Aus dem Deutschen Herzzentrum Berlin
Stiftung des bürgerlichen Rechts

DISSERTATION

Design changes in continuous-flow left ventricular assist devices
and life-threatening pump malfunctions

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

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aus Berlin

Datum der Promotion: 22. September 2017

Inhaltsverzeichnis

1. Abstract

1.1. Deutsch

Designveränderungen linksventrikulärer Unterstützungssysteme mit kontinuierlichem Fluss und lebensbedrohliche Pumpendysfunktionen.

Zielsetzung:

Evaluation der Auswirkung von Designveränderungen implantierbarer linksventrikulärer Unterstützungssysteme (LVADs) vom Typ HeartMate II (HM II) und HeartWare (HW) auf das Auftreten lebensbedrohlicher Pumpendysfunktionen.

Methoden:

Patienten mit primär implantierten HM II (n = 191) und HW (n = 347) Unterstützungssystemen wurden in je zwei Gruppen mit altem und neuem Pumpendesign unterteilt und retrospektiv auf die Inzidenz von Pumpenthrombosen und Kabelbrüchen analysiert. 2010 wurde der Kabelstrang des HM II modifiziert (132 Patienten mit altem und 79 mit neuem Kabeldesign). Ebenso wurden die Ein- und Ausflussprothesen mit einer Beschichtung versehen (= *sealed graft*; 68 Patienten mit und 125 Patienten ohne beschichtete Ein- und Ausflussprothese). Titanium-gesinterte Einflusskanülen wurden 2011 in das HW System eingeführt (137 Patienten ohne und 210 Patienten mit gesinterter Einflusskanüle).

Ergebnisse:

Die mediane Unterstützungszeit lag bei 1.12 (0-6.1) Jahren für alle HM II und 0,59 (0-4,2) Jahren für alle HW Patienten. Die kumulative Rate an Ereignissen pro Patientenjahre (*events per patient-year*; *EPPY*) betrug 0.11 für HM II und 0.09 für HW Patienten (P = 0.32). Nach Einführung des neuen Kabelstranges fiel die Inzidenz der Kabelbrüche bei HM II Pumpen von 0.06 Fällen pro Patientenjahr auf 0, wohingegen es nach Einführung der beschichteten Prothesen zu einem Anstieg von Pumpenthrombosen kam (0.02 vs. 0.14 *EPPY*; P < 0.001). Insgesamt traten Pumpenthrombosen bei 4% der HeartWare- Patienten mit gesinterter Kanüle sowie 15% der HeartWare- Patienten ohne gesinterte Kanüle auf. Dabei zeigte sich kein signifikanter Unterschied in der Inzidenz von Pumpenthrombosen (0.07 vs. 0.10 *EPPY*; P = 0.45). In der Kaplan-Meier Analyse ergaben sich über einen Zeitraum von 2.5 Jahren keine signifikanten Unterschiede im Vergleich der HM II Kohorte mit *sealed graft* und modifiziertem Kabeldesign (n = 68) zu HW Pumpen mit gesinterter Kanüle (P = 0.14).

Schlussfolgerungen:

Sowohl die Einführung des modifizierten Kabeldesigns der HM II Pumpe, als auch die Sinterung der Einflusskanüle der HW Pumpe führten zu einer signifikanten Reduktion der Inzidenz von lebensbedrohlichen Pumpenkomplikationen. Hingegen führten beschichtete Ein- und Ausflussprothesen zu einem vermehrten Auftreten von Pumpenthrombosen. Über einen Beobachtungszeitraum von 2.5 Jahren, zeigten beide Unterstützungssysteme nach Designmodifikationen eine vergleichbare Rate an Pumpenkomplikationen.

1.2. Englisch

Design changes in continuous-flow left ventricular assist devices and life-threatening pump malfunctions

Objectives:

The implantable continuous-flow left ventricular assist devices (LVADs) HeartMate II (HM II) and HeartWare HVAD (HW) underwent design modifications. The impact of these changes on life-threatening pump malfunctions was evaluated.

Methods:

We retrospectively analysed pump malfunctions due to thrombosis or cable damage in patients supported with primarily implanted HM II (n = 191) and HW (n = 347), separated into patients supported with the old and new pump designs. In 2010, the cable strain relief of the HM II device was improved (132 patients with old and 79 with new) and sealed grafts were introduced (68 patients with sealed inflow connector and outflow graft and 125 without). In 2011, titanium sintering of the inflow cannula of HW pumps was introduced (137 patients with a non-sintered and 210 with a sintered inflow cannula).

Results:

The median support time was 1.12 (0-6.1) years for all HM II and 0.59 (0-4.2) years for all HW patients. The cumulative rate of events per patient-year (EPPY) was 0.11 in HM II patients, compared with 0.09 EPPY in HW patients (P = 0.32). After introduction of the new cable design, incidence of cable damage in HM II patients dropped from 0.06 to 0 EPPY (P = 0.03), whereas pump thrombosis increased from 0.02 to 0.14 EPPY (P < 0.001) after the sealed graft was introduced. Pump thrombosis occurred in 4% of patients supported with HW with a sintered inflow cannula vs 15% with a non-sintered pump; the incidence changed from 0.10 to 0.07 EPPY in sintered pumps (P = 0.45). Kaplan-Meier analysis showed no differences over a period of 2.5 years for events when the HM II cohort with sealed graft and new cable design (n = 68) was compared with the HW group with a sintered cannula (P = 0.14).

Conclusions:

The modified cable strain relief of the HM II pump and the sintering of the inflow cannula of the HW pump demonstrated a significant reduction in the incidence of life-threatening pump-related complications, whereas the sealed inflow connector and outflow graft seem to be associated with a higher incidence of pump thrombosis. However, the overall incidence of pump-related complications after the latest design changes was similar for both pumps over a 2.5-year period.

