. The risk for right-sided pump complications included clots formation on the following parts of the pump: outflow tract (1, 2%), membrane (13, 27%), dome (6, 12.5%), and periphery (1, 2%). The overall risk for device thrombosis was 41%. The risk for thromboembolic complications was CRP-dependent regarding conglomerates of fibrin and platelets formation (p<0.05). The risk for left-sided pump complications included clots formation on the outflow tract (1, 2%), membrane (9, 19%) and dome (3, 6%). The overall risk for device thrombosis was 27%. The risk for clots formation on the membrane (*P*<0.05) and dome of the pump depended on time (*P*<0.07).

Conclusions: Mechanical circulatory support with a paracorporeal pump is a safe option for biventricular heart dysfunction as a bridge to heart transplantation. The risk for thrombi formation is relatively high but acceptable within 30 days after implantation.

Keywords: Advanced Cardiac Life Support • Embolism and Thrombosis • Heart Failure • Heart-Assist Devices • Pulsatile Flow

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Background

Congestive heart failure is a challenging problem due to increasing prevalence in developed countries [1]. Acute decompensations are the major indication for hospitalization with the symptoms of fluid retention as the result of dysregulation of neurohumoral compensatory mechanisms [2,3]. Disease is characterized by an insidious course and may lead to severe circulatory decompensation [4]. Repeated hospitalizations are associated with worse outcomes, including decreased 1-year survival to as low as 20-40% [5,6]. Progressive decompensations of congestive heart failure can be pharmacologically treated based on results of VERITAS (Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure), REVIVE (Randomized Evaluation of Intravenous Levosimendan Efficacy), PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist), RELAX-AHF (Relaxin in Acute Heart Failure), and TRUEAHF (Trial to Evaluate the Efficacy and Safety of Ularitide Intravenous Infusion in Patients Suffering From Acute Decompensated Heart Failure) trials. However, the results are still insufficient. Patients admitted due to decompensated congestive heart failure symptoms who do not respond to medical therapy including diuretics, pressor amins, or levosimendan infusion require mechanical circulatory support. Patients with biventricular failure are at particularly high mortality risk. The ultimate therapeutic solution is heart transplantation, which has good long-term results, or a left ventricle system device, with midterm results comparable to transplantation when the right ventricle is not dysfunctional [7,8].

Material and Methods

We analyzed the function of 49 pumps (POLVAD-MED, FRK Intra-cordis, Poland) implanted to rescue INTERMACS 1 and 2 profile patients referred to our department due to severe congestive heart failure. The study was approved from the local Institutional Ethics Committee.

All patients were waiting for heart transplantation and were readmitted due to acute decompensations of congestive biventricular heart failure with resistance to medical therapy.

We evaluated pumps by screening after explantation to assess safety in terms of device thrombosis and risk factors for complications.

The pumps were implanted through median sternotomy. The left-sided pumps were placed into the left atrium (inflow canula) and ascending aorta (outflow canula) with pledget sutures. The right-sided pumps were placed into the right atrium (inflow canula) and pulmonary truck (outflow canula) with pledget sutures.

The INR ratio (international normalized ratio) and CRP (C-reactive protein) were estimated every second day after surgery. The pumps were checked by physicians daily.

Results

During the observational period, there were no technical problems regarding pump function. The mean duration of pump therapy was 30.6±8.3 (5-49) days. The pumps were replaced by physicians if thrombi were detected.

The risk for right-sided pump complications included clots formation on the following parts of the pump: outflow tract (1, 2%), membrane (13, 27%), dome (6, 12.5%), and periphery (1, 2%). The overall risk for device thrombosis was 41%. The risk for thromboembolic complications was CRP-dependent regarding conglomerates of fibrin and platelets formation ($P<0.05$). Details of the relationship between right pump parts and risk for thrombus formation are presented in **Figures 1, 2**.

The risk for left-sided pomp complications included clots formation on the outflow tract (1, 2%), membrane (9, 19%), and dome (3, 6%). The overall risk for device thrombosis was 27%. The risk for clots formation on the membrane ($P<0.05$) and dome of the pump depended on time ($P<0.07$) (**Table 1**). Mann-Whitney U tests revealed no relationship between clot formations and time within mean 30-day observation intervals. Details of the relationship between left pump parts and risk for thrombus formation are presented in **Figure 3, 4**.