2. Eidesstattliche Versicherung und Anteilserklärung

„Ich, Sajjad Soltani, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Design changes in continuous-flow left ventricular assist devices and life-threatening pump malfunctions."
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Datum   Unterschrift

Ausführliche Anteilserklärung an der erfolgten Publikation

Publikation:

Soltani S, Kaufmann F, Vierecke J, Kretzschmar A, Hennig E, Stein J, Hetzer R, Krabatsch T, Potapov EV.
Design changes in continuous-flow left ventricular assist devices and life-threatening pump malfunctions.
Eur J Cardiothorac Surg.
2015 Jun

Beitrag im Einzelnen:

1. Erarbeitung der Fragestellung und Festlegung des Studiendesigns:

1.1.   Recherche bereits vorhandener Veröffentlichungen zum Thema Pumpenthrombosen und Kabelbrüche im Allgemeinen. Hiernach Erarbeitung der Fragestellung, die als solche bis zu dem Zeitpunkt nicht bearbeitet oder publiziert wurde.

1.2.   Auswahl der Patienten und der sinnvollen primären Studienparameter in Supervision mit PD Dr. med. E. Potapov.

1.3.   Entschluss zur Durchführung einer retrospektiven Studie, hier vorteilhaft mit einer im Vergleich zu vorhandenen Single-Center Studien hohen Anzahl an eingeschlossen Patienten.

2. Erhebung der Daten:

2.1.   Hauptverantwortliche Zusammenstellung und Einschluss der Patienten mit linksventrikulären Unterstützungssystemen vom Typ HeartWare und Heartmate und Durchsicht sämtlicher stationär und ambulant erhobener Patienteninformationen.

2.2.   Ständige Aktualisierung der Primärdaten der eingeschlossenen Patienten, die im Beobachtungszeitraum in externen Krankenhäusern behandelt wurden, Pumpenthrombosen oder Kabelbrüche erlitten haben oder gar verstorben sind.

3. Statistische Analyse:

3.1.   Statistische Auswertung durch Frau Julia Stein. Hier genaue Besprechung der Fragestellung.

4. Ergebnisse und Klinische Relevanz:

4.1. In Zusammenarbeit mit Herrn PD Dr. med. E. Potapov Erstellung des Manuskripts einschließlich der Formatierung und graphischen Darstellung der Kaplan-Meyer-Kurven.

4.2 Eigenständiges Einreichen des Papers als „corresponding author" und Bearbeitung der Reviewer-Kommentare.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

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3. Auszug aus der Journal Summary List
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   Aktueller IF lt. offizieller Website: 2.803

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MARK ALL   UPDATE MARKED LIST   *Ranking is based on your journal and sort selections.*

Mark	Rank	Abbreviated Journal Title *(linked to journal information)*	ISSN	JCR Data ⓘ						Eigenfactor® Metrics ⓘ	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor® Score	Article Influence® Score
☐	41	J NEUROSURG ANESTH	0898-4921	1219	2.828	2.147	0.649	37	7.0	0.00186	0.530
☐	42	J GASTROINTEST SURG	1091-255X	9507	2.807	2.858	0.623	281	6.4	0.02204	0.985
☑	43	EUR J CARDIO-THORAC	1010-7940	12115	2.803	2.702	1.289	305	6.9	0.03027	1.069
☐	44	J TRAUMA ACUTE CARE	2163-0755	4214	2.802	2.848	0.554	305	2.7	0.02026	0.958
☐	45	HEAD NECK-J SCI SPEC	1043-3074	8900	2.760	2.790	0.706	303	6.7	0.01889	0.898
☐	46	DIGEST ENDOSC	0915-5635	1782	2.715	2.434	0.894	104	3.4	0.00492	0.600
☐	47	JAMA OTOLARYNGOL	2168-6181	891	2.705	2.705	0.431	137	2.1	0.00465	1.007
☐	48	WORLD NEUROSURG	1878-8750	2850	2.685	2.590	0.385	382	2.7	0.01300	0.828
☐	49	BONE JOINT J	2049-4394	1722	2.660	2.662	0.463	272	2.1	0.00845	0.940
☐	50	WOUND REPAIR REGEN	1067-1927	4820	2.628	3.232	0.333	102	7.6	0.00583	0.846
☐	51	INT WOUND J	1742-4801	1782	2.594	2.432	0.514	111	4.1	0.00414	0.608
☐	52	NEUROSURG FOCUS	1092-0684	5211	2.546	2.922	0.358	151	6.7	0.01123	0.994
☐	53	WORLD J SURG	0364-2313	14176	2.523	2.823	0.602	364	7.3	0.02836	0.953
☐	54	AESTHET SURG J	1090-820X	1915	2.502	2.214	0.983	119	4.3	0.00498	0.657
☐	55	LASER MED SCI	0268-8921	3607	2.461	2.702	0.466	296	4.3	0.00702	0.559
☐	56	COLORECTAL DIS	1462-8910	5390	2.452	2.409	0.643	182	4.6	0.01747	0.821
☐	57	J SHOULDER ELB SURG	1058-2746	8827	2.412	2.967	0.370	322	6.8	0.01816	0.930
☐	58	AM J SURG	0002-9610	15730	2.403	2.649	0.384	331	>10.0	0.02157	1.006
☐	59	INT J COLORECTAL DIS	0179-1958	4780	2.383	2.432	0.368	190	6.1	0.01056	0.744
☐	60	TECH COLOPROCTOL	1123-6337	1523	2.320	1.954	1.035	85	3.9	0.00419	0.578

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Journals 41 - 60 (of 200) |◀ ◀◀ ◀ [1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10] ▶ ▶▶ ▶| Page 3 of 10

4. Druckexemplar der Publikation

Cite this article as: Soltani S, Kaufmann F, Vierecke J, Kretzschmar A, Hennig E, Stein J et al. Design changes in continuous-flow left ventricular assist devices and life-threatening pump malfunctions. Eur J Cardiothorac Surg 2015;47:984–9.

Design changes in continuous-flow left ventricular assist devices and life-threatening pump malfunctions

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Abstract

OBJECTIVES: The implantable continuous-flow left ventricular assist devices (LVADs) HeartMate II (HM II) and HeartWare HVAD (HW) underwent design modifications. The impact of these changes on life-threatening pump malfunctions was evaluated.

METHODS: We retrospectively analysed pump malfunctions due to thrombosis or cable damage in patients supported with primarily implanted HM II ($n = 191$) and HW ($n = 347$), separated into patients supported with the old and new pump designs. In 2010, the cable strain relief of the HM II device was improved (132 patients with old and 79 with new) and sealed grafts were introduced (68 patients with sealed inflow connector and outflow graft and 125 without). In 2011, titanium sintering of the inflow cannula of HW pumps was introduced (137 patients with a non-sintered and 210 with a sintered inflow cannula).

RESULTS: The median support time was 1.12 (0–6.1) years for all HM II and 0.59 (0–4.2) years for all HW patients. The cumulative rate of events per patient-year (EPPY) was 0.11 in HM II patients, compared with 0.09 EPPY in HW patients ($P = 0.32$). After introduction of the new cable design, incidence of cable damage in HM II patients dropped from 0.06 to 0 EPPY ($P = 0.03$), whereas pump thrombosis increased from 0.02 to 0.14 EPPY ($P < 0.001$) after the sealed graft was introduced. Pump thrombosis occurred in 4% of patients supported with HW with a sintered inflow cannula vs 15% with a non-sintered pump; the incidence changed from 0.10 to 0.07 EPPY in sintered pumps ($P = 0.45$). Kaplan–Meier analysis showed no differences over a period of 2.5 years for events when the HM II cohort with sealed graft and new cable design ($n = 68$) was compared with the HW group with a sintered cannula ($P = 0.14$).

CONCLUSIONS: The modified cable strain relief of the HM II pump and the sintering of the inflow cannula of the HW pump demonstrated a significant reduction in the incidence of life-threatening pump-related complications, whereas the sealed inflow connector and outflow graft seem to be associated with a higher incidence of pump thrombosis. However, the overall incidence of pump-related complications after the latest design changes was similar for both pumps over a 2.5-year period.

Keywords: HeartMate II • HeartWare HVAD • LVAD • Pump exchange • Cable damage • Pump thrombosis

INTRODUCTION

Implantable continuous-flow left ventricular assist devices (LVADs) are now a routine treatment for end-stage heart failure. Several factors are currently driving the implantation numbers upwards— the shortage of donor organs, especially in Europe, increasing numbers of patients suffering from end-stage heart failure and ageing of the population. Nevertheless, modern pumps such as the HeartWare HVAD (HW; HeartWare International, Inc., Framingham, MA, USA) and HeartMate II (HM II; Thoratec Corp., Pleasanton, CA, USA) have their limitations, which are being addressed by continuous design improvements. Pump malfunctions due to cable damage or thrombosis are the most important pump-related complications and, if not treated immediately, are potentially fatal.

Given that both pumps are commercially available, with studies having shown similar survival times in the first 2 years [1], and the fact that both pumps are potentially suitable for the vast majority of patients, pump selection is the main question for the surgeon and referring cardiologist. Selection [2] is subjective and based mainly on surgical preferences including simplicity of surgical technique [3] and patient satisfaction with the external component [4], but above all on the complication profile. In 2011, HeartWare introduced a titanium sintered inflow cannula as a reaction to an unexpectedly high incidence of pump thrombosis [5, 6]. In 2010, Thoratec introduced a new cable design for HeartMate II in response to a high incidence of cable damage during long-term support [7] as well as a sealed inflow connector and outflow graft to counteract perioperative bleeding complications. The strain

relief at the connection site to the pump was made from a more flexible type of silicone and the mould was smoothened to diminish stress concentration (notching effect), both changes done to prevent the breaking of the outer silicone insulation, which subsequently led to weakening of the inside cable at the feed-through into the pump, ultimately causing motor wire fractures. Whether these modifications have had an impact on life-threatening pump malfunctions remains uncertain. Additionally, several questions arise regarding the association of pump thrombosis with low anticoagulation status and the use of antiplatelet drugs [8–11].

We performed a single-centre retrospective analysis of pump malfunctions related to cable damage and pump thrombosis with the aim of comparing the effects of the design changes. Further, we compared the latest generation of both LVADs with regard to cable damage and pump thrombosis. Additionally, anticoagulation status was investigated in terms of its effect on pump thrombosis.

MATERIALS AND METHODS

We retrospectively analysed our database for pump-related life-threatening events due to cable damage or pump thrombosis (leading to pump exchange or explantation, high urgency heart transplantation or death).

Patients

We analysed consecutive patients supported with HeartMate II (HM II) and HeartWare HVAD (HW) continuous-flow ventricular assist devices at our institution. Pump selection for individual patients was not random and was based on the surgeon's choice (Roland Hetzer, Thomas Krabatsch and Evgenij V. Potapov) for the individual patient's condition.

Under German law, retrospective data analysis of an institution's own data does not require ethics committee approval.

Anticoagulation

In the early postoperative period, we focus our anticoagulation on the activated partial thromboplastin time (aPTT) with a target of 45–55 s for HM II and 50–70 s for HW for the entire study population. In the case of heparin-induced thrombocytopaenia type II, argatroban is administered intravenously with the same aPTT target. Aspirin is added approximately 7–10 days after surgery if platelet count and function have returned to nearly normal values as monitored by platelet aggregation tests (light transmission aggregometry, platelet function analyser 100 and Multiplate).

In all patients, Coumadin is started on approximately postoperative day 10 after the chest tubes have been removed and oral feeding has started. The target international normalized ratio (INR) is set at 2–2.5 for HM II and 2.5–3.0 for HW (measured by CoaguChek) with additional administration of Aggrenox [containing dipyridamol 200 mg and acetylsalicylic acid (Aspirin) 25 mg] and Aspirin 100 mg (total Aspirin dose up to 125 mg per day), depending on platelet aggregation tests. In outpatients, the anticoagulation monitoring and adjustment are based on daily use of the CoaguChek device and platelet aggregation tests performed during visits to the outpatient department.

The last INR and aPTT values measured before diagnosis of pump thrombosis or the last available values from outpatient visits in patients without pump thrombosis were collected and analysed.

The anticoagulation regime—based on our experience with over 2000 pumps implanted over a period of more than 25 years—remained similar throughout the study and is described in detail in several earlier publications [5, 12, 13]. In general, only the target aPTT and INR differed between patients supported with HM II and HW pumps.

Pump thrombosis

An event was defined as pump thrombosis if a thrombus was found in the explanted pump.