Comparing the risk for thrombus formation between both pumps, we found statistically significant differences in the risk for thrombus formation on the membrane and dome. The mechanical valves and outflow or inflow tracts were not found to be significantly affected. The detailed data are presented in **Table 1**. Thrombus deposits on the right and left pump membranes were found in 13 (27%) and 9 (19%), respectively. Thrombus deposits on the right and left pump dome were found in 6 (13%) and 3 (6%), respectively.

Thrombi formation was not related to lower INR ratios. This may be explained by the fact that the dual therapy with vitamin K antagonists (VKA) and antiplatelets drugs was enhanced by low-molecular-weight heparin (LMWH) additions when INR decreased below 2.5.

Inflammatory markers were found to be risk factor for thrombi formation in multivariate analysis. The mean C-reactive protein (CRP) in the non-thrombotic subgroup was 10.3±4.4 mg/L vs 60.5±8.1 mg/L in the thrombotic group ($P<0.05$). CRP level above 23 mg/L was related to thrombus formation in ROC analysis (**Figure 2, 4**) with a cut-off value of 20 mg/L. Thrombi
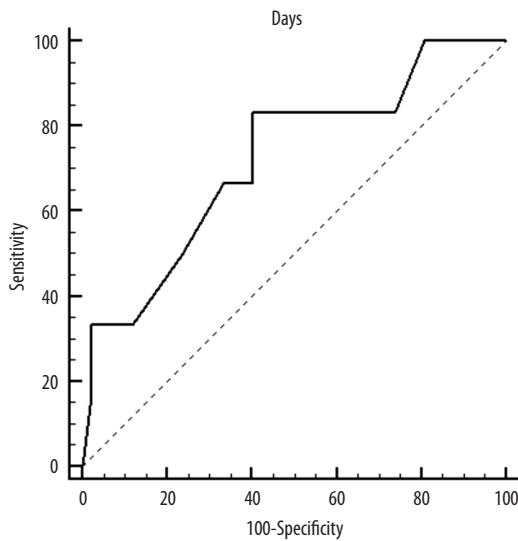
Figure 1. ROC curves of thrombotic events on right pumps. Overall risk for thrombus formation.
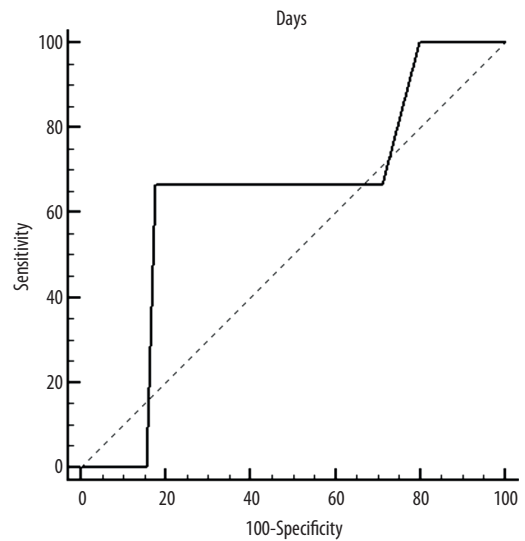

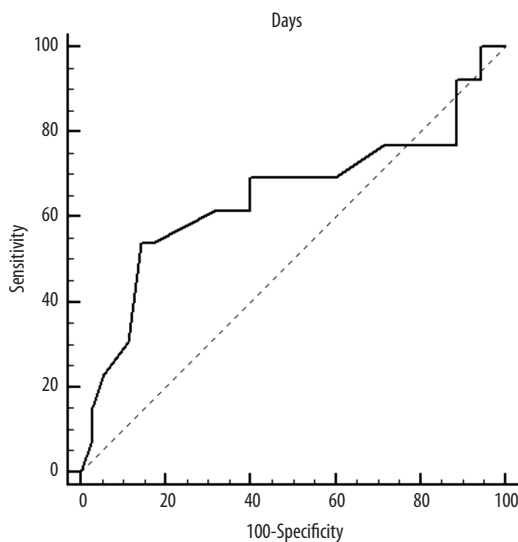**Figure 3.** ROC curves of thrombotic events on left pumps. Overall risk for thrombus formation.