In two patients supported with HW (one with and one without sintering) clinical and technical parameters suggested pump thrombosis. In these patients left ventricular function improved and the HW pump was stopped and, due to the clinical situation, left in place. In both cases the pumps were not investigated and these patients are therefore not included in the analysis. Similarly, suspected pump thrombosis (in both HM II and HW) based on technical pump data or on elevated laboratory markers of haemolysis but 'not confirmed' by pump investigation is not defined as a thrombotic event.

Cable damage

Cable damage was defined as present with any pump malfunction caused by acute or chronic damage to the leads or connector, leading to pump exchange, high urgency heart transplantation or death before admission to hospital. One HM II patient with iatrogenic cable damage during abdominal surgery was included in the analysis.

Statistical analysis

Firstly, patients supported with HM II are compared with those supported with HW regarding life-threatening pump-related events. Secondly, in relation to cable damage, including accidental damage, events are compared among patients with the old and those with the newly designed HM II cable and against the entire HW study population (no change in cable design over time). Thirdly, in relation to pump thrombosis, events are compared among patients supported with HW pumps without and with the titanium sintered inflow cannulas, and also with the entire HM II study population before and after introduction of a sealed inflow connector and outflow graft. Finally, the latest versions of both pumps (currently commercially available) were compared with regard to life-threatening pump-related malfunctions.

For each patient, only data on the first pump implanted were included in the statistical analysis, except for two secondary HM II pump reimplantations due to worsening of myocardial function after recovery following a long off-pump period, which were included.

Continuous data are expressed as median and range, categorical data as absolute and relative frequencies. Device failures (cable damage or pump thrombosis) are reported as rate of events per patient-year (EPPY) of follow-up on the device. Freedom from event is evaluated by Kaplan–Meier analysis, censoring at the time of HTx or explantation for recovery. Comparisons between different patient groups were calculated by the χ^2 test, Fisher's exact test or Mann–Whitney U-test.

IBM SPSS Statistics 22 was the statistical package used for analysis.

Table 1:   Key preoperative demographic and clinical data of the entire study population

Parameters	HeartMate II (*n* = 193)	HeartWare HVAD (*n* = 347)	*P*-value
Age (years)	56.00 (20–79)	56.00 (6–82)	0.32
Gender (m/f)	167/26	280/67	0.34
Aetiology (ICMP/DCMP/other)	84/100/9	161/159/24	0.38
BMI (kg/m^2)	25.8 (15.4–42.5)	25.3 (9.8–50.9)	0.34
INTERMACS level (1/2/3/4+)	20/77/63/26	76/140/100/30	<0.01
HIT II preop (%)	19 (10%)	21 (6%)	0.11
HIT II postop (%)	53 (28%)	70 (20%)	0.06
Median time on support (years)	1.12 (0–6.1)	0.59 (0–4.2)	n.a.
Cumulative time on support (years)	297	355	n.a.

Data are presented as median and ranges or absolute and relative frequencies.
BMI: body mass index; DCMP: dilative cardiomyopathy; HIT: heparin-induced thrombocytopaenia; ICMP: ischaemic cardiomyopathy; n.a.: not applicable.

RESULTS

The study analysed 193 HM II pumps implanted in 191 patients. The HM II study population consisted of 123 patients supported with the old and 70 with the new cable design pumps. There are 68 latest versions of the HM II pump (new cable design plus sealed graft) implanted and analysed.

Since 2009, 382 HW LVAD pumps have been implanted in 347 patients. The present study analysed 347 patients implanted with HW; patients supported with biventricular HW were excluded from the analysis. In the HW population, 137 patients are supported with pumps with the non-sintered and 210 with the sintered inflow cannula. Demographic and clinical data are given in Table 1.

Life-threatening pump-related events occurred in 33 patients (17%) at an event rate of 0.11 EPPY in HM II patients and in 33 patients (10%) at 0.09 EPPY in HW patients, *P* = 0.44. The data are shown in Fig. 1.

Cable damage

Cable damage led to pump explantation or exchange (HM II, *n* = 12; HW, *n* = 2), high urgency heart transplantation (HM II, *n* = 3) or death before admission to hospital (HM II, *n* = 3) in a total of 18 HM II patients at a rate of 0.06 EPPY and in 2 HW patients at a rate of 0.005 EPPY, *P* < 0.001. Since improvement in the strain relief in HM II in 2010, the incidence of cable damage in HM II patients dropped from 0.08 to 0 EPPY (*P* = 0.01) in the first 3 years. The median time on support until cable damage occurred was 763 days (range 105 days to 5 years) for the old cable design HM II vs 132 days (range 27–248 days) for HW patients. Cable damage (*n* = 18) in HM II pumps with the old cable design occurred in 4 cases beyond 3 years of support. Kaplan–Meier analysis for cable damage in the entire HW population and two subgroups of HM II patients with implantation before and after introduction of the new cable design showed significant differences between the old and the improved cable design, but no differences during 2.5 years between the whole HW population and patients with the improved cable design of HM II (Fig. 2). The 30-day survival after pump exchange was 95% for both pumps.

Pump thrombosis

The incidence of pump thrombosis in the entire HM II population was 15 of 193 pumps at a rate of 0.05 EPPY and occurred after a
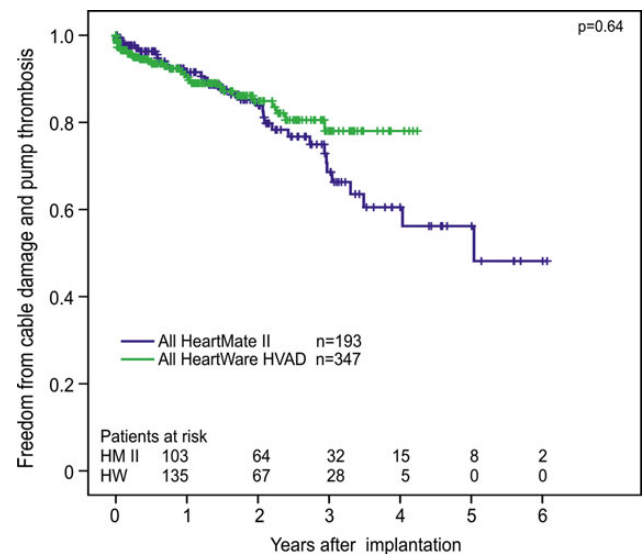

Figure 1: Kaplan–Meier analysis of life-threatening events (cable damage or pump thrombosis) in all. HeartMate II (HM II) and HeartWare HVAD (HW) patients.

median time on support of 217 days (range 7 days to 2.7 years). For HW, the incidence was 31 of 347 pumps at a rate of 0.09 EPPY and occurred after a median support time of 176 days (range 1 day to 3 years). The difference in incidence between the entire group of HM II and HW was not significant (*P* = 0.07).

After the sealed inflow connector and outflow graft (gelatine-sealed grafts) were introduced in 2010 (first implantation at the Deutsches Herzzentrum Berlin, 16 February 2011), the incidence of pump thrombosis increased from 0.02 to 0.14 EPPY (*P* < 0.001). The median time until pump thrombosis occurred was 215 (range 23–997) days in pumps with sealed grafts vs 260 (range 7–803) days in pumps with non-sealed grafts (sealed on site with the patient's whole blood during surgery).

Since the sintered inflow cannula was introduced for HW, 11 cases of pump thrombosis occurred in 210 patients compared with 20 in 137 patients supported with non-sintered pumps. The incidence of pump thrombosis in HW patients changed from 0.15 to 0.05 EPPY (*P* = 0.002). The median time until pump thrombosis occurred was 217 days in non-sintered pumps (range 2 days to 3 years) vs 176 days in pumps with a sintered inflow cannula (range
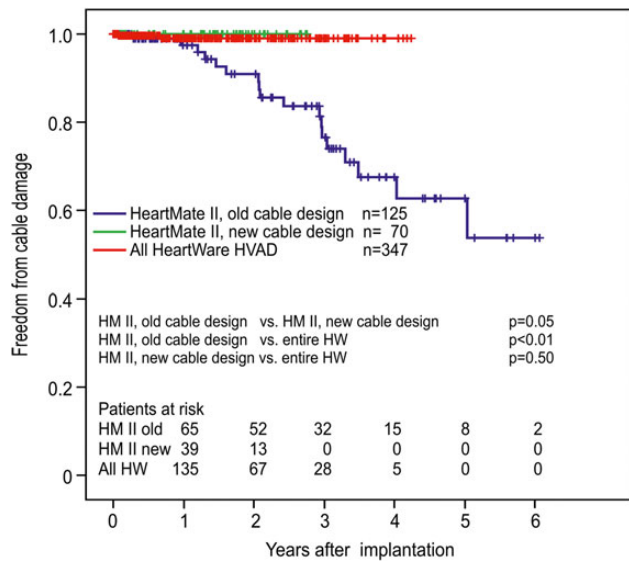
Figure 2: Kaplan–Meier analysis for cable damage in the entire HW population and two subgroups of HM II patients with pumps before and after introduction of the new cable design. HM II: HeartMate II; HW: HeartWare HVAD.

Figure 3: Kaplan–Meier analysis of pump thrombosis in two subgroups of HM II patients with pump implantation before and after the introduction of the sealed inflow connector or outflow graft and two subgroups of patients with HW implanted before and after the introduction of titanium sintering of the inflow cannula. HM II: HeartMate II; HW: HeartWare HVAD.

1 day to 1.5 years). Kaplan–Meier analysis showed no differences for a period of 2.5 years for pump thrombosis when the sealed HM II cohort was compared with that of the sintered HW ($P = 0.136$) (Fig. 3). Adjusted for age, use of Aggrenox and documented infections, the risk ratio for pump thrombosis was 2.4 (confidence interval 1.0–5.7, $P = 0.05$) for patients with sealed HM II pumps compared with the sintered HW. The 30-day survival after pump exchange was 73% in HM II patients and 67% in HW patients ($P = 0.74$).

Anticoagulation

The last documented coagulation parameters and use of antiaggregation drugs in patients supported with both subgroups of HM II and both subgroups of HW before pump thrombosis occurred are presented in Table 2.

Coagulation parameters in patients supported with the non-sealed and the sealed version of HM II are given in Table 3.

DISCUSSION

This study showed that improvement in the design of the strain relief in HM II pumps led to a reduced incidence of cable damage, at least for the first 2.5 years. Sintering of the inflow cannula of the HW device led to a reduction in pump thrombosis, while the introduction of a sealed graft in the HM II pump led to a significant increase in the incidence of pump thrombosis. However, the overall incidence of pump-related complications analysed in this study after the latest design changes was similar for both pumps (Fig. 4).

Our data show an increased incidence of pump thrombosis in HM II patients since 2011 despite the very conservative definition of pump thrombosis employed in the present study. Lactate dehydrogenase or free haemoglobin elevation as a marker for pump thrombosis has been mainly evaluated for HM II pumps [14] and only in a few HW patients [15] and, similarly to early elevation in pump power of the HM II, may be caused by reasons other than pump thrombosis [2]; these parameters are therefore excluded
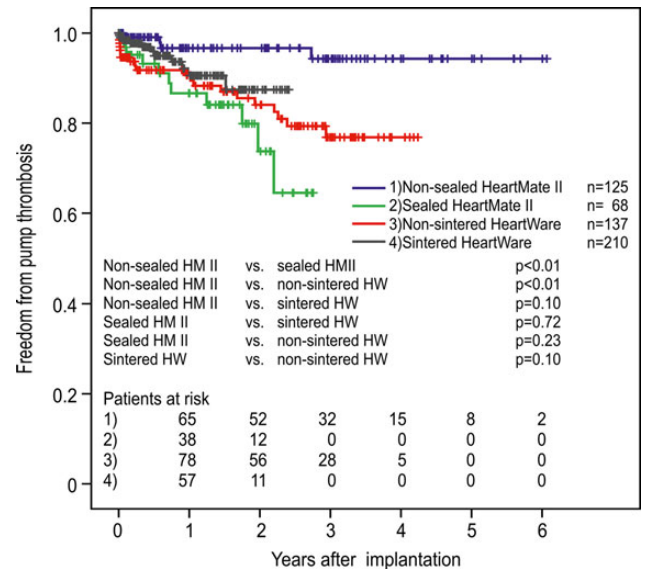
from the definition of pump thrombosis adopted in the present study. Nevertheless, our data are consistent with data published recently by Starling *et al.* [16]. It may be speculated that liberal anticoagulation in patients supported with HM II suggested in recent reports [10, 17] would inadvertently lead to tolerance of low INR with a subsequent increase in late pump thrombosis. This was not the case in our centre, where the INR was similar in earlier and later (since 2011) HM II and HW patients (Table 3). This fact clearly excludes low anticoagulation as a reason for increased HM II thrombosis. Deposition of material (fibrin and denatured protein) in proximity to the inflow bearing, which has been seen increasingly in our centre and is described by Starling *et al.* [16], depends on fluid for lubrication and flow to dissipate heat. Heat generation and the subsequent deposition of fibrin around the bearing narrow the inflow pathway, increasing shear stress on the red cells and leading to haemolysis and finally to pump thrombosis. We speculate that the introduction of a gelatine-sealed inflow connector may lead to activation of coagulation on the gelatine-sealed surface with a subsequent increase of fibrin concentration in the blood entering the pump and, consequently, deposition of fibrin around the first bearing.