Figure 2. ROC curves of thrombotic events on right pumps. Risk of thrombosis depending on CRP.
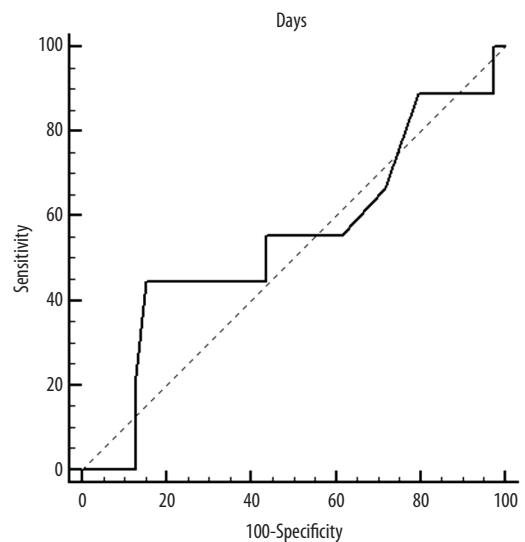

Figure 4. ROC curves of thrombotic events on left pumps. Risk of thrombosis depending on CRP.

in 3 different locations (inflow tract, membrane deposits, and thrombotic conglomerates on the pump dome) are presented in **Figures 5-7**.

Discussion

The growing number of left ventricular assist devices (LVAD) implanted worldwide for long-term circulatory support and extracorporeal membrane-oxygenation (ECMO) for short-term support have decreased the utility of paracorporeal VADs [9].

However, paracorporeal pneumatic pumps are still the best option for biventricular dysfunction, which accounts for 10-20% of the entire VAD population [10]. The number of BIVAD implantations is currently decreasing, mainly due to earlier LVAD implantation along with perioperative right ventricle function management [11]. Use of BIVADs consisting of 2 HeartWare HVAD® (HVADs) is associated with high mortality and thrombus formation risk [12].

Biventricular dysfunction is a major indication for implantation pulsatile paracorporeal pumps. One of the advantages of

Table 1. Risk for thrombus formation in left and right pumps.

	Left-sided pump		Right-sided pump		p
Time overall (days)	30.6±8.3 (5-49)				
Frequency of thrombosis	n (%)		n (%)		
Overall (%)	13	(27%)	20	(41%)	p=0.1435
Outflow (%)	1	(2%)	1	(2%)	p=1.0000
Membrane (%)	9	(19%)	13	(27%)	p=0.3467
Dome (%)	3	(6%)	6	(12.5%)	p=0.2668
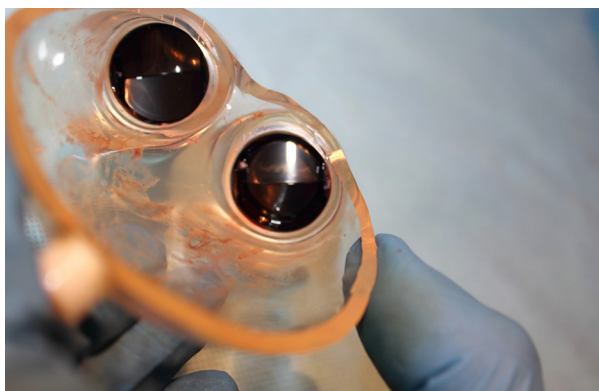
Figure 5. Deposits on the pump dome.
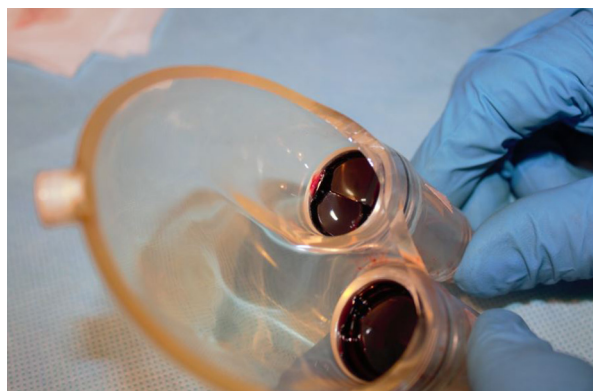
Figure 7. Deposits on mechanical valves of the pump.

Figure 6. Deposits on the pump membrane.

pneumatic pumps is microcirculation preservation by pulsatile flow. Maintaining physiological blood flow may improve tissue perfusion and capillary flow and decrease the risk for acquired von Willebrand syndrome.

ECMO is relatively easy and available but has some disadvantages, including the lack of ventricular unloading compounded with creation of high afterload and a secondary decrease in coronary perfusion [13]. A sequence of therapies from ECMO through POLVAD-MED and finally into solid organ transplantation were documented, providing possible solutions while transplant centers struggle with the organ donor shortage [14]. The multicenter ECMELLA study (ECLS and Impella application) demonstrated a significant improvement in outcomes in patients receiving short-term mechanical support therapy [15]. Impella allows for left ventricle unloading. Both devices are effective for a very short time (5-6 days) after application [16].

Paracorporeal pneumatic biventricular support is a life-saving technology while bridging to heart transplantation. The major disadvantages are bleeding, thrombosis, and infection [17]. POLVAD-MED generates pulsatile blood flow and is comparable to left ventricle system devices (LVADs) in producing continuous blood flow [18]. The main advantage is that it provides the possibility to replace function of both ventricles.

The major disadvantage of any mechanical support implantation device is the risk for thrombosis [19,20]. We evaluated the risk for thrombus formation by visual assessment after device explantation. Coagulopathy related to mechanical support was reported previously and was called the Vroman effect [20]. It is related to absorption of activated contact proteins on mechanical support device surfaces.

In our study, we found the risk for thrombus formation on certain parts of pumps depends on the CRP ratio. The right pump, especially the membrane and dome of the pump, had high risk of thrombus formation during the study. Daily visual inspection for thrombus formations is a standard clinical practice. We evaluated the risk for thrombi what was non-visually detected but was demonstrated after pump explantation. We found that the major risk for any regional coagulopathies is related to inflammatory state. During the POLVAD patients' follow-up, the high-sensitive C-reactive protein was checked every second day. The mean CRP values throughout the pump function periods were considered in analysis. We found that statistically significant risk for thrombi formation is related to increased CRP values, as previously reported in LVAD patients [21].

Systemic inflammation following LVAD implantation can be fatal when systemic inflammatory reaction develops, especially during surgical procedures in cardiopulmonary bypass operations [22]. The overall results of LVAD patients are related to preoperative and postoperative inflammatory triggers. Inflammatory reactions in patients on mechanical support can cause right ventricle failure, which complicates up to 40% of implantations [23]. Midterm mortality rates are also affected by preoperative increased inflammatory parameters [24]. Moreover, the risk for cerebral microembolization in relation to C-reactive protein has been proposed [25].

In the present study, the INR ratio was checked every second day and vitamin K antagonist doses were adjusted. Patients were on dual therapy with oral anticoagulants and antiplatelet agents. If INR results were below 2.5, we followed our protocol to add low-molecular-weight heparin (LMWH) to therapy and increased oral anticoagulants.

Although the use of external pulsatile pumps is decreasing, we want to highlight their advantages in certain patients. Patients referred for mechanical circulatory support in end-stage biventricular dysfunction may benefit from therapy. Moreover, paracorporeal pneumatic pumps are postulated to prevent collapse of capillaries and nitric oxide release in the microcirculation due to the pulsatile pattern of blood flow [26]. Use of BIVAD can be especially helpful for patients admitted due to circulatory collapse caused by fulminant myocarditis, as recovery of the failing myocardium was reported to be more effective in pulsatile mechanical therapy [27]. Recently, third-generation LVADs have a speed pump modulation algorithm, termed the Lavare cycle, to partially mimic pulsatile flow and prevent thrombus formation [28,29].

Conclusions

Mechanical circulatory support with a paracorporeal pump is a safe option for biventricular heart dysfunction as a bridge to heart transplantation. The risk for thrombi formation is relatively high but acceptable within 30 days after implantation. The risk for thrombi formation in our group was lower than that reported in the Euromacs Registry (27% and 41% vs 48%, respectively). We found that inflammatory activity was the highest within 30 days of use, and was a risk factor for thrombotic complications.

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