The definition of pump thrombosis used in the present study has great advantages there is no doubt that the reported cases are true as the thrombus was seen at the time of device exchange. However, there is possible under-reporting of the incidence, since some patients undergo lysis treatment and some experience transient signs of haemolysis or changes in power consumption and/or flow. In many cases, though, a transient increase of power consumption is not associated with pump thrombosis [2] and there is no international consensus on the definition of haemolysis.

Our study documented similar rates of Aspirin and Aggrenox use in patients with and without pump thrombosis supported by both types of pumps. It appears that neither substance influences pump thrombosis. Similar results were recently presented by Litzler *et al.*, who showed that oral vitamin K antagonist administration without Aspirin during long-term HM II support appears

Table 2: Coagulation parameters at admission in patients with pump thrombosis supported with HM II and HW, both subgroups

Parameters	HM II not sealed (*n* = 4)	HM II sealed (*n* = 11)	*P*-value	HW with non-sintered inflow cannula (*n* = 20)	HW with sintered inflow cannula (*n* = 11)	*P*-value
INR[a]	2.4 (2.4–3.0)	2.4 (2.2–2.5)	0.23	2.4 (1.8–3.1)	2.7 (2.0–3.9)	0.42
aPTT (s)[b]	55	55 (40–65)	1.0	39.6 (39–49)	38.4 (36–98)	0.42
Platelets (T/μl)	166 (18–330)	211 (80–638)	0.41	153 (34–335)	204 (106–276)	0.10
Aspirin use	0	0	n.a.	3 (27%)	3 (15%)	0.23
Aggrenox use	1 (25%)	7 (64%)	0.28	6 (55%)	4 (20%)	0.14

Data are presented as median and ranges or absolute and relative frequencies.
aPTT: activated partial thromboplastin time; INR: international normalized ratio; n.a.: not applicable.
[a]In patients receiving vitamin K antagonists (HM II not sealed *n* = 3, sealed *n* = 3; HW sintered *n* = 5, non-sintered *n* = 5).
[b]In patients without oral anticoagulation (HM II not sealed *n* = 1, sealed *n* = 8; HW sintered *n* = 6, non-sintered *n* = 15).

Table 3: Last available coagulation parameters in patients supported with the sealed and non-sealed version of HM II

Parameter	HM II not sealed (*n* = 125)	HM II sealed (*n* = 68)	*P*-value
INR[a]	2.4 (1.1–6.8)	2.4 (1.1.–9.0)	0.25
aPTT (s)[b]	50 (32–95)	56 (40–89)	0.28
Platelets (T/μl)	190 (14–730)	214 (38–638)	0.11
Aspirin use	33 (18%)	6 (9%)	0.08
Aggrenox use	37 (30%)	27 (40%)	0.15

There were no changes in our anticoagulation protocol over the study period.
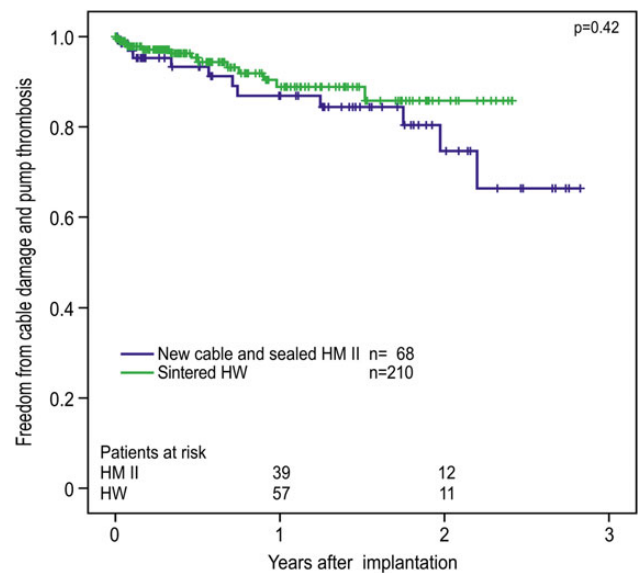Data are presented as median and ranges or absolute and relative frequencies.
aPTT: activated partial thromboplastin time; INR: international normalized ratio.
[a]In patients receiving vitamin K antagonists (HMII sealed, *n* = 42, non-sealed, *n* = 81).
[b]In patients without oral anticoagulation (HM II sealed, *n* = 26, non-sealed, *n* = 44).

Figure 4: Kaplan–Meier analysis of life-threatening events (cable damage or pump thrombosis) after recent modifications of HeartMate II (HM II) and HeartWare HVAD (HW) pumps.

not to increase thromboembolic events [18]. For HW pumps Slaughter *et al.* suggested that increasing the Aspirin dose up to 325 mg daily reduces pump thrombosis compared with 81–162 mg [6]. However, both events—the introduction of titanium sintering of the inflow cannula and the adjustment of the anticoagulation protocol—took place simultaneously, making it impossible to conclude which is responsible for the decrease in the pump thrombosis rate in this study [6]. Since our Aspirin use and measured INR values were consistent throughout the study period (Table 3, sintered vs non-sintered HW pumps) and the daily dose in patients receiving Aspirin ranged between 25 and 150 mg, we conclude that the titanium sintering alone resulted in the decreased incidence of pump thrombosis shown in our study. The percentage of reduction is similar to that described by Slaughter *et al.* Therefore, our results suggest that the titanium sintering alone is a crucial factor for reducing pump thrombosis in HW HVADs. Absence of a relation between freedom from pump thrombosis in HW patients and high Aspirin dose was reported recently by Najjar *et al.* [19]. The effect of 325 mg Aspirin daily as well as the role of dipyridamol in preventing thrombosis should be investigated in prospective multicentric studies.

The decreased incidence of pump thrombosis in HW pumps after inflow sintering and its increased incidence after the introduction of the sealed graft in HM II support the thesis that pump thrombosis is more likely to be related to pump design than to the body's inflammation status [20].

Since the last changes were made to the cable design of HM II in 2010, the incidence of cable damage in HM II patients dropped to zero in the first 3 years. Cable damage in HM II pumps with the 'old' strain relief design mostly occurred spontaneously as a result of chronic tension after a change in the pump or cable position only, and in four cases beyond 3 years of support [7]. Cable damage in the HM II pumps typically occurred at a 'weak' spot–the feedthrough of the driveline to the pump body [7, 21]. In HW patients all three instances of cable damage were caused by short-term extensive external impact [5]. The long-term durability of the HW driveline is excellent.

Owing to the shortage of donor organs and the rapid development of destination therapy programmes, LVAD support times are increasing in most centres across North America [22] and Europe [23]. Cable durability plays an important role in patients' lives, with a growing number living at home and engaging in work, sexual activity [24] and even extreme sports such as sky-diving, mountain

biking, hunting and so on. Both manufacturers (Thoratec and HeartWare) have recognized the problem and improved their cable design, aiming for more flexibility and durability. Upcoming devices such as HeartMate III or HeartWare MVAD already have an improved type of cable. However, in the longer term, a transcutaneous energy and information transfer system would be the best solution to reduce morbidity and mortality in patients on LVAD support.

CONCLUSION

The design modifications to both pumps, HM II and HW, may be one of the important factors that resulted in a significant change in the incidence of pump-related complications analysed in this study. While changes in the cable design of HM II and the sintering of the inflow graft of the HW pump have been seen to have a positive impact, the use of a gelatine-presealed inflow connector and outflow graft may be associated with an increased incidence of pump thrombosis. However, at our centre, the overall incidence of pump malfunctions related to cable damage or pump thrombosis has been similar for both pumps after the most recent modifications.

Limitations

The study is limited by its retrospective design. However, from our point of view, in this patient cohort, it would be unethical to perform a randomized study to compare different pumps or pumps with an old and new design.

Use of the last available INR value prior to device thrombosis may inadequately reflect the overall anticoagulation status of the patient but it does represent the real situation during outpatient visits or immediately before pump thrombosis. The study was performed with the largest single-centre population, where the vast majority of implantations were performed by two surgeons employing similar implanting techniques and anticoagulation; pump thrombosis detection and exchange protocols remained similar over the study period. However, a significantly larger cohort may be obtained from international MCS registries such as EUROMACS or IMACS. Although registry-based studies will have all the known limitations of multicentre studies, they should be initiated in the near future to further pursue answers to the questions discussed above.

ACKNOWLEDGEMENT

REFERENCES

[1] Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA *et al*. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation 2011;125:3191–200.

[2] Salerno CT, Sundareswaran KS, Schleeter TP, Moanie SL, Farrar DJ, Walsh MN. Early elevations in pump power with the HeartMate II left ventricular assist device do not predict late adverse events. J Heart Lung Transplant 2014;33:809–15.

[3] Popov AF, Hosseini MT, Zych B, Simon AR, Bahrami T. HeartWare left ventricular assist device implantation through bilateral anterior thoracotomy. Ann Thorac Surg 2012;93:674–6.

[4] Geidl L, Deckert Z, Zrunek P, Gottardi R, Sterz F, Wieselthaler G *et al*. Intuitive use and usability of ventricular assist device peripheral components in simulated emergency conditions. Artif Organs 2011;35: 773–80.

[5] Potapov EV, Stepanenko A, Kaufmann F, Henning E, Vierecke J, Lehmkuhl E *et al*. Thrombosis and cable damage in the HeartWare pump: clinical decisions and surgical technique. ASAIO J 2013;59:37–40.

[6] Slaughter MS, Pagani FD, McGee EC, Birks EJ, Cotts WG, Gregoric I *et al*. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. J Heart Lung Transplant 2013;32:675–83.

[7] Potapov EV, Kaufmann F, Stepanenko A, Hening E, Vierecke J, Low A *et al*. Pump exchange for cable damage in patients supported with HeartMate II left ventricular assist device. ASAIO J 2012;58:578–82.

[8] Hasin T, Marmor Y, Kremers W, Topilsky Y, Severson CJ, Schirger JA *et al*. Readmissions after implantation of axial flow left ventricular assist device. J Am Coll Cardiol 2013;61:153–63.

[9] Menon AK, Gotzenich A, Sassmannshausen H, Haushofer M, Autschbach R, Spillner JW. Low stroke rate and few thrombo-embolic events after HeartMate II implantation under mild anticoagulation. Eur J Cardiothorac Surg 2012;42:319–23; discussion 323.

[10] Slaughter MS, Naka Y, John R, Boyle A, Conte JV, Russell SD *et al*. Postoperative heparin may not be required for transitioning patients with a HeartMate II left ventricular assist system to long-term warfarin therapy. J Heart Lung Transplant 2010;29:616–24.

[11] Moazami N, Milano CA, John R, Sun B, Adamson RM, Pagani FD *et al*. Pump replacement for left ventricular assist device failure can be done safely and is associated with low mortality. Ann Thorac Surg 2013;95: 500–5.

[12] Potapov EV, Ignatenko S, Nasseri BA, Loebe M, Harke C, Bettmann M *et al*. Clinical significance of PlA polymorphism of platelet GP IIb/IIIa receptors during long-term VAD support. Ann Thorac Surg 2004;77:869–74; discussion 874.

[13] Potapov EV, Loforte A, Weng Y, Jurmann M, Pasic M, Drews T *et al*. Experience with over 1000 implanted ventricular assist devices. J Card Surg 2008;23:185–94.

[14] Cowger JA, Romano MA, Shah P, Shah N, Mehta V, Haft JW *et al*. Hemolysis: a harbinger of adverse outcome after left ventricular assist device implant. J Heart Lung Transplant 2014;33:35–43.

[15] Shah P, Mehta VM, Cowger JA, Aaronson KD, Pagani FD. Diagnosis of hemolysis and device thrombosis with lactate dehydrogenase during left ventricular assist device support. J Heart Lung Transplant 2014;33: 102–4.

[16] Starling RC, Moazami N, Silvestry SC, Ewald G, Rogers JG, Milano CA *et al*. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med 2014;370:1466–7.

[17] John R, Kamdar F, Liao K, Colvin-Adams M, Miller L, Joyce L *et al*. Low thromboembolic risk for patients with the Heartmate II left ventricular assist device. J Thorac Cardiovasc Surg 2008;136:1318–23.

[18] Litzler PY, Smail H, Barbay V, Nafeh-Bizet C, Bouchart F, Baste JM *et al*. Is anti-platelet therapy needed in continuous flow left ventricular assist device patients? A single-centre experience. Eur J Cardiothorac Surg 2013; 45:55–9; discussion 59–60.

[19] Najjar SS, Slaughter MS, Pagani FD, Starling RC, McGee EC, Eckman P *et al*. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. J Heart Lung Transplant 2014;33:23–34.

[20] May-Newman K, Wong YK, Adamson R, Hoagland P, Vu V, Dembitsky W. Thromboembolism is linked to intraventricular flow stasis in a patient supported with a left ventricle assist device. ASAIO J 2013;59:452–5.

[21] Stulak JM, Cowger J, Haft JW, Romano MA, Aaronson KD, Pagani FD. Device exchange after primary left ventricular assist device implantation: indications and outcomes. Ann Thorac Surg 2013;95:1262–7; discussion 1267–1268.

[22] Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA *et al*. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant 2013;32:141–56.

[23] Emin A, Rogers CA, Parameshwar J, Macgowan G, Taylor R, Yonan N *et al*. Trends in long-term mechanical circulatory support for advanced heart failure in the UK. Eur J Heart Fail 2013;15:1185–93.

[24] Sims DB, Vink J, Uriel N, Cleary KL, Smiley RM, Jorde UP *et al*. A successful pregnancy during mechanical circulatory device support. J Heart Lung Transplant 2011;30:1065–7.

5. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

6. Publikationsliste

6.1. Publikationen

1. **Soltani S**, Kaufmann F, Vierecke J, Kretzschmar A, Hennig E, Stein J, Hetzer R, Krabatsch T, Potapov EV.
    Design changes in continuous-flow left ventricular assist devices and life-threatening pump malfunctions.
    Eur J Cardiothorac Surg. 2015 Jun;47(6):984-9. doi: 10.1093/ejcts/ezu347.
    PMID: 25209626

    Impact Factor: 2,803 (2015)

2. Krabatsch T, Potapov E, **Soltani S**, Dandel M, Falk V, Knosalla C.
    Ventricular long-term support with implantable continuous flow pumps: on the way to a gold standard in the therapy of terminal heart failure.
    Herz. 2015 Apr;40(2):231-9. doi: 10.1007/s00059-015-4209-3. Review. German.
    PMID: 25822421

    Impact Factor: 0,54 (2015)

3. Kaufmann F, Hörmandinger C, Stepanenko A, Kretzschmar A, **Soltani S**, Krabatsch T, Potapov E, Hetzer R.
    Acoustic spectral analysis for determining pump thrombosis in rotary blood pumps.
    ASAIO J. 2014 Sep-Oct;60(5):502-7. doi: 10.1097/MAT.0000000000000097.
    PMID: 24814834

    Impact Factor: 2,35 (2014)

6.2. Kongressbeitrag

S. Soltani, F. Kaufmann, J. Vierecke, A. Kretzschmar, E. Hennig, J. Stein, T. Krabatsch, R. Hetzer, E. Potapov
Cable design improvements and sintering of the inflow cannula in continuous flow LVADs reduce the occurrence of life-threatening pump stops
43. Jahrestagung der Deutschen Gesellschaft für Thorax-, Herz- & Gefäßchirurgie.
Freiburg, Februar 2014

7. Danksagung

Lieber Gott, ich danke Dir für das Leben und meinen Glauben. Danke für die wunderbaren Eltern, die mir eine unersetzbare Stütze im Leben sind.
Jeder Tag mit euch ist ein Geschenk.

Ich danke dem, der mich nie vergaß und mich mit seiner Familie seit meiner Kindheit beschützt.
Friede sei mit Euch, ich bin Euch auf ewig dankbar.

Ich danke Herrn PD Dr. med. Evgenij Potapov, meinem Mentor und Oberarzt, der mich ausnahmslos unterstützt hat, und mit dem ich während meiner Dienste auf der Intensivstation viel erleben durfte.
Ich habe in jeder Hinsicht von Dir gelernt. Du gehörst zu meinen Vorbildern.

Ich danke Herrn Dipl. Ing. Friedrich Kaufmann und den Kollegen vom Assistteam, die mir mit Rat und Tat zur Seite standen. Frau Julia Stein danke ich für die statistischen Berechnungen.

Nicht zuletzt danke ich Herrn Prof. Dr. med. Dr. h.c.mult. Roland Hetzer, der mir all die lehrreichen Jahre im Deutschen Herzzentrum ermöglicht hat.
Es wird mir immer viel bedeuten, für Sie gearbeitet und Sie kennengelernt zu haben.

Diese Dissertation widme ich meiner Frau, die mich immer motiviert hat und ohne die ich nicht der sein könnte, der ich jetzt bin. Danken möchte ich auch meinen Kindern, durch die mein Leben eine neue Bedeutung gewonnen hat.
Ihr seid das Licht in meinen Augen